Founded 1897 • New Series
Vol. CXXIII • No. 4/2020 • November

Romanian Journal of Military Medicine

REVISTA DE MEDICINĂ MILITARĂ

CiteFactor IF 1.90

CLARIVATE ANALYTICS EMERGING SOURCES CITATION INDEX INDEXED

Journal included in *Web of Science, Emerging Sources Citation Index, CiteFactor, Index Copernicus International, National Library of Medicine Catalog, Ulrich's Periodicals Directory database, Directory of Open Access Journals, Directory of Research Journals Index, Eurasian Scientific Journal Index, Science Library Index* and *Open Academic Journals Index*.

www.revistamedicinamilitara.ro

REDACTION

B-dul Eroii sanitari, Nr.8, Sector 5, București, Tel/fax 021/318.07.59, tel. 021/318.08.62/Int. 199; Email rjmilmed@yahoo.com
Romanian Journal of Military Medicine (RJMM) is included in the Romanian College of Physicians Medical Publications Index.

www.revistamedicinamilitara.ro

Romanian Journal of Military Medicine, New Series, vol. CXXIII, No 4/2020, November
ISSN-L1222-5126; eISSN 2501-2312; pISSN 1222-5126

Romanian Journal of
Military
Medicine

Founded 1897•New Series
Vol. CXXIII• No. 4/2020, November

Contents

The article was received on March 17, 2020, and accepted for publishing on July 23, 2020.

REVIEW ARTICLE

Current treatment of posttraumatic stress disorder – A review of therapeutic guidelines and good practice recommendations

Octavian Vasiliu, Daniel Vasile, Andrei G. Mangalagiu, Bogdan M. Petrescu, Cristian A. Candea, Corina Tudor, Daniela Ungureanu, Madalina Miclos, Alina Draghici, Catalina Florescu, Roxana E. Bratu-Bazic

Abstract: *A unique approach to the treatment of posttraumatic stress disorder (PTSD) is difficult to support, because of the complexity and heterogeneity of this pathology. Multiple evidence-based guidelines for PTSD treatment exist, elaborated by prestigious institutions around the world, but a certain level of the inconsistency of their recommendations appears when these sources are compared with each other. Therefore, a review of current guidelines and extraction of the most supported by evidence recommendations is considered important for clinical practice, due to the need to approach such complex cases as PTSD-diagnosed patients in a stepwise manner. Structured monitoring of the clinical status during the treatment is also an important and rather neglected aspect of the case management in PTSD, and the necessity of follow-up visits for efficacy and tolerability should be taken into consideration. Psychotherapy (especially cognitive-behavioral oriented therapies and eye movement desensitization and reprocessing therapy) is supported by evidence as a first-line approach, as well as certain antidepressants, like the selective serotonin reuptake inhibitors and venlafaxine. Many second-line pharmacological agents and psychotherapies are also available, but there is an obvious need for more pragmatic trials with PTSD patients.*

Keywords: *post-traumatic stress disorder, psychotherapy, case management, antidepressants, therapeutic guidelines, good clinical practice*

BACKGROUND

While definitions of the diagnostic criteria for posttraumatic stress disorder (PTSD) are articulate and comprehensive in both the World Health Organization and American Psychiatric Association classifications of mental disorders [1-3], pragmatic recommendations for the treatment of this disorder are still lacking. Although there are several guidelines dedicated to this subject, they are based on randomized trials, and not on pragmatic, naturalistic studies, which leave some important questions unanswered. Even if the case management is based on these guidelines, there are several contradictions based on the different data they included. Therefore, we consider the first necessary step to be a critical analysis of these therapeutic guidelines, followed by the formulation of good practices and hierarchized recommendations, according to the GRADE level [4].

The diagnosis of PTSD could be formulated, according to ICD-11, if an extremely threatening or horrific event or series of events is followed by re-experiencing this trauma as intrusive memories, flashbacks, nightmares, accompanied

„Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, Romania

by strong or overwhelming emotions and strong physical sensations; avoidance of thoughts and memories of the event(s), or avoidance of activities, situations, or people reminiscent of the events(s); persistent perceptions of heightened current threat, for example, indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises [1]. These symptoms have to persist for at least several weeks and to cause significant impairment in personal, family, social, educational, occupational, or other important areas of functioning to support a PTSD diagnosis [1]. The ICD-10 mentions the capacity of the stressful event to cause pervasive distress in almost anyone who has been removed from the latest edition of this classification [1,3]. Also, differences in the structure of the symptoms list necessary to establish the PTSD criteria have been formulated between the two editions of ICD, from 13 in the tenth edition, to only 6, by removing the non-specific manifestations [1,3]. In the latest edition of the American Psychiatric Association classification of mental disorders (2013), there are 4 clusters of symptoms needed for the diagnosis: (1) intrusion symptoms associated with the traumatic event, (2) persistent avoidance of stimuli associated with the traumatic event, (3) negative alterations in cognitions and mood associated with the traumatic event, (4) marked alterations in arousal and reactivity associated with the traumatic event, and the duration of these manifestations are more than one month [2].

Complex PTSD may develop following exposure to an event or series of events of an extremely threatening or horrific nature, commonly prolonged or repetitive events from which escape is difficult or impossible [1]. Complex PTSD is characterized by severe and persistent problems in affect regulation, beliefs about oneself as diminished, defeated, or worthless, accompanied by feelings of shame, guilt, or failure related to the traumatic event; difficulties in sustaining relationships, and feeling close to others [1]. These symptoms cause significant impairment in personal, family, social, educational, occupational, or other important areas of functioning [1].

A high rate of comorbid major depressive disorder (up to 50%) has been reported in PTSD patients, a phenomenon which underlines the necessity for a thorough psychiatric evaluation, both initially and during the monitoring period [5,6]. Also, there has been described as an overlap between PTSD and psychosis that may raise important diagnosis challenges and treatment dilemmas [7, 8]. Substance-related disorders have also been described with relatively high incidence in this population, and specific psychotherapy algorithms have been developed for these patients with dual diagnosis, based on imaginal and in vivo exposure for PTSD, applied concomitantly with cognitive-behavioral techniques for substance use disorders [9]. Also, the pharmacological treatment should be adjusted according to the existing comorbidities, and the case manager should integrate all the data, taking into account the risk of pharmacologic interactions, contraindications, and side effects (e.g., avoidance of drugs with the risk of addiction, like benzodiazepines, is recommended in PTSD patients) [10].

ANALYSIS OF THE CURRENT THERAPEUTIC GUIDELINES FOR PTSD

Several prestigious institutions have elaborated evidence-based guidelines for the treatment of PTSD, therefore an important number of recommendations for approaching these patients to exist. While some therapeutic guidelines are focused on psychotherapy, others are based on pharmacological research, while still others encompass both types of treatment.

American Psychological Association Clinical Practice Guideline for the Treatment of PTSD (2017) strongly recommends as evidence-based psychotherapies in adults cognitive-behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy (CT), and prolonged exposure therapy (PE), and suggests the use of brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing therapy (EMDR), and narrative exposure therapy (NET) [11].

According to the **Australian Guidelines for the Treatment of Acute Stress Disorder and Posttraumatic Stress Disorder** (2013), individual-trauma focused CBT, including exposure and/or cognitive therapy, should be recommended if symptoms are consistent with acute stress disorder or posttraumatic stress disorder in the initial 4 weeks after a potentially traumatic event (level C evidence) [12]. Individuals with posttraumatic stress disorder benefit from trauma-focused CBT or EMDR (level A recommendation), and if the symptoms did not respond to these interventions, non-trauma focused approaches may be considered (e.g., stress inoculation technique) [12]. Also, there is some evidence that supports the efficacy of in vivo exposure therefore, by expert consensus, it is recommended to include this method in the treatment [12]. Group CBT (trauma-focused or non-trauma focused) may be offered as an adjunctive to trauma-focused individual therapy [12].

Medication should not be used for the treatment of acute stress reaction or posttraumatic stress disorder within the four weeks of symptom onset unless the severity of such symptoms- associated distress cannot be managed by psychological means alone [12]. The pharmacological

approach may be continued while people are undertaking psychological treatments, but several agents, like benzodiazepines, may interfere with some effective psychological treatments [12]. SSRIs are considered the first line for the treatment of posttraumatic stress disorder [12].

According to the **Maudsley Prescribing Guidelines** (13th edition, 2018) patients diagnosed with posttraumatic stress disorder should be offered as the first line of treatment paroxetine, sertraline, fluoxetine (up to the maximum tolerated doses) or venlafaxine (37.5-300 mg/day) [13]. As second-line treatment the case manager could choose between antipsychotics (olanzapine 5-20 mg/day, risperidone 0.5-6 mg/day, quetiapine 50-800 mg/day), mirtazapine 15-45 mg/day, monoaminoxidase (MAO) inhibitors (phenelzine 15-75 mg/day), tricyclic antidepressants (amitriptyline 50-300 mg/day, imipramine 50-300 mg/day), and prazosin (2-15 mg nocte) for nightmare and sleep disturbances [13]. Possible choices if the first and second lines failed are duloxetine (60-120 mg/day), lamotrigine (up to 500 mg/day), phenytoin, valproate, or i.v. ketamine, and as non-drug therapies- eye-movement desensitization and reprocessing (EMDR) and trauma-focused CBT [13].

According to the **VA/DOD Clinical Practice Guideline for the Management of PTSD and ASD** (2017) pharmacotherapy in PTSD is classified as follows: sertraline, paroxetine, fluoxetine, venlafaxine as monotherapy (moderate evidence), nefazodone (low evidence), imipramine, phenelzine (very low evidence) [14]. The Work Group recommended against the use of atypical antipsychotics, benzodiazepines, and Divalproex as augmentation therapy due to low-quality evidence and potential adverse effects [14]. Also, prazosin is not supported by this guideline for the use in monotherapy or combination with other agents [14]. Individual trauma-focused psychotherapy for PTSD are Prolonged Exposure, Cognitive Processing Therapy, and EMDR, which are supported by the strongest evidence, but other therapies like specific cognitive therapies for PTSD, Brief Eclectic Psychotherapy, Narrative Exposure Therapy, written narrative exposure may be recommended [14]. If individual trauma-focused psychotherapy is not available, Stress Inoculation Therapy, Interpersonal Therapy, or Present-Centered Therapy may be recommended [14].

The **International Society for Traumatic Stress Studies new guidelines for the Prevention and Treatment of Posttraumatic Stress Disorder** (2019) has formulated the following recommendations according to their evidence-based status: (1) strong support for cognitive processing therapy, cognitive therapy, EMDR, individual CBT with a trauma focus, prolonged exposure; (2) standard recommendations for CBT without a trauma focus, guided Internet-based CBT with a trauma focus, narrative exposure therapy, present-centered therapy; (3) emerging evidence-couples CBT with a trauma focus, group and individual CBT with a trauma focus, reconsolidation of traumatic memories, single-session CBT, written exposure therapy, and virtual reality therapy [15].

Individual trauma-focused CBT intervention may be useful for adults who have acute stress disorder or clinically important symptoms of PTSD and have been exposed to 1 or more traumatic events within the last month- cognitive processing therapy, cognitive therapy, narrative exposure therapy, prolonged exposure therapy, according to the **NICE Guidelines** (2018) [16]. In adults with PTSD symptoms should be offered trauma-focused CBT, during 8-12 sessions, accompanied by psychoeducation about reactions to trauma, strategies for managing arousal and flashbacks, safety planning, or EMDR for patients with PTSD symptoms, if the patient has a preference for this method [16]. Trauma-focused computerized CBT for adults with a diagnosis of PTSD or clinically important symptoms of PTSD more than 3 months after a traumatic event, who do not want to be engaged in trauma-focused CBT or EMDR [16]. Symptom-specific CBT interventions for adults with a diagnosis of PTSD or clinically important symptoms of PTSD more than 3 months after traumatic events who are unable or unwilling to engage in a trauma-focused intervention that targets PTSD or have residual symptoms after a trauma-focused intervention [16].

Medication should not include benzodiazepines for the prevention of PTSD in adults, but venlafaxine or an SSRI may be chosen [16]. Antipsychotics may be offered if patients have disabling symptoms (psychotic) or if their symptoms have not responded to other drug or psychological treatments [16].

For patients with complex PTSD the case manager should help the patient control any symptoms (e.g. dissociation or emotional dysfunctions) that might interfere with engaging in trauma-focused therapies; ensure adequate time for the construction of the therapeutic relationship; to increase the number of trauma-focused therapy sessions according to the person's needs; plan any ongoing support the person needs and has implications in the therapeutic management [16].

DESCRIPTION OF THE MAIN PSYCHOTHERAPEUTIC METHODS IN PTSD

Cognitive-behavioral therapy (CBT) in PTSD is focused on the relationship among thoughts, feelings, and behaviors that are present-oriented and target current problems and

symptoms [17]. CBT is based on emotional processing theory and social cognitive theory, therefore it claims that changing associations between reminders of the traumatic event and responses will lead to healthier behaviors while reframing the relation between trauma and existing beliefs about self, others and the world will also help decrease self-blame and improve the processing of the trauma [17].

Cognitive distortions in PTSD include perceiving the world as dangerous, seeing him/herself as powerless, and feeling guilty about surviving while other significant ones have died [18]. Cognitive therapy fosters the development of more realistic and adaptive cognitions, by successful processing of the traumatic event, with engaging and organization of the trauma narrative [18, 19].

Cognitive processing therapy (CPT) is an efficient method for treating PTSD as demonstrated by a recent meta-analysis (n=11 studies, N=1130 participants), outperforming inactive control conditions on PTSD outcome measures at posttreatment and follow-up, but also other active treatments at posttreatment but not at follow-up [20]. Effect sizes of CPT were superior to 89% of the inactive control conditions at posttreatment and 82% at follow-up, which indicates a large and sustained effect of the CPT [20].

Veterans who were diagnosed with both PTSD and alcohol use disorder (AUD) completed a 6-week CPT-based program had significantly better outcomes, including trauma-related cognitive distortions, PTSD symptoms, depressive symptoms, and trauma-cued substance craving [21]. In another study that included veterans (n=465), enrolled in CPT plus a written trauma account either group format or individual, the PTSD and depressive symptoms decreased significantly, with medium effects for the first option, and large effects for the second treatment [22].

Cognitive therapy (CT) has proven efficient in a group of 20 patients diagnosed with PTSD, as it decreased core PTSD features, but also depressive and anxiety symptoms [23]. Good treatment outcomes were related to more changes in dysfunctional cognitions related to the trauma [23]. Intensive CT was applied in 14 patients diagnosed with PTSD, in an 18-hour format during 5-7 working days, followed by one session a week later and up to 3 follow-up sessions; intensive CT led to similar outcomes as weekly-administered CT, but the intensive treatment improved the key PTSD symptoms over a shorter period and led to greater reductions in depression [24].

Prolonged exposure therapy (PE) is another trauma-focused CBT effective for improving PTSD, with response rates in 60-65% of trauma victims suffering from this disorder [25]. PE is based on two types of exposure techniques, imaginal exposure, and in vivo exposure, and it is used for enhancing emotional processing through systematic confrontation with trauma-related stimuli [26-28]. Intensive PE therapy (12 sessions, 90 minutes each, during 4 days) followed by four weekly 90-minute booster PE sessions in an open trial (n=73) patients diagnosed with PTSD who presented multiple interpersonal trauma had positive results after repeated treatment attempts [29]. Exposure therapy has an impact on the fear and contextualization circuits by facilitating communication between the ventromedial prefrontal cortex, hippocampus, and the amygdala [30].

Brief eclectic psychotherapy (BEP) for PTSD is a manualized technique that combines elements from psychodynamic, cognitive-behavioral, and directive psychotherapy [31]. Psychoeducation with the participation of the spouse, and exposure used to help the patient to access his or her feelings related to the traumatic event are also used during BEP [31]. A 16-session protocol of BEP in PTSD includes the following steps: psychoeducation for the development of self-control and motivation for therapy (the patient is invited to call up his memories and related emotions one last time); imaginal exposure or guidance (brief periods of muscle relaxation, relieving of the traumatic experience by imaginal exposure of 20-30 minutes); writing tasks and mementos (for uncovering the difficult feelings that may be related to the traumatic experience); meaning and integration (exploring and accepting a new view of the world and the self); farewell ritual (symbolic ritual created to encourage the expression of the sorrow the patient may still feel, and then to leave behind these feelings) [31, 32].

The first randomized clinical trial for BEP in patients with PTSD included 42 police officers who received 16 weekly sessions (60 minutes each) of psychotherapy [32]. At posttest and follow-up (at 3 months) BEP had produced significant improvement in PTSD symptoms, work functioning, and several comorbid conditions (e.g., agoraphobia) [32].

Another clinical trial included patients diagnosed with PTSD (n=24) randomly assigned to BEP or a waitlist group for 4 months, with superior efficacy on PTSD core symptoms and general anxiety symptoms in the active intervention group [33]. In this trial, BEP consisted of 16 weekly sessions (45-60 minutes each), and a high rate of the dropout was recorded (25% for the treatment group) [33].

Eye movement desensitization and reprocessing therapy (EMDR) is a type of psychotherapy developed by F.Shapiro for intervention in emotional trauma and other negative life experiences [34]. This psychotherapy consists of a protocol with 8 phases and bilateral stimulation targeting patient

desensitization from the discomfort induced by traumatic memories [35]. The final objective of the EMDR is to achieve the reprocessing of these memories and to integrate them within the autobiographical memory [35].

According to a review of 24 randomized controlled trials, EMDR is an evidence-based approach for this kind of disorder, with 7 out of 10 studies reporting EMDR to be faster acting and/or more effective than trauma-focused CBT [34]. Two meta-analyses supported the efficacy of EMDR in treating PTSD, with results superior to various interventions and control conditions, and showed the efficacy of this psychotherapy over symptoms of depression, anxiety, and subjective distress [36,37]. A review of the trials published between 2014 and 2017 regarding the efficacy of EMDR in PTSD further supported this method, because it improved core symptoms over time, compared to relaxation therapy and a waiting-list control group [38].

Narrative exposure therapy (NET) is a psychotherapeutic intervention dedicated to the treatment of survivors of multiple and severe traumas, and 3-6 sessions may be sufficient to provide significant relief [39]. It is a short-term approach based on CBT and testimony therapy [40]. NET was evaluated in a group of 59 political detainees, 18 of which had full PTSD criteria, who were allocated in a randomized manner to either one session of psychoeducation or five sessions of NET [41]. After 6 months, NET but not psychoeducation produced a significant reduction in PTSD symptoms and depression scores, although four out of the nine patients receiving NET and eight out of the nine patients undergoing psychoeducation still had PTSD symptoms at 6 months [41]. In another trial, NET was compared to supportive counseling and psychoeducation (4, 4 and one sessions, respectively) in a group of Sudanese refugees (n=43), and the results after one year of treatment were superior for NET (29% vs. 79% vs. 80% still had PTSD criteria) [40].

Interpersonal therapy (IPT) is a time-limited focused on the patient's actual events and reframing of the social functioning as a way to tackle the symptoms and may be recommended where the patient does not want to be exposed to exposure-based approaches [42]. In a case study, IPT proved itself efficient comparative to the other two psychotherapies, after 14 weekly sessions [42]. In a 14-week randomized trial, IPT was compared to prolonged exposure and relaxation therapy in 110 unmedicated patients with chronic PTSD and the response rates were 63% for IPT, 47% for prolonged exposure, and 38% for relaxation therapy, without significant differences between groups [43]. IPT and exposure therapy improved the quality of life and social functioning more than relaxation therapy [43].

Group Interpersonal Therapy (G-IPT) was evaluated in 13 patients diagnosed with chronic PTSD, in an 8-week treatment program, with favorable results [44]. The improvement was significant in social functioning, general wellbeing and depressive symptoms, and a moderate reduction in the avoidant symptom cluster of PTSD [44]. These positive effects were stable at 3 months and associated with perceived intra-therapy progress in solving problematic domains identified during IPT [44].

Present-Centered Therapy (PCT) for PTSD is a manualized psychotherapy originally designed as a treatment comparator in studies focused on the effectiveness of trauma-oriented CBT [45]. A systematic review of the randomized trials (n=12, N=1837 participants) states that moderate-quality evidence supports a superior efficacy of PCT in reducing PTSD severity compared to control conditions, and PCT was associated with lower drop-out rates comparative to trauma-focused CBT [45].

Stress inoculation training (SIT) is derived from CBT and proved itself efficient in veterans with PTSD [46]. According to this model, PTSD symptoms are maintained by an imbalance between perceived situational demands and perceived resources to fulfill the environmental and personal demands [47, 48]. The purpose of SIT is to increase the patient's feeling of self-confidence by helping him or her to control anxiety and related symptoms and to inoculate patients against possible future episodes of severe anxiety [48].

In a population with PTSD and traumatic brain injury (n=65 veterans), SIT was applied for 18 months in an outpatient clinic and the results supported the efficacy of this psychotherapy because significant reductions in PTSD and depressive symptoms were detected, as well as increases in perceived stress tolerance and performance in multiple life domains [46]. Improvements in social and occupational functioning were also reported [46].

In another trial, 96 female assault victims with chronic PTSD were randomized on prolonged exposure, SIT, combined prolonged exposure-SIT, or wait-list control [49]. All active treatments (9 twice-weekly individual sessions) decreased PTSD and depression symptoms compared to wait-list but did not differ significantly from each other, and these results persisted at follow-ups (3, 6, and 12 months) [49].

GOOD CLINICAL PRACTICE RECOMMENDATIONS

Therapeutic guidelines offer various and sometimes contradictory recommendations, therefore a critical analysis of the literature is granted to find common management strategies. While several guidelines are more cautious when

recommending pharmacotherapy [12] and support a psychotherapeutic-based approach especially in the first stage of the PTSD, others are more focused on drug therapy [13], and still, others consider the type of approach should be selected according to the individual variables, including patient's preference, availability, etc [14].

We formulated GRADE recommendations according to 4 levels: A= high quality, defined as the level to what future research are very unlikely to change the validity of these recommendations; B= moderate quality, meaning that future research is likely to have an important impact on the appreciation of the recommendations; C=low quality, which means that it is very likely that future research will have an important impact over the confidence in the estimate of effect and is likely to change the recommendations; D= very low quality, defined by the uncertainty of any estimate of the effect [4].

A wide range of psychotherapies have been studied for patients with PTSD, but CBT and related techniques (CPT, CT, PE), as well as EMDR, are the most evidence-based approaches [11-15]. We consider a GRADE level A for these therapies is granted, based on the existing evidence. Level B evidence exists for BEP, NET, IPT, PCT, and SIT [31-33, 39-49].

The same level of evidence exists for SSRIs and venlafaxine, as these are the most supported by evidence pharmacological agents in PTSD patients [12-15]. If the first-line agents fail, then second-line agents may be used-mirtazapine, MAO inhibitors or tricyclics, or add-ons like atypical antipsychotics (level B of evidence) [13].

A structured diagnostic approach is strongly encouraged and adequate instruments should be used. Structured interviews (e.g., Mini-International Neuropsychiatric Interview, Composite International Diagnostic Interview, or Schedules for Clinical Assessment in Neuropsychiatry) are considered useful because of the high comorbidity rate met in PTSD patients [50-52]. Because the evolution of PTSD is not linear, even under treatment, detection of new-onset psychiatric disorders is also important because of their high impact over the treatment plan. Therefore, using structured clinical interviews during the first 6-12 months of the treatment is also recommended.

Monitoring treatment efficacy in PTSD using standardized instruments is strongly encouraged. For this purpose, we recommend validated scales, inventories, or structured interviews, like the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), PTSD Symptom Scale Interview (PSS-I), Mississippi Scale for Combat-related PTSD (MISS) [53-55]. This is considered a good clinical practice because it may increase the objectivity of the psychiatric evaluation, although it is not specifically recommended in all the reviewed therapeutic guidelines.

We consider good clinical practice in the PTSD treatment to actively monitor the tolerability of the pharmacological treatment, to detect early adverse events that may decrease therapeutic adherence [56]. For this purpose, the administration of the Treatment Satisfaction Questionnaire for Medication (TSQM) [57] or a simpler visual analogic scale for self-evaluation is considered useful.

CONCLUSIONS

A review of the existing therapeutic guidelines focused on PTSD management detected several common recommendations. These refer to the use of CBT and related therapies and EMDR as a first-line approach and SSRIs or venlafaxine as the main pharmacologic agents [1-5, 11]. Our team has added as good practice recommendations the necessity to use validated instruments for initial and follow-up diagnostic evaluations, as well as the monitoring of treatment tolerability and efficacy. Because of the high rate of comorbid disorders in PTSD patients, the case manager should be alert to new-onset psychiatric disorders that may appear as complications or just comorbidities in this population.

An integrated, psychological, and pharmacological approach should be considered for these patients, with frequent follow-up visits, and emergent disorders have to be integrated into the case management plan as soon as they are detected.

Disclaimer

No funding was received for this research.

The first author was a speaker for Servier, Eli Lilly, and Bristol-Myers, and participated in clinical trials funded by Janssen Cilag, Astra Zeneca, Otsuka Pharmaceuticals, Sanofi-Aventis, and Sunovion Pharmaceuticals.

References:

1. World Health Organization. International Classification of Diseases, 11th Edition. Retrieved online at https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/ entity/2070699808 on 21/02/2020.

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. APA, Arlington, 2013.

3. World Health Organization. International statistical classification of diseases and related health problems, 10th Edition, revised.

Geneva, Switzerland, WHO, 1992.

4. The GRADE Working Group. GRADE Recommendations. Retrieved online at https://www.gradeworkinggroup.org/ in 21/02/2020.

5. Marinescu I, Vasiliu O, Vasile D. Translational approaches in treatment-resistant depression based on animal model. Romanian Journal of Morphology and Embryology 2018;59(3):955-964.

6. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin Neurosci 2015;17(2):141-150.

7. Vasiliu O, Vasile D, Voicu V. Efficacy and tolerability of antibiotic augmentation in schizophrenia spectrum disorders- A systematic literature review. Romanian Journal of Military Medicine 2019;CXXIII(1):3-20.

8. Compean E, Hamner M. Posttraumatic stress disorder with secondary psychotic features (PTSD-SP): diagnostic and treatment challenges. Prog Neuropsychopharmacol Biol Psychiatry 2019;88:265-275.

9. Killeen TK, Back SE, Brady KT. The use of exposure-based treatment among individuals with PTSD and co-occuring substance use disorders: clinical considerations. J Dual Diagn 2011;7(4):194-206.

10. Vasiliu O. Maintenance pharmacologic therapies for opioid use disorders: beyond opioid agonists. Romanian Journal of Military Medicine 2019;CXXII(1):52-70.

11. American Psychological Association. American Psychological Association Clinical Practice Guideline for the Treatment of PTSD. APA, 2017. Retrieved online at https://www.apa.org/ptsd-guideline/ptsd.pdf on 10/02/2020.

12. Australian Guidelines for the Treatment of Acute Stress and Posttraumatic Stress Disorder. Retrieved online at https://www.phoenixaustralia.org/wp-content/uploads/2015/03/Phoenix-ASD-PTSD-Guidelines.pdf on 18/02/2020.

13. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry, 13th edition. Wiley Blackwell, West Sussex, 2018.

14. US Department of Veteran Affairs and US Department of Defense. VA/DoD clinical practice guideline for the management of posttraumatic stress disorder and acute stress disorder. 3rd Ed, 2017. Retrieved online at https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGClinicianSummaryFinal.pdf in 19/02/2020

15. Bisson JI, Berliner L, Cloitre M, et al. The International Society for Traumatic Stress Studies new guidelines for the Prevention and Treatment of Posttraumatic Stress Disorder: Methodology and development process. J Trauma Stress 2019;32(4):475-483.

16. National Institute for Health and Care Excellence. Post-traumatic stress disorder. NICE Guideline 116. Published date: December 2018. Retrieved online at https://www.nice.org.uk/guidance/ng116/chapter/Recommendations in 19/02/2020.

17. Cognitive behavioral therapy (CBT). Retrieved online at https://www.apa.org/ptsd-guideline/treatments/cognitive-behavioral-therapy in 24/02/2020.

18. Kar N. Cognitive behavioral therapy for the treatment of post-traumatic stress disorder: a review. Neuropsychiatr Dis Treat 2011;7:167-81.

19. Hembree EA, Foa EB. Posttraumatic stress disorder. Psychological factors and psychosocial interventions. J Clin Psychiatry 2000;61(Suppl.7):33-39.

20. Asmundson GJG, Thorisdottir AS, Roden-Foreman JW, et al. A meta-analysis review of cognitive processing therapy for adults with posttraumatic stress disorder. Cogn Behav Ther 2019;48(1):1-14.

21. Peck KR, Coffey SF, McGuire AP, et al. A cognitive processing therapy-based treatment program for veterans diagnosed with co-occuring posttraumatic stress disorder and substance use disorder: the relationship between trauma-related cognitions and outcomes of a 6-week treatment program. J Anxiety Disord 2018;59:34-41.

22. Lamp KE, Avallone KM, Maieritsch KP, et al. Individual and group cognitive processing therapy: effectiveness across two veterans affairs posttraumatic stress disorder treatment clinics. Psychol Trauma 2019;11(2):197-206.

23. Ehlers A, Clark DM, Hackmann A, et al. Cognitive therapy for post-traumatic stress disorder: development and evaluation. Behav Res Ther 2005;43(4):413-31.

24. Ehlers A, Clark DM, Hackmann A, et al. Intensive cognitive therapy for PTSD: a feasibility study. Behav Cogn Psychother 2010;38(4):383-398.

25. Grunert BK, Weis JM, Smucker MR, Christianson HF. Imagery rescripting and reprocessing therapy after failed prolonged exposure for post-traumatic stress disorder following industrial injury. J Behav Ther Exp Psychiatry 2007;38(4):317-28.

26. Asukai N. Prolonged exposure therapy for post-traumatic stress disorder. Seishin Shinkeigaku Zasshi 2015;117(6):457-64.

27. Foa EB. Prolonged exposure therapy: past, present, and future. Depress Anxiety 2011;28:1043-47.

28. Stojek MM, McSweeney LB, Rauch SAM. Neuroscience informed prolonged exposure practice: increasing efficiency and efficacy through mechanisms. Front Behav Neurosci 2018;12:281.

29. Hendriks L, de Kleine RA, Broekman TG, et al. Intensive prolonged exposure therapy for chronic PTSD patients following multiple trauma and multiple treatment attempts. Eur J Psychotraumatol 2018;9(1):1425574.

30. Helpman L, Marin MF, Papini S, et al. Neural changes in extinction recall following prolonged exposure treatment for PTSD: a longitudinal fMRI study. Neuroimage Clin 2016;12:715-23.

31. Gersons BPR, Schyder U. Learning from traumatic experiences with brief eclectic psychotherapy for PTSD. Eur J Psychotraumatol 2013;4:10.3402/ejpt.v4i0.21369.

32. Gersons BP, Carlier IV, Lamberts RD, van der Kolk BA. Randomized clinical trial of brief eclectic psychotherapy for police officers with posstraumatic stress disorder. J Trauma Stress 2000;13(2):333-47.

33. Lindauer RJL, Gersons BPR, van Meijel EPM, et al. Effects of brief eclectic psychotherapy in patients with posttraumatic stress disorder: randomized clinical trial. J Trauma Stress 2005;18(3):205-12.

34. Shapiro F. The role of eye movement desensitization and reprocessing (EMDR) therapy in medicine: addressing the psychological and physical symptoms stemming from adverse life experience. Perm J 2014;18(1):71-77.

35. Valiente-Gomez A, Moreno-Alcazar A, Treen D, et al. EMDR beyond PTSD: A systematic literature review. Front Psychol 2017;8:1668.

36. Chen YR, Hung KW, Tsai JC, et al. Efficacy of eye-movement desensitization and reprocessing for patients with posttraumatic-stress disorder: a meta-analysis of randomized controlled trials. PLoS ONE 2014;9:e0103676.

37. Chen YR, Zhang G, Hu M, Liang X. Eye movement desensitization and reprocessing versus cognitive-behavioral therapy for adult posttraumatic stress disorder: systematic review and metaanalysis. J Nerv Mental Dis 2015;203:443-451.

38. Wilson G, Farrell D, Barron I, et al. The use of eye-movement

desensitization reprocessing (EMDR) therapy in treating post-traumatic stress disorder- a systematic narrative review. Front Psychol 2018;9:923.

39. Schauer M, Neuner F, Elbert T. Narrative exposure therapy: A short-term intervention for traumatic stress disorders after war, terror, or torture. Hogrefe&Hogrefe, Germany, 2005.

40. Neuner F, Schauer M, Klaschik C, et al. Supportive counseling, and psychoeducation for treating posttraumatic stress disorder in an African refugee settlement. J Consult Clin Psychol 2004;72(4):579-87.

41. Bichescu D, Neuner F, Schauer M, Elbert T. Narrative exposure therapy for political imprisonment-related chronic posttraumatic stress disorder and depression. Behav Res Ther 2007;45(9):2212-20.

42. Rafaeli AK, Markowitz JC. Interpersonal psychotherapy (IPT) for PTSD: A case study. Am J Psychother 2011;65(3):205-23.

43. Markowitz JC, Petkova E, Neria Y, et al. Is exposure necessary? A randomized clinical trial of interpersonal psychotherapy for PTSD. Am J Psychiatry 2015;172(5):430-40.

44. Robertson M, Rushton P, Batrim D, et al. Open trial of interpersonal psychotherapy for chronic posttraumatic stress disorder. Australas Psychiatry 2007;15(5):375-9.

45. Belsher BE, Beech E, Evatt D, et al. Present-centered therapy (PCT) for post-traumatic stress disorder (PTSD) in adults. Cochrane Database Syst Rev 2019;11. DOI: 10.1002/ 14651858.CD012898.pub2

46. Jackson S, Baity MR, Bobb K, et al. Stress inoculation training outcomes among veterans with PTSD and TBI. Psychol Trauma 2019;11(8):842-850.

47. Meichenbaum D. Important facts about resilience: A consideration of research findings about resilience and implications for assessment and treatment. Melissa Institute, Miami, USA, 2007.

48. Lancaster C, Teeters JB, Gros DF, Back SE. Posttraumatic stress disorder: Overview of evidence-based assessment and treatment. J Clin Med 2016;5(11):105.

49. Foa EB, Dancu CV, Hembree EA, et al. A comparison of exposure therapy, stress inoculation training, and their combination for reducing posttraumatic stress disorder in female assault victims. J Consult Clin Psychol 1999;67(2):194-200.

50. Sheehan DV, Lecrubier Y, Sheehan KH, et al. J Clin Psychiatry 1998;59(Suppl.20):22-23.

51. Nienhuis FJ, van de Willige G, Rinders CA, et al. Validity of a short clinical interview for psychiatric diagnosis: the mini SCAN. Br J Psychiatry 2010;196(1):64-8.

52. Janca A, Robins LN, Cottler LB, Early TS. Clinical observation of assessment using teh Composite International Diagnostic Interview (CIDI). An analysis of the CIDI Field Trials- Wave II at the St Louis site. Br J Psychiatry 1992;160:815-8.

53. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial evaluation in military veterans. Psychological Assessment 2017;30(3):383-395.

54. Foa E, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. Journal of Traumatic Stress 1993;13(2):181-191.

55. Keane TM, Caddell JM, Taylor KL. Mississippi Scale for Combat-related Posttraumatic Stress Disorder: Three studies in reliability and validity. Journal of Consulting and Clinical Psychology 1988;56(1):85-90.

56. Vasiliu O. Effects of the selective serotonin reuptake inhibitors over coagulation in patients with depressive disorders- a systematic review and retrospective analysis. Romanian Journal of Military Medicine 2019;CXXII(2):7-11.

57. Atkinson MJ, Kumar R, Cappelleri JC, Hass SL. Hierarchical construct validity of the treatment satisfaction questionnaire for medication (TSQM version II) among outpatient pharmacy consumers. Value Health 2005;8(Suppl.1):S9-S24.

The article was received on January 20, 2020, and accepted for publishing on September 23, 2020.

ORIGINAL ARTICLES

A practical approach of the pediatric patient with obstetrical brachial plexus palsy starting from 28 cases – Single-center experience over 6 years

Alice Dica[1], Diana Barca[1,2], Oana Tarta-Arsene[1,2], Ioana Minciu[1,2], Catrinel Iliescu[1,2], Carmen Burloiu[1], Niculina Butoianu[1,2], Magdalena Budisteanu[1,3,4], Cristina Pomeran[1,2], Carmen Sandu[1,2], Ligia Robanescu[1], Cristina Anghelescu[1], Dragos Zamfirescu[5], Gabriela Musat[6,7], Ovidiu Musat[8], Dana Craiu[1,2]

Abstract: *Neonatal brachial plexus palsy is a complication that occurs during difficult vaginal delivery or due to unexplained causes, probably prenatal in which some or all brachial plexus branches are affected (avulsion, rupture, stretching). A cohort of 28 cases evaluated in our clinic in 6 years and 6 months (Jan 2007-July 2013) from the clinical and paraclinical point of view, treatment, and the outcome were analyzed. 17 (60.7%) of the patients were boys and 11 (39.2%) were girls. 14 (50%) had right brachial plexus palsy, 12 (42.8%) had left brachial plexus palsy and 2 (7.1%) had bilateral involvement. 5 (17.8%) of them had reconstructive surgery done. 11 (39.2%) had good to complete recovery. The purpose of this paper is to underline the importance of early presentation for neurological evaluation and the beginning of physical therapy.*

Keywords: *brachial plexus palsy, physical therapy, reconstructive surgery of brachial plexus*

INTRODUCTION

Neonatal brachial plexus palsy (NBPP) – is a functional disturbance due to brachial plexus injury, characterized by deficits in the areas served by the brachial plexus branches (C5 to T1). The following NBPP types have been described according to the lesion's level: total (C5 to T1) or partial – superior (C5 to C6), middle (C5 to C7), inferior (C8 to T1). The name of this dysfunction is controversial, some authors calling it obstetrical, because the trauma during a difficult delivery is the most common cause, while others name it congenital including obstetrical and unexplained cases due to a prenatal cause. In these circumstances, an umbrella term will be NBPP [2, 3, 6, 9]. Some or all the fibers of the brachial plexus branches suffer stretching, rupture or avulsion. The incidence is 0.1 - 0.4% of live births and has remained relatively constant over time [3, 6, 7, 9]. A multidisciplinary approach and consensus are needed for a better outcome.

[1] Alexandru Obregia Clinical Phychiatric Hospital, Department of Pediatric Neurology, Bucharest, Romania
[2] Carol Davila Univesity of Medicine and Pharmacy, Department of Pediatric Neurology, Bucharest, Romania
[3] Victor Babes Institute of Pathology, Medical Genetic Laboratory, Bucharest, Romania
[4] Titu Maiorescu University, Faculty of Medicine, Department of Genetics, Bucharest, Romania
[5] Floreasca Emergency Hospital, Department of General Surgery, Bucharest, Romania
[6] Saint Mary Clinical Hospital, Department of Otolaryngology, Bucharest, Romania
[7] Carol Davila University of Medicine and Pharmacy, Department of Otolaryngology, Bucharest, Romania
[8] Carol Davila Univeristy Central Emergency Military Hospital Bucharest

OBJECTIVES

This paper aims to analyze the cohort of patients with NBPP followed in the Pediatric Neurology Department, to highlight the variability of NBPP symptoms at presentation, to identify and correlate specific items related to clinical signs, investigations, and outcome, and to establish a protocol of diagnosis and follow-up for children with NBPP, according to the international recommendations adapted to the local needs. We propose a treatment algorithm, allowing optimum outcomes for these children.

MATERIALS & METHOD

The archive of the Pediatric Neurology Clinic was retrospectively analyzed over 6.5 years (January 2007 – July 2013), selecting the patients with NBPP. Approval from the Local Ethics Committee was obtained. Narakas's classification was used at the first admission to diagnose the NBPP type: superior, middle, inferior, and total [7]. The clinical status was registered at different times: at presentation, at 3, 6, 12 months follow-up. Active motor scale [1, 2, 4, 8, 9], Toronto score [1, 2, 4, 8, 9], and protocol for obstetrical brachial plexus palsy (Hospital for Sick Children Seattle) [8] were retrospectively applied, using registered neurological examinations, reports of physical therapy specialist, from files. Laboratory findings, EMG and nerve conduction velocities of the upper limb and brachial plexus MRI (performed if needed), treatment choices, and their results were also evaluated [10]. We designed a separate questionnaire for present status evaluation, including data about active movements, strength, trophic changes summarized in a score. The prognosis was quantified as follows: score 0-12 – poor recovery, score 13-24 – moderate recovery, 25-36 – good recovery, or complete remission. Statistical analysis used the SPSS17 program.

RESULTS

28 patients with the diagnosis of NBPP were identified between January 2007 – July 2013.

Evaluation schedule. All patients came at 3 months for neurological evaluation; 23 children (82.1%) returned for reevaluation at 6 months, and only 10 (35.7%) at 12 months.

History and clinical data. Among them, 17 were boys (60.7%) and 11 girls (39.3%), 4 days to 13 years old at admission. 14 (50%) cases had the right side, 12 (42,8%) had left side, and 2 (7.1%) had bilateral brachial plexus involvement. 6 (21.4%) of the cases have total NBPP and 22 (78.6%) – partial – superior (C5-C6) or extended superior (C5-C7) NBPP. All the children were born spontaneously, 13 (46.4%) of them had > 4000 g, another 8 (28.5%) had birth weight > 3900 g and eight (28.5%) patients had 2800 – 3900 g, but with difficult labor and delivery. Four patients (14.2%) had Claude Bernard Horner syndrome (CBH) and 3 (10.7%) had further associated pathology – global developmental delay, diplegia, microcephaly in evolution. 13 patients (46.4%) were first evaluated in our clinic in the first month of life, 12 (42.8%) between 1 and 3 months, 2 (7.1%) between and 1 (3.5%) after 6 months. 2 (7.1%) mothers had prenatal hypertension and hypertension during pregnancy, but that didn't affect the children.

Investigations. 6 patients (21.4%) had electrophysiological studies (EMG and nerve conduction velocities) performed in the first 2 months of life, in 3 cases (10.7%) repeated at 3 months and in 5 (17.8%) after 6 months. 6 patients were evaluated with MRI of the cervicobrachial region. 3 (10,7%) of them had avulsion (preganglionic lesions, usually associate pseudomeningoceles), 1(3.5%) had rupture (usually are postganglionic lesions, could associate pseudomeningoceles) and 2 (7.1%) had stretching/ elongation (postganglionic lesions, neuroma or hematoma or diffuse lesions). 4 (14.2%) of the children who had brachial plexus surgery had pre- and postganglionic lesions and 1 (3.5%) had postganglionic lesions.

Treatment. All patients received physical therapy, Vojta method (in our clinic); among them, two patients (7.1%) had already started physiotherapy through the Bobath method (in another Clinic). 12 patients (42.8%) were included in an intensive physical therapy program and 16 (57.1%) received inconstant or for a short period physical therapy. Good recovery was registered in 6 patients (21.4%) who performed intensive physical therapy and 5 patients (17.8%) among those with inconsistent therapy. Five patients (17.8%) had surgical reconstruction of the brachial plexus, 3 (10.7%) of them had total brachial plexus palsy and two (7.1%) had extended superior brachial plexus palsy.

Follow-up. Evolution at 3 month after physical therapy, evaluated with Toronto score (T score) showed score > 3.5 in five patients (17.8%) and values < 3.5 in 23 patients (82.1%). From the 23 patients (82.1%) with T score < 3.5, 6 (21.4%) were evaluated for surgical procedure and five (17.8%) were operated, in one (3.5%) case it was not necessary. The rest continued physical therapy. 18 patients (64.2%) with a T score <3.5 were not evaluated for surgery because they did not come for their scheduled evaluation/ follow-up.

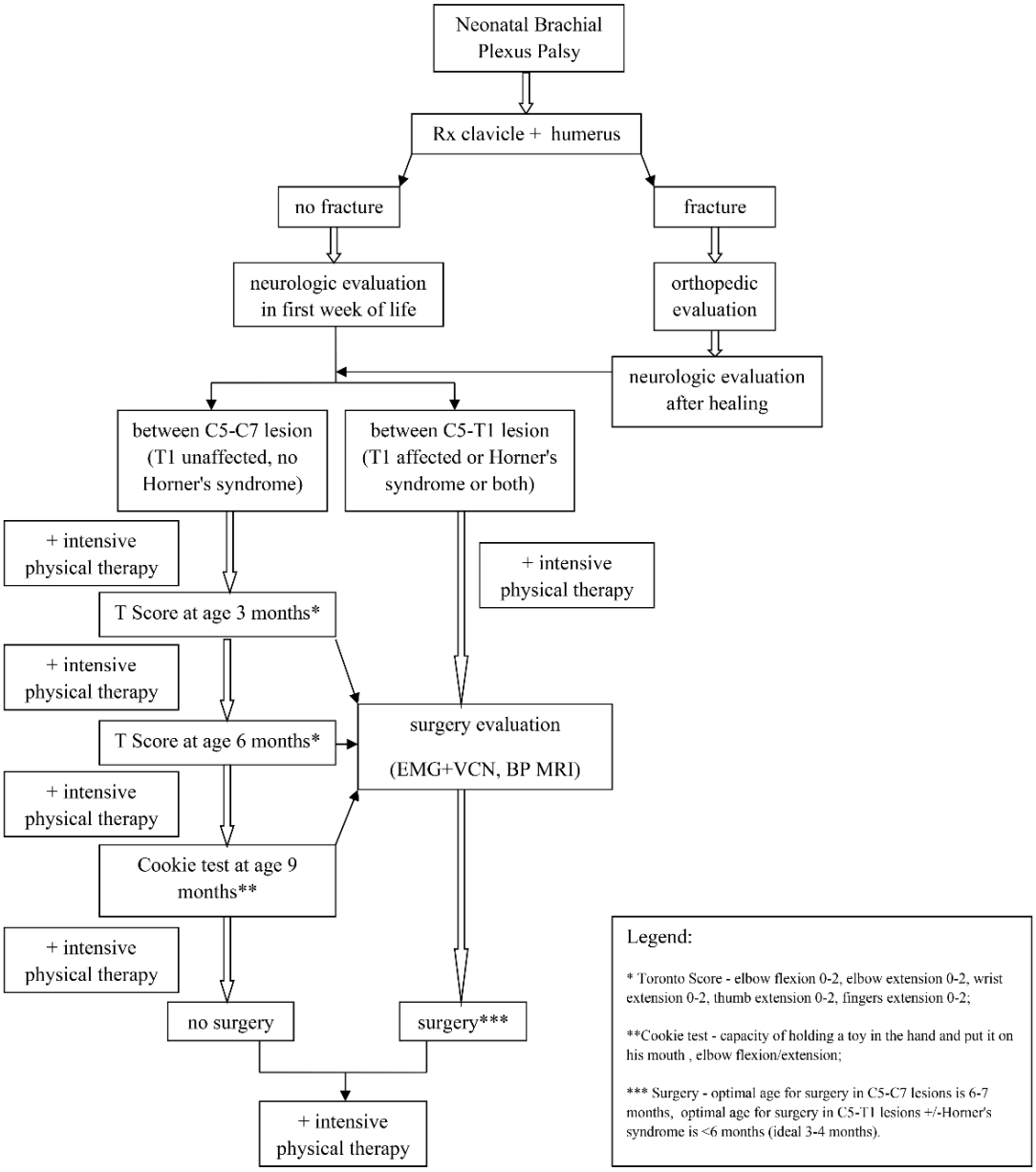
Outcome. Eight (28.5%) patients had a poor recovery, 9 (32.1%) patients had a moderate recovery, 11 children (39.2%) had good recovery, among them 6 (21.4%) with complete remission. All of the children with good recovery to complete remission had superior or extended superior

NBPP.

DISCUSSIONS

Most of the children (18 – 64.2%) did not comply with the follow-up schedule. That is because they recovered with physiotherapy or spontaneously or because they were lost to follow-up. The last evaluation, consisting of a questionnaire applied on the phone showed that the majority had a good outcome, most probably because most of the cases were mild, superior type, and a good response to therapy (even those who have made physical therapy at home with their parents). Besides, we could not compare the types of reconstructive surgery, because the number of children undergoing surgery was too small (5). Among them, 4 children had reconstruction of the brachial plexus, and for one patient neurotomy was performed (the fibrous sleeve around the brachial plexus was removed).

Figure 1: Algorithm for diagnosis and treatment of NBPP



Age at first presentation in NBPP is of paramount importance for the subsequent treatment choice. It is important that the children with BPP to be early referred – even from birth for evaluation and treatment, in this way – T score at age 3 months will be the most valuable tool for an indication of early surgery if needed.

Cervico-brachial MRI was performed only in some of the patients with a T score <3.5. The importance of MRI is high for the treatment choice – in case of the complete avulsion, surgery is indicated.

Although some studies report 80-90% of the good recovery in unilateral, superior brachial plexus palsy, in our cohort we had only 11 (39.2%) patients with good recovery, probably due to inconsistent physical therapy and non-compliance to scheduled evaluations.

The results cannot be applied in the general population due to the small number of patients analyzed. A larger, prospective study is needed in the future to fill in the gaps. To be noted the good clinical practice of neonatology specialists, pediatricians, and general practitioners who evaluate the children in the first days of life and immediately take action, sending them immediately to pediatric neurology for evaluation and treatment.

– the age of first neurological evaluation and initiation of physical therapy decreased and the number of evaluated children with NBPP increased in the last few years in Romania although this is purely based on anecdotal data as no national registry exists for NBPP. That is why we strongly agree that the first protocol of diagnosis and treatment was needed in our country (Figure 1). Of course, that the experience of the next few years and the discoveries in the field will help us to permanently improve the protocol for better practice, according to the international rules.

CONCLUSIONS

The use of protocols for diagnosis and follow-up makes us „speak the same language", have the same criteria for diagnosis, evaluation, and treatment, with some particular situations due to the local needs.

Early diagnosis and treatment are important because the outcome is better – than raises the quality of life of these patients and the addressability for physical therapy. Vojta therapy has good results in NBPP. Better information of the patients concerning the steps of evaluation of NBPP and the importance of compliance with the protocol is critical for a better outcome and for avoiding a permanent deficit.

Reconstructive surgery must be done in selected cases for a better recovery.

This is a pilot study, with a proposal of protocol for diagnosis and treatment, according to the international protocols in force, but larger, prospective studies are mandatory to complete and refresh the existing data (Figure 1).

References:

1. Akel BS et all, Can Active Movement Scale (AMS) be an indicator of Functioning in Obstetrical Brachial Plexus Palsy?, MUSBED 2012;2(2):57-63.

2. Bialocerkowsky AE, Galea M, Comparaison of visual and objective quantification of elbow and shoulder movement in children with brachial plexus palsy, Journal of Brachial Plexus and Peripheral Nerve Injury 2006;I:5.

3. Chung KC, Yang LJ-S, Practical Management of Pediatric and Adult Brachial Plexus Palsies, Toronto 2012;35-172.

4. Curtis CG, The Active Movement Scale: an evaluative tool for infants with obstetrical brachial plexus palsy 2000, Masters Degree Thesis, Institute of Medical Science, University of Toronto;1-85.

5. Dunham EA, Obstetrical Brachial Plexus Palsy, Ortopaedic Nursing march/april 2003;22(2):106-116.

6. Evans-Jones G et all, Congenital brachial palsy: incidence, causes and outcome in the United Kingdom and Republic of Ireland, Arch Dis Child Fetal Neonatal Ed2003;88:F185-F189.

7. Herzberg G, Narakas A, Comtet JJ et all, Microsurgical relations of the roots of the brachial plexus. Practical applications, Ann Chir Main 1985;4:120-133.

8. Raymond Tse, Brachial plexus palsies in infants and children, March11,2011, North Pacific Pediatric Society, Hospital for Sick Children, Seatle;1-21.

9. Ruchelsman DE et all, Brachial plexus birth palsy, an overview of early treatment considerations, Bulletin of the NYU Hospital for Joint Diseases 2009;67(1):83-9.

10. Toupchizadeh V et all, Obstetrical Brachial Plexus Palsy: Electrodiagnostical Study and Functional Outcome, Pakistan Journal of Biological Sciences 2010;13(24):1166-1177.

The article was received on December 20, 2019, and accepted for publishing on June 23, 2020.

ORIGINAL ARTICLES

Medical devices in current medicine

Viorel Ordeanu[1,2], Lucia E. Ionescu[1], Victoria G. Dumitrescu[1], Roxana G. Pricop[1], Răzvan Neagu[1], Diana M. Popescu[1]

Abstract: *The treatment of diseases is based on pharmacological and non-pharmacological means, but adequate devices are needed for their application. Medicine uses a wide range of medical devices. Currently, many medical devices are used, many of them being disposable. As recognition of the importance of medical devices, the national authority of the drug is the ANMDM (National Agency for Medicines and Medical Devices).*

Medical devices are indispensable for therapy, and their evolution has led to an extraordinary diversification of the field and the emergence of industry related to the pharmaceutical industry, with specific laws and regulations.

Keywords: *medical device, medicine, pharmacological action, non-pharmacological action, health legislation*

INTRODUCTION

The treatment of diseases is based on pharmacological and non-pharmacological means, but for whose application different devices are needed, suitable physical objects, without which treatment cannot be applied. Modern medicine uses a wide range of medical devices, some derived from classical forms, and others that are new and more complex, which revolutionize therapy. Although their use is very old, the term as such has been newly introduced in medical terminology, from the English terminology medical device. Another neologism, related to this, is disposable = available, which, together with a noun, also means "disposable". Currently, many medical devices are used, either small or large, simple or complex, many of them being disposable. As a recognition of the importance of medical devices for the medical and pharmaceutical field, as well as for the medical and pharmaceutical industry, the current national authority of the medicines (not a drug, apud WHO) has been renamed the ANMDM (National Agency for Medicines and Medical Devices) [1, 2].

GENERALITIES

Definition: "Medical device" means any instrument, apparatus, machine, appliance, or other item used alone or in combination, including the software necessary for its correct application, intended by the manufacturer to be used for human beings, and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its intended function by such means, for one or more of the specific medical purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of the pain,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- the investigation, replacement, modification, or support of

Corresponding author: Ionescu Lucia
ionescu.lucia@gmail.com

[1] Military Medical Research Center, Bucharest, Romania
[2] "Titu Maiorescu" University, Bucharest, Romania

the anatomy or a physiological process,
- control of conception (Law 176/2000).

Legislation

The specific legislation, including regarding medical devices, also appeared later on - in 1976, the Regulatory System for the MD - US. In 1993, the EU Regulatory System 93/42/EEC and Romania: Law 176/2000 on medical devices and Law 434/2004, with the Government Decision and Orders of the Ministry of Health. Example: HM Order 253/2010 regarding the reclassification of medical devices and 75/2010 for the Rules for Good Pharmaceutical Practice.

Within the HM, operate specific structures such as the Commission for Medical Devices and the National Agency for Medicines and Medical Devices. We mention that in the European Union, the pharmaceutical field was removed from the Health and included in the Industry, which caused some controversy in the medical world [3-23].

Authorization

Medical devices can only be marketed if they are effective, meet the intended purpose, and ensure patient safety. The certificate of conformity issued by the manufacturer guarantees the attestation of the product for being placed on the market and the classification in the corresponding risk class. The inscription must comply with the European Conformity Marking "CE" (conformitè europèene), which allows free movement in the EU space and should not be confused with "C E" (China Export), which has a space between letters. It turns out that a new medical device, being a product of the scientific research of development-innovation, will go through the following stages: Experimental model, Functional experimental model, Prototype (technological demonstrator), and zero series (at the manufacturer). The technical file of a medical device, which is subject to the approval of the NAMMD, contains information regarding the: device description, type of raw materials used for manufacturing, stability study, analysis bulletin, validation, description of the packaging, and instructions for use. The serial products must be manufactured with the technical assistance of those who have the patent for the product.

CLASSIFICATION

There are many types of medical devices and they can be classified according to several criteria:

1. Risk level
- Class I, Low risk: non-invasive medical devices (eg patches, bandages) and invasive (eg surgical gloves);
- Class II, Medium risk (use 1h-30 days) invasive (eg needles, catheters);
- Class II b, potentially high risk (use - more than 30 days) invasive (eg: probes, devices for repeated administration) and non-invasive (eg: modern dressings that come in contact with the damaged skin);
- Class III, High risk: surgically invasive, a tissue of animal origin, implantable or an integral part of a drug (eg dressings with antibiotics).

2. Access path
- Urinal,
- Digestive,
- Surgical,
- Respiratory,
- Parenteral.

3. Duration of use
- Transitional action, less than 1 hour,
- Short term, less than 1 month,
- Long term, over 1 month.

4. Frequency of use
- Single-use,
- Repeated,
- Permanent,
- When necessary.

5. Impact on the body
- Non-invasive,
- Invasive,
- Surgically-invasive,
- Implantable.

6. Method of manufacture
- Sterile (disposable or re-sterilizable),
- Nonsterile/aseptic.

7. Mode of operation
- With power source (eg electric battery),
- Without a power source.

8. Place of use
- Medical institution,
- Home,
- Portable.

After use in different activities:
Medical devices for:
- Diagnosis and monitoring,
- Administration of medicines,
- Parapharmaceutical (ex: dressings),
- Damaged tissue (orthopedics, surgery, burns),
- Oral hygiene,
- Sexual protection,
- Childcare,
- Medical imaging.

Categories of users:
- Manufacturing companies,
- Suppliers and distributors,
- Sanitary units,
- Medical technical workshops,
- Patients and clients.

QUALITY

The quality requirements are set out in the specific Reference Standards. Starting with 01.03.2019, ISO 13485: 2016 is mandatory. This standard is designed for organizations involved in the design, production, installation, and maintenance of medical devices and for risk management.

• Sterility

All devices and technical-medical products that come into direct contact with tissues and biological fluids are required to be sterile.

Sterilization by heat, gas, or radiation is chosen depending on the nature of the material to be sterilized and the efficiency of sterilization is checked according to FR X unless otherwise provided.

• Storage

The storage and transport of medical devices are done according to the general provisions of FR X unless otherwise provided. Some materials must be stored under special conditions: rubber, plastics, metal tools, dressing materials, and utensils.

LABELING

Markings

Medical devices must be labeled, on the product, on the packaging and the instructions for use with the information essential to the safety of the user:
- The product's name,
- Identification of the manufacturer,
- Lot number and series, including the date,
- Storage conditions,
- Method of operation.

In some cases, additional data is required for special labeling:
- Sterile,
- Disposable,
- Exclusively for clinical investigations;

Different graphic symbols or warnings can be added.

RISK MONITORING

The safe handling of health products is called vigilance:
- Pharmacovigilance for pharmaceuticals and pharmaceutical raw materials,
- Materiovigilance for medical devices,
- Reacto-vigilance for in vitro diagnosis,
- Biovigilance for temporary-use cellular products,
- Hemovigilance for blood products.

Materiovigilance pursues the incidents arising from the use of the technical-medical products, to ensure the safety of the medical procedures, permanent monitoring of the incidents, and the risks of their occurrence. On the Materiovigilance Data Sheet are reported the essential information related to erroneous indications, omissions, or incomplete instructions. On their basis, studies and expertise are also carried out for the continuous evaluation of the risk level after being launched on the market.

RAW MATERIALS AND PACKAGING

The raw materials can be natural or artificial, single or in combinations: cellulose, cotton, metals, and alloys, natural and synthetic rubber, ceramic materials, glass, plastics, etc. or combinations thereof. All materials used must be compliant for medical use, from pharmaceuticals to the finished product, including packaging. As an example, medical devices for the application of innovative antibacterial and/or antibiofilm drugs fall within the general definition, according to the legislation in force. They must meet all the conditions for authorization, both as a package and/or applicator, and as a medicine administered for the treatment of the patient; they must come accompanied by a Technical File, Analysis Report, and a Conformity Certificate endorsed by the HM through the NAMMD. They fall into Class II b of Potentially High Risk, non-invasive as modern dressings, which are exposed to damaged skin or Class I Low risk, non-invasive. All components must be sterile or aseptic and must be stored and used properly. The labeling must be complete, accompanied by the appropriate markings and with the follow-up on the Materiovigilance. The pharmaceutical forms and the packages (applicators) in which they can be presented may differ, depending on the particularities of the treatment, being required several experimental models for choosing the prototype. Each of the components must come accompanied by a medical opinion for use, and if it does not, it must be requested from the NAMMD, which means time and money for taxes [3, 4, 9, 12].

As examples of medical devices for the application of pharmacologically active drugs may be listed the following:

1. Paper sachets, amylaceous, etc.
2. Capsules: soft or hard, gastro-soluble or gastro-resistant, with compartments or concentric (delayed), etc.
3. Pencils: liquid or powder dosage, etc.
4. Ampoules: glass or plastic, brittle, compartmentalized (lyophilized powder and solvent).
5. Bottles: glass or plastic, perforable, dropper, jet, sprayer (passive, active)
6. Bottle/dose atomizer under pressure (spray)
7. Patches: fast or delayed (for different areas) etc.
8. Implants: in an orifice, subcutaneous, submucosal, and visceral (eg: ovules, suppositories, spark plugs, cones, etc.)
9. Impregnated dressings: solutions, powders, solubles, ointments, absorbable or non-absorbable, hydrogel, etc.

COMMENTS

Currently, our research team is studying medical devices for the application of pharmacologically active drugs, for the substitute, adjuvant or complementary treatment to the anti-infective treatment, especially against resistant bacteria.

There are different medical devices, suitable for types of substances and dosages, authorized for medical use, from which we can choose the most suitable for the purpose; creating a new device, simple or complex, would require a complicated and costly procedure, but unnecessary in this case. The range of medical devices that can be filled with the appropriate pharmaceutical preparation is currently provided by the pharmaceutical industry upon request.

By combining the newly proposed drug with the chosen medical device, experimental model variants are achieved [24]. After experimenting with these under different conditions, the functional experimental model is obtained, as a masterful and/or galenic pharmaceutical preparation for the testing provided by the Law on medicinal products, and will subsequently enter under the pharmaceutical authorization procedures.

CONCLUSIONS

Medical devices are indispensable for therapy, pharmacological, or non-pharmacological. Their evolution has led to an extraordinary diversification of the field and the emergence of industry related to the pharmaceutical industry, with specific laws and regulations. Medical devices play a very important role in modern medicine.

References:

1. Sandulovici RC, “Curs de tehnică farmaceutică” UTM FF, 2018
2. Sevastre AS, Belu I., “Produse tehnico-medicale” editura SITECH, Craiova, 2017
3. *** Regulatory system for MD-USA, 1976
4. *** Regulatory system 93/42/EEC, 1993
5. *** Legea nr. 95/2006 privind reforma în domeniul sănătății, republicată (Text în vigoare începând cu 25.07.2018).
6. *** HG Nr. 306 din 23 martie 2011 privind unele măsuri de supraveghere a pieței produselor reglementate de legislația Uniunii Europene care armonizează condițiile de comercializare a acestora.
7. *** HG Nr. 55 din 29 ianuarie 2009 privind dispozitivele medicale implantabile active, cu modificările și completările ulterioare.
8. *** HG Nr. 54 din 29 ianuarie 2009 privind condițiile introducerii pe piață a dispozitelor medicale, cu modificările și completările ulterioare.
9. *** ANMDM Ordonanța și hotărârile guvernamentale, Dispozitive medicale, 2017.
10. *** Ordinului Ministrului Sănătății nr. 1009/2016 privind înregistrarea dispozitelor medicale în baze naționale de date.
11. *** Ordinul Ministrului Sănătății nr. 1008/2016 pentru aprobarea Normelor metodologice de aplicare a titlului XX din Legea nr. 95/2006 privind reforma în domeniul sănătății, referitoare la avizarea activităților în domeniul dispozitivelor medicale.
12. *** Ordinul Ministrului Sănătății nr. 874/2015 pentru aprobarea formularelor de declare a activităților de sponsorizare în domeniul dispozitivelor medicale și al materialelor sanitare.
13. *** Ordinul Ministrului Sănătății nr. 308/2015 privind controlul prin verificare periodică a dispozitivelor medicale puse în funcțiune și aflate în utilizare.
14. *** Ordinul Ministrului Sănătății nr. 373 din 26.03.2014 privind aprobarea formularului cu regim special al procesului verbal de constatare și aplicare a sancțiunilor contravenționale privind nerespectarea dispozițiilor legale referitoare la dispozitivele medicale și activitățile conexe acestora.
15. *** Ordinul Mnistrului Sănătății nr. 1356/2013 privind aprobarea tarifelor aplicate de către ANMDM pentru activitățile desfășurate în domeniul dispozitivelor medicale.
16. *** Ordinului Ministrului Sănătății nr. 1032/2011 pentru aprobarea Normelor privind donațiile de medicamente, materiale sanitare, dispozitive medicale, vaccinuri, seruri și consumabilele aferente.
17. *** Ordinul Ministrului Sănatății nr. 792 din 29 iunie 2006 privind desfășurarea procedurii de investigație clinică și a procedurii de evaluare a performanței pentru dispozitivele medicale, cu modificările și completările ulterioare.
18. *** Regulamentul (CE) nr. 765/2008 al Parlamentului European și al Cosiliului din 9 iulie 2008 de stabilire a cerințelor de acreditare și de supraveghere a pieței în ceea ce privește comercializarea produselor și de abrogare a Regulamentului (CEE) nr. 339/93.
19. *** NSR-04 “Norme privind radioprotecția persoanelor în cazul expunerilor medicale” aprobate prin Ordinul comun MSF/285/79/2002.
20. *** NSR- 04- Anexa 5: „Criterii de acceptabilitate pentru instalațiile radiologice”.
21. *** Lege nr. 176 din 18 octombrie 2000 privind Dispozitivele

medicale.

22. *** Tănăsescu Rodica, 2019, Despre sănătate cu responsabilitate- Dispozitive medicale de uz personal, ce nu știați despre ele (Internet)

23. *** Monitorul Oficial al României, nr. 544/02.11.2000.

24. Dragomiroiu GTAB, Popa DE, Velescu BS, Andrieș AA, Ordeanu V, Nicolae AC, Drăgoi CM, Barca M, Ginghina O, "Synthesis, characterization and microbiological activity evaluation of novel hard gelatine capsules with cefaclor and piroxicam", Farmacia 64, 6, 887-895, 2016.

The article was received on March 30, 2020, and accepted for publishing on July 23, 2020.

ORIGINAL ARTICLES

Emergency surgery for complicated colorectal cancer – What we choose: a retrospective cohort study

Georgiana B. Constantin[1], Dorel Firescu[2,3], Dragoș Voicu[2], Bogdan Ștefănescu[2,3], Raul Mihailov[1], Cristina Șerban[2,3], Eugenia Panaitescu[1], Rodica Bîrlă[1,4], Silviu Constantinoiu[1,4]

Abstract: *Introduction: Despite the progress that has been made regarding the diagnosis, a worrying percentage of patients are still admitted in an emergency, with complicated colorectal tumors, which often require interventions without a curative visa. The study aims to analyze the factors involved in choosing the type of surgical treatment.*

Patients and methods: We included in the study a group of 431 patients admitted and operated in an emergency for complicated colorectal cancer in the Surgery II Clinic of the Clinical Emergency County Hospital "Sf. Ap. Andrei" from Galați, between 2008-2017. We retrospectively analyzed the patients' data and we made statistical correlations between the type of emergency surgery and epidemiological, clinical, paraclinical, and intraoperative factors.

Results: Colostomy was mainly practiced in older patients (p<0.01), from rural areas (p<0.01), with associated cardiac diseases (p<0.01), with hydro electrolytic disorders (p<0.03), rectal tumors (p<0.01), peritoneal carcinomatosis (p<0.02), frozen pelvis (p<0.01). Hartmann's operations were associated with patients with: leukocytosis (p<0.01), intestinal perforation (p<0.01), sigmoid tumors (p<0.01). Internal derivations were associated with patients with: liver metastases (p<0.01), splenic angle tumors (p<0.01), tumors invading other organs (p<0.01), and stage IV of the disease (p<0.01). Resections with anastomosis were associated with transverse colon tumors (p<0.01), well-differentiated tumors (p<0.01).

Conclusions: The type of emergency surgery performed correlated well with the age of patients, the area, the comorbidities, the history of the disease, cachexia, anemia, oligoanuria, hydroelectrolyte disorders, tumor complication, and location of the tumor, hepatic metastases, and tumors' invasion in other organs, tumor grading and stage of the disease.

Keywords: *surgical treatment, colorectal cancer, emergency, correlations*

[1] Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
[2] Dunarea de Jos University, Faculty of Medicine and Pharmacy, Galati, Romania
[3] Sf. Ap. Andrei Clinical Emergency County Hospital, Galati, Romania
[4] Sf. Maria Clinical Hospital, Bucharest, Romania

INTRODUCTION

In Romania, according to the GLOBOCAN 2012 analysis, colorectal cancer was the second [1]. According to the data provided by the GLOBOCAN 2018 statistics, colorectal cancer ranks third in incidence globally (after lung and breast

Corresponding author: Rodica Bîrlă
birlarodica@yahoo.com

cancer) and at the 2nd place as cancer mortality (after lung cancer) [2].

The incidence is increasing both in developed countries and in those where until a few decades ago, the colorectal cancer was not a major concern [1].

Both sexes are affected in approximately equal proportions and the most affected decades of age are the sixth and the seventh [1].

Despite the improvements that have been made regarding the diagnosis and the possibilities of screening, a worrying percentage of patients are still admitted in an emergency, with complicated colorectal tumors, which often require interventions without a curative visa [3].

Of all the complications of colorectal cancer, the intestinal occlusion is the most frequent and it occurs especially in the case of tumors located in the left colon and rectum [4].

There are no clearly established protocols regarding the choice of the type of emergency surgery for colorectal cancer. Various standardizations have been tried, but no consensus has yet been reached [5]. The most debated issue is the choice of the optimal intervention for occlusive left colon cancers [6].

The choice of the surgical treatment method in an emergency is made according to several factors, such as the biological status of the patients, the duration of the complication, comorbidities, age, local invasion of the tumors, the presence of metastases, the appearance of the affected colon. Whenever possible, it is ideal to choose a method that involves the tumor resection or allows it in a second time [7].

The most recent recommendations of the WSES Scientific Committee indicate in the case of occlusive or perforated colon tumors to practice a right hemicolectomy with a terminal ileostomy. The right hemicolectomy with ileocolic anastomosis can be performed if there is no significant increase in operative time and good bowel vascularization. For left colon occlusive tumors, the Hartmann operation is considered the procedure of choice. In patients with severe instability, a colostomy should be performed. For perforations on the left colon, Hartmann's procedure is recommended, with the mention of considering the open abdomen [8].

PATIENTS AND METHODS

We included in the study a group of 431 patients admitted and operated in an emergency for complicated colorectal cancer in the Surgery II Clinic of the Clinical Emergency County Hospital “Sf. Ap. Andrei” from Galați, between 2008-2017.

The patients’ data were collected from observation sheets, operating protocols, and pathological exams. The following epidemiological and clinical factors were analyzed: age, sex, provenance area, hereditary-collateral history, abdominal surgical history, comorbidities, preoperative diagnosis, and clinical status at admission (weight, height, diuresis).

We analyzed the following paraclinical factors: the values of hemoglobin, hematocrit, leukocytes, platelets, and ionograms at admission. Among the therapeutic factors, we analyzed the tumor location, the invasion in other organs, the intraoperative appearance of the frozen pelvis, the presence of hepatic metastases and peritoneal carcinomatosis, the type of surgery performed in an emergency, lymph node dissection, liver biopsy, stoma reversal after Hartmann procedure.

The inclusion criteria were patients with colorectal malignancies hospitalized and surgically treated in the Surgery II clinic of the Clinical Emergency County Hospital “Sf. Ap. Andrei" from Galați, between 2008-2017, patients over 18 years old.

The exclusion criteria were patients with benign colorectal pathology, patients with malignant colorectal tumors operated electively, patients whose observation sheets no pathological reports were attesting the type of tumor, grading, and classification in the pTNM system were not found.

Study design

Epidemiological, clinical, paraclinical, and therapeutic factors were retrospectively analyzed, to correlate them with the four types of surgery (external derivations, Hartmann procedure, internal derivations, and resections with anastomosis).

Statistical analysis

Using the SPSS version 23.0, statistical correlations were obtained, indicating the p-value with the Pearson, Chi-Square, and Likelihood Ratio tests. Statistical conclusions were formulated using a statistically significant difference threshold the value $p < 0.05$ for all calculations performed.

RESULTS

In each of the 10 years included in the observation period of this study, an average of 43 patients was hospitalized and operated in an emergency.

There have been practiced 179 (41.5%) external derivatives

(of which 158 colostomies and 21 Pezzer cecostomies), 134 (31.1%) Hartmann operations, 29 internal derivatives (of which 16 ileo-transverse, 9 transverse-descending, 2 ileo-sigmoid, 1 ileo-descending, and 1 transverse-sigmoid anastomosis) and 89 (20.9%) resections with anastomosis (of which 47 right hemicolectomies, 13 left hemicolectomies, 26 transverse/sigmoid/descending segmental colectomies, 1 subtotal colectomy, 1 ileo-transverse anastomotic resection for a relapsed tumor and 1 rectal tumor resection with mechanical anastomosis).

The sex distribution of patients in the study reveals the predominance of men, with a ratio M/F = 256/175. Comparing the types of surgery performed (1 - colostomy/ cecostomy, 2 - Hartmann, 3 - internal derivations, 4 - resections with anastomosis), no association with the sex of the patients is obtained.

In the studied group, the patients from the urban area predominated. Patients in rural areas were associated with a colostomy ($p<0.01$) (Table 1).

Most patients (55.92%, n = 241) included were in the 5th and 6th decades of age. An association of the advanced age of the patients with the colostomy is noted ($p<0.01$) (Table 1).

43 (9.97%) of the patients had a significant hereditary-collateral history, as follows: 19 had a brother/sister with colorectal cancer, another 18 patients had a father diagnosed with colon or rectal cancer, and six patients had a son with colorectal cancer. Patients with a significant heredocolateral history for colorectal cancer were associated with colostomy and with Hartmann's procedure ($p<0.02$) (Table 1).

174 patients (40.37%) had a personal history of abdominal surgery, as follows: appendectomy - 72 patients, hysterectomy - 31 patients, cholecystectomy - 29, gastric resections (for gastroduodenal ulcer disease) – 12, caesarean section - 8, splenectomy (post-traumatic spleen rupture) -6, nephrectomy (renal lithiasis) - 6, segmental colectomy (descending colon cancers) - 4, right hemicolectomy - 2, adnexectomy - 2, hepatic hydatic cyst operated - 1 patient and colon esophagoplasty (for accidental ingestion of sodium hydroxide in adolescence) -1 patient. Comparing the patients with or without a surgical history, no statistical associations are found with the type of surgery.

Most patients (51.04%) included in the study had comorbidities. 148 of the patients (34.33%) had associated cardiac pathology, of which 77 (17.86%) with high blood pressure, 38 (8.81%) with atrial fibrillation with chronic anticoagulant treatment, 8(1.85%) with a history of myocardial infarction, 13 (3.01%) with varying degrees of heart failure, 12 (2.78%) with ischemic stroke; 42 (9.74%) patients were diabetic; 9 (2.08%) patients were diagnosed with liver cirrhosis, with thrombocytopenia; 9 other patients had colonoscopically diagnosed colon pathology, 5 of whom had colonic polyposis, 3 with Crohn's disease and one with diverticulosis. 2 of the patients had active pulmonary tuberculosis at the time of admission (transferred from another hospital). We also found statistical association by correlating the type of surgery with the presence of heart disease and atrial fibrillation, but not with liver cirrhosis. Thus, in patients with cardiac disease or atrial fibrillation, type 1 surgery (colostomy) was performed ($p<0.01$), respectively ($p<0.01$) (Table 1).

The majority of patients (87.94%, n = 379) had as main symptoms at admission the abdominal pain and the disorders of intestinal transit, and the rest (12.06%, n = 52) presented with rectal bleeding. Regarding the beginning of the symptomatology, the majority of patients (58%, n = 250) had symptoms (intestinal transit disorders and rectal bleeding) that they neglected. In patients with neglected symptomatology, it was performed a Hartmann procedure or colostomies ($p<0.01$). Patients with abdominal pain and intestinal transit disorders were associated with colostomy/ Hartmann ($p<0.01$) (Table 1).

Figure 1: Perforated sigmoid tumor (Surgery Clinic II of the County Hospital of Emergency Clinic „Sf. Ap. Andrei „Galati)

The preoperative diagnosis was intestinal obstruction in 332 patients (77.03%); 36 patients (8.35%) had intestinal perforation (tumor/diastatic) (Figure 1), 14 (3.25%) with imminent diastatic perforation (Figure 2) and 49 (11.37%) had rectal bleeding. Patients with hemorrhage or with imminent intestinal perforation (tumor/diastatic) at admission were associated with a colostomy; patients with intestinal occlusion were associated with internal derivations and resections with anastomosis. Patients with intestinal perforation were associated with the Hartmann

procedure (p<0.01) (Table 1).

Table 1: Statistical correlations of the main types of surgery

	Type 1 (N=179 – 41.5%)	Type 2 (N=134 – 31.1%)	Type 3 (N=29 – 6.7%)	Type 4 (N=89 – 20.9%)	p_value (test)
Sex					
F	74/179	47/134	12/29	42/89	0.341089 (1)
M	105/179	87/134	17/29	47/89	
Age	72.35±12.5117	67.88±12.3811	62.72±10.2396	64.89±11.2426	0.000001 (2)
Area					
R	98/179	52/134	7/29	20/89	0.000001 (1)
U	81/179	82/134	22/29	69/89	
Number of days of hospitalization	10.0 [7.0, 15.0]	13.0 [10.0, 16.2]	14.0 [12.0, 16.5]	15.0 [12.0, 17.0]	0.000000 (3)
Abdominal pain=yes	135/179	133/134	29/29	83/89	0.000000 (1)
Intestinal transit disorders=yes	135/179	133/134	28/29	81/89	0.000000 (1)
HCA=yes	10/179	20/134	1/29	12/89	0.017821 (1)
Surgical abdominal antec.=yes	81/179	50/134	13/29	30/89	0.243466 (1)
History=yes	118/179	87/134	11/29	31/89	0.000001 (1)
Anemia=yes	134/179	76/134	22/29	67/89	0.002115 (1)
Anemia transfusions=yes	55/179	27/134	2/29	23/89	0.018961 (1)
Leukocytosis=yes	13/179	33/134	4/29	13/89	0.000342 (1)
Trombocytosis=yes	4/179	5/134	0/29	0/89	0.092185 (4)
Cachexia=yes	80/179	36/134	4/29	8/89	0.000000 (1)
HE disorders=yes	82/179	54/134	7/29	27/89	0.029122 (1)
Oligoanuria=yes	72/179	35/134	2/29	5/89	0.000000 (1)
Preop. diagnosis					
H	42/179	1/134	0/29	6/89	0.000000 (4)
I	11/179	3/134	0/29	0/89	
O	120/179	106/134	29/29	77/89	
P	6/179	24/134	0/29	6/89	
Tumor location					
Ascendant	1/179	0/134	14/29	45/89	0.000000 (4)
Descendant	6/179	23/134	12/29	16/89	
Rectum	149/179	0/134	0/29	2/89	
Sigmoid	19/179	102/134	0/29	12/89	
Transverse	4/179	9/134	3/29	14/89	
Tumor invasion=yes	69/179	26/134	22/29	9/89	0.000000 (1)
Synchronous tumors=yes	1/179	0/134	0/29	2/89	0.232949 (4)
Frozen pelvis=yes	38/179	5/134	0/29	2/89	0.000000 (1)
Hepatic MTS=yes	37/179	23/134	16/29	5/89	0.000000 (1)
Carcinomatosis=yes	9/179	2/134	2/29	0/89	0.019195 (4)
Cardiac diseases=yes	83/179	38/134	7/29	20/89	0.000133 (1)
FiA=yes	26/179	7/134	2/29	3/89	0.005035 (1)
HC=yes	4/179	5/134	0/29	0/89	0.092185 (4)
HP					
ADK	179/179	134/134	28/29	89/89	0.142874 (4)
GIST	0/179	0/134	1/29	0/89	

Grading					
1	60/179	26/134	1/29	28/89	0.002476 ([1])
2	104/179	97/134	22/29	52/89	
3	15/179	11/134	6/29	9/89	
Mucoid=yes	6/179	3/134	1/29	6/89	0.411940 ([4])
pTNM					
2	20/179	51/134	0/29	35/89	0.000000 ([1])
3	120/179	59/134	12/29	50/89	
4	39/179	24/134	17/29	4/89	

Figure 2: Rectosigmoid tumor with necrosis and imminence of diastatic perforation (Surgery Clinic II of the County Hospital of Emergency Clinic „Sf. Ap. Andrei „Galati)

All patients benefited from preoperative imaging investigations, such as empty abdominal radiography and for those with a clinical diagnosis other than intestinal obstruction, abdominal ultrasonography was performed.

128 patients (29.69%) presented with cachexia when admitted (BMI <18.5). 114 patients (26.45%) had oliguria at admission (diuresis <= 500 ml). We found statistically significant differences in the cases of cachectic and oliguric patients at admission. In these patients, the colostomies were mainly practiced and only in very few cases the internal derivations/resections with anastomosis were chosen (p<0.01) (Table 1).

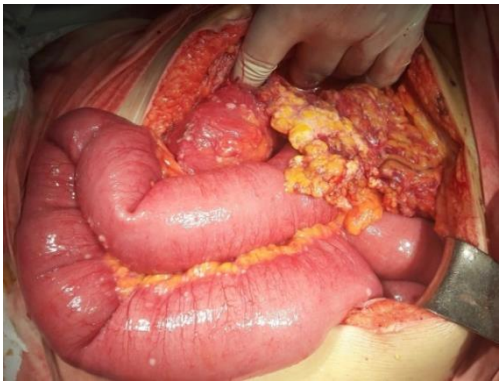
299 (69.37%) of all patients had anemia at admission. Of these, 107 required full blood transfusions or erythrocyte mass. According to the reference interval of our laboratory, we considered anemia values of hemoglobin less than 11g/dl and hematocrit less than 35%. Statistical analysis revealed the association of patients with anemia with a colostomy, and Hartmann's operations (p<0.01); as well as patients with anemia with blood transfusion with a colostomy, or internal derivations (p<0.02) (Table 1).

63 patients (14.61%) had leukocytosis at admission (a number of leukocytes> 10,000/µl). Thus, patients with leukocytosis were associated with Hartmann's interventions (p<0.01) (Table 1).

170 patients (39.44%) had hydro electrolytic disorders at admission (especially hypopotassemia). We considered that the patients with hydro electrolytic disorders were those whose ionograms on admission showed values of Na <136 mmol/l and potassium values <3.5 mmol/l. Patients with hydro electrolytic disorders were associated with a colostomy (p<0.03) (Table 1).

During the emergency surgery, in 13 cases (3.01%) the presence of peritoneal carcinomatosis was found (Figure 3). Peritoneal carcinomatosis has been associated with a colostomy (p<0.02). 81 (18.79%) patients had liver metastases, found either on preoperative ultrasound examination or the occasion of laparotomy (in most cases). Patients with liver metastases were associated with internal derivations (p<0.01) (Table 1).

Figure 3: Ascendant colon tumor, peritoneal carcinomatosis (II Surgery Clinic, Sf. Ap. Andrei Clinic Emergency County Hospital Galati)



45 (10.44%) of the patients had "frozen pelvis" (tumor block comprising other pelvic organs, to which there is firm adherence, with very difficult or non-existent cleavage planes, to which small bowel loops adhere). Patients with frozen pelvis were associated with a colostomy (p<0.01) (Table 1).

Regarding the location of tumors, 60 (13.92%) were located at the level of the ascendant and hepatic angle of the colon, 30 (6.98%) at the level of the transverse colon, 57 (13.22%) at the level of the descending and splenic angle of the colon, 133 (30.85%) in the sigmoid colon and recto-sigmoid junction and 151 (35.03%) were rectal tumors.

For the tumors of the ascending colon and hepatic angle, in most cases, resections with anastomosis (right hemicolectomies) were practiced, followed by internal derivations and cecostomies ($p<0.01$), the patients with tumors located on the descending colon and the splenic angle mainly benefited from internal derivations or Hartmann's interventions ($p<0.01$), for patients with tumor location in the rectum, colostomies were practiced ($p<0.01$) and for the transverse colon locations, resections with anastomosis ($p<0.01$) were performed (Table 1).

In 126 cases (29.23%) we encountered tumors invading other organs: 27 invasive tumors in the prostate, 26 cases with tumors that invaded the small intestine, 18 invasive tumors in the gastrocolic ligament/large epiploon, 13 in the vagina, 11 in the abdominal wall, 10 in the sacrum bone, 6 tumors were invasive in the bladder, 4 in the duodenum (+/- head of the pancreas) and spleen, 3 invasive tumors in the right/left annexes, 2 in the left renal capsule and 2 tumors that invaded the pelvic ureter. The subset of patients with invasive tumors in other organs was associated with internal derivations ($p<0.01$) (Table 1).

Data from the histological reports revealed the predominance of adenocarcinomas (99.76% of cases) and only one GIST tumor. 16 (3.71%) of the patients had tumors with a mucoid component.

Regarding tumor grading, 115 (26.68%) were well-differentiated adenocarcinomas (grade 1), 275 (63.8%) medium differentiated tumors (grade 2) and 41 (9.52%) weak tumors differentiate (grade 3). Well, and medium differentiated tumors were associated with colostomies or with resections with anastomosis ($p<0.01$).

For postoperative staging, we used the classification recommended by The Union for International Cancer Control (UICC). Thus, according to pTNM staging, tumors in stages II and III predominated - 106 (24.59%), tumors in stage II, 241 (55.91%) in stage III, and 84 (19.5%) in stage IV. The patients in stage II were associated with resections with anastomosis or Hartmann operations ($p<0.01$), patients with tumors in stage III were associated with colostomies ($p<0.01$), and patients in stage IV were associated with internal derivations and colostomies ($p<0.01$) (Table 1).

DISCUSSIONS

According to literature data, up to 30% of colorectal cancer patients present with complicated tumors in emergency [9]. Despite many standardization attempts, the best surgical option for patients with complicated colorectal tumors is still under debate. [5, 10]

We have shown in this study that the type of surgery in patients with complicated colorectal cancer correlates with: age, provenance area, associated cardiac diseases, history of the disease, cachexia at admission, oliguria and hydro electrolytic disorders, diagnosis, presence of liver metastases, and frozen pelvis appearance, tumor location, tumor invasion in other organs and staging.

There is no consensus regarding the surgical treatment of the elderly affected by colorectal cancer, but it is generally accepted that patients over 80, who present in an emergency, compared to the younger ones, have a higher risk of postoperative complications and mortality, despite the progress made in preoperative care, surgical techniques, and intensive care.[11] Most authors reported significant correlations between the type of intervention and the age of the patients [6, 12], as we found in our study, but different from the data obtained by other authors.[13]

Several authors found significant correlations between the type of operation and the patients coming from the rural area [14], as we found in our study. Most authors agree that patients in rural areas have lower addressability due to more difficult access to medical services and therefore tend to show up later, with more advanced tumors.[15, 16]

The comorbidities, especially the cardiac ones, are associated in many studies with the practice of non-curative interventions in patients with complicated colorectal cancer.[17, 18] We also found this correlation in our study.

The pathophysiology of cachexia syndrome is characterized by negative energy and protein balance. In neoplastic patients, it is a major cause of morbidity and mortality [19-22]. A recent study, which included 235 patients with advanced colorectal cancer, reaffirms the negative impact of cachexia on the evolution of the patients with complicated colorectal cancer.

Oliguria is considered a specific and sensitive biomarker of renal dysfunction and a good predictor of mortality risk in critically ill patients, including complicated colorectal tumors.[24, 25] For patients with complicated colorectal cancer, with oligoanuria at admission, colostomies are performed, according to several reports [26, 27], as we found in our study.

Neoplastic patients frequently present with hydroelectrolyte balance disorders. These occur during tumor growth, because of inadequate absorption of electrolytes or because of the secretion of metabolically active substances by the tumor [28]. The hydroelectrolyte disorders present at admission are associated with the type of surgery performed in patients with complicated colorectal cancer [29], as we have shown in our study.

The liver is the most common location of secondary dissemination of primary colorectal tumors. Between 10% and 25% of colorectal cancer patients have liver metastases at the time of surgery [30]. Despite all the therapeutic progress made in recent years, the presence of liver metastases remains a negative prognostic factor.[31] Most of the time, these patients have advanced tumors and the only viable option in an emergency is a colostomy, which will allow them to survive for several months.[32] We made the same finding in our study.

The type of surgery is associated with the preoperative diagnosis, which, most commonly, is the intestinal obstruction. The therapeutic attitude in these cases depends on the location of the primary tumor, the stage, the general state of the patient, and the local changes (tumor resectability, colic distention, ischemic lesions of the colic wall, integrity of the ileocecal valve).[33, 34]

For perforated tumors, Hartmann's intervention is the recommended option in most published works [35-37], as we have shown in our study. For hemorrhagic tumors, the options are different depending on the location of the tumor.

In our study, most hemorrhagic tumors were rectal, and the emergency surgical option was most often a colostomy, after a local bleeding control. In the literature, there is also mentioned the practice of arteriographic embolization in these situations [38], a technical possibility that we did not have.

Patients with locally advanced colorectal tumors, with invasion in other organs, can be a therapeutic challenge [39-41].In most cases, in these situations, a terminal colostomy is practiced [42], which also happened in our study group. Other authors have considered the practice of plurivisceral resections in these situations.

The first such series was reported by Sugarbaker in 1946.[43] Croner et al. performed a study on 174 patients who underwent plurivisceral resections during the period 1978-2002 [44]. Most of the patients had sigmoid colon cancers and the most commonly invaded organs were the small intestine, the bladder, and the abdominal wall.

The type of emergency surgery performed for complicated colorectal cancer is significantly statistically correlated with the colorectal tumor location in all the analyzed studies. Most authors consider, as in our study, that single-phase procedures for left colon tumors are not indicated in emergency and that in these situations the Hartmann procedure is preferable.[45, 46] But some authors believe that, including for occlusive left colon tumors, the first option should be a resection with anastomosis [7, 13, 47, 48]. For the complicated tumors located on the right colon, there seems to be unanimity regarding the surgical option, in these cases the right hemicolectomy being the option.[8, 49]

The TNM staging proposed by the AJCC has remained a universal model since its first edition in 1977 [50]. Since then, the guides have been revised several times and the last update was proposed in 2018 [51]. In our study, stage II of disease correlated with Hartmann's operation and stage IV with a colostomy, as we found in other works.[52, 53]

CONCLUSIONS

1) The colostomy was associated with: older age, rural area, associated cardiac diseases, especially atrial fibrillation, neglected symptomatology, cachexia, oliguria, anemia, and hydro electrolytic disorders at admission, tumors complicated with hemorrhage or with imminent diastatic perforation, the intraoperative aspect of the frozen pelvis, rectal tumors, well or medium differentiated tumors, advanced stages of disease (III or IV pTNM).

2) Hartmann's operations were associated with the significant hereditary-collateral history, neglected symptomatology, intestinal transit disorders and abdominal pain upon admission, leukocytosis, intestinal perforation, sigmoid, and recto-sigmoid junction tumors, and stage II TNM.

3) Internal derivations were associated with the presence of intestinal occlusion at admission, liver metastases, and invasion in other organs, with tumors of splenic angle or descending colon and with stage IV disease.

4) Resections with anastomosis per primam were associated with the absence of comorbidities, tumors located at the level of the ascendant colon, hepatic angle, or transverse colon and well-differentiated tumors.

References:

1. Ferlay J, Soerjomataram I, Diskshit R, Eser S, Mathers C, Rebelo M et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136(5),E359-386

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424

3. Baer C, Menon R, Bastawrous S, Bastawrous A. Emergency presentations of colorectal cancer.SurgClin North Am. 2017 Jun;97(3):529-545

4. Yang XF, Pan K. Diagnosis and management of acute complications in patients with colon cancer: bleeding, obstruction, and perforation. Chin J Cancer Res. 2014;26(3):331–340

5. Tebala GD, Natili A, Gallucci A, Brachini G, Quayyum Khan A, Tebala D et al. Emergency treatment of complicated colorectal cancer. Cancer Manag Res. 2018;10:827–838

6. De Salvo GL, Gava C, Lise M, Pucciarelli S. Curative surgery for obstruction from primary left colorectal carcinoma: Primary or staged resection?. Cochrane Database of Systematic Reviews 2004, Issue 2. Art. No.: CD002101

7. Tohme C, Chakhtoura G, Abboud B, Noun R, Sarkis R, Ingea H et al. Place de la colectomie subtotale ot totale dans le traitement en urgence des cancers du colon gauche et du sigmoide en occlusion. Journal Medical Libanais 2008; 56(4):198-202

8. Pisano M, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M et al. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. World J EmergSurg 2018;13-36

9. Al Shehhi, Ruqaiya Mohammed. Emergency Management of Patients with Colorectal Cancer. Electronic Theses and Dissertations (ETDs) 2008+.T, University of British Columbia, 2016.Accessed December 25, 2019

10. van Hooft JE, Bemelman WA, Oldenburg B, et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. Lancet Oncol.2011;12(4):344–352

11. Belinda De Simone, Catena F. Emergency Surgery for Colorectal Cancer in Patients Aged Over 90 Years: Review of the Recent Literature. 2016;4(1):349-353

12. Formisano V, Di Muria A, Connola G, Cione G, Falco L, De Angelis CP, Angrisani L. Our experience in the management of obstructing colorectal cancer.AnnItal Chir.2014;85(6):563-568

13. Poon RT, Law WL, Chu KW, Wong J. Emergency resection and primary anastomosis for left-sided obstructing colorectal carcinoma in the elderly. BJS 1998;85 (11):1539-1542

14. Bain N, Campbell N. Treating patients with colorectal cancer in rural and urban areas: a qualitative study of the patients' perspective, Family Practice, 2000;17(6):475–479

15. Bosma NA, Tilley D, Cheung WY. Reasons for urban-rural differences in colon cancer outcomes: a population-based analysis. Journal of Clinical Oncology 2018;36(15)Supl3609

16. Bergin R, Emery J, Bollard R, Falborg AZ, Jensen H, Weller D et al. Cancer Epidemiol Biomarkers Prev; 2018;27(9):1036–46

17. Cuthbert CA, Hemmelgarn BR, Xu Y, Cheung WY. The effect of comorbidities on outcomes in colorectal cancer survivors: a population-based cohort study. J Cancer Surviv. 2018 Dec;12(6):733-743

18. Fu AZ, Zhao Z, Gao S, Barber B, Liu GG. Comorbid Conditions in Patients With Metastatic Colorectal Cancer. World J Oncol. 2011;2(5):225–231.

19. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus. The Lancet Oncology.2011;12(5):489–495

20. Tisdale MJ, Dhesi JK. Inhibition of weight loss by omega-3 fatty acids in an experimental cachexia model.Cancer Res. 1990;50(16):5022–5026

21. Loberg RD, Bradley DA, Tomlins SA, Chinnaiyan AM, Pienta KJ. The lethal phenotype of cancer: the molecular basis of death due to malignancy. CA Cancer J Clin.2007;57(4):225–241

22. Penet MF, Bhujwalla ZM. Cancer cachexia, recent advances, and future directions. Cancer J. 2015;21(2):117–122.)

23. Charette N, Vandeputte C, Ameye L, Bogaert CV, Krygier J, Guiot Tet al. Prognostic value of adipose tissue and muscle mass in advanced colorectal cancer: a post hoc analysis of two non-randomized phase II trials. BMC Cancer 2019;19:134

24. Cruz DN, Mehta RL. Acute kidney injury in 2013: Breaking barriers for biomarkers in AKI-progress at last. Nat Rev Nephrol.2014;10:74–76

25. Macedo E, Malhotra R, Claure-Del Granado R, Fedullo P, Mehta RL. Defining urine output criterion for acute kidney injury in critically ill patients. Nephrol Dial Transplant.2011;26:509–515

26. Yang XF, Pan K. Diagnosis and management of acute complications in patients with colon cancer: bleeding, obstruction, and perforation. Chin J Cancer Res. 2014;26(3):331–340.

27. Chiang SF, Chen JS, Tang R, Yeh CY, Hsieh PS, Tsai WS, et al. The impact of kidney function on colorectal cancer patients with localized and regional diseases: An observational study from Taiwan. Indian Journal of cancer 2019; 56(3):241-247

28. Wakui A. Electrolyte abnormalities associated with cancer: a review. GanTo Kagaku Ryoho. 1986 Jun;13(6):2031-8

29. Lee MG, Chiu C, Wang C et al. Trends and Outcomes of Surgical Treatment for Colorectal Cancer between 2004 and 2012- an Analysis using National Inpatient Database. Sci Rep 2017;7:2006

30. Scoggins C, Meszoely I, Blanke C, et al. Nonoperative management of primary colorectal cancer in patients with stage IV disease. Ann SurgOncol. 1999;6:651–657.

31. Valderrama-Treviño AI, Barrera-Mera B, Ceballos-Villalva JC, Montalvo-Javé EE. Hepatic Metastasis from Colorectal Cancer.Euroasian J Hepatogastroenterol. 2017;7(2):166–175.

32. Reding D, Pestalozzi B, Breitenstein S, Stupp R, Clavien PA, Slankamenac K, Samaras P. Treatment strategies and outcome of surgery for synchronous colorectal liver metastases. Swiss Medical Weekly 2017;33-34

33. Sargent D, Sobrero A, Sargent D, Grothey A. Evidence for cure by adjuvant therapy in colon cancer: observations based on individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol.2009;27(6):872–877

34. DR Marcu, F Ionita Radu, LD Iorga, M Manea, B Socea, I Scarneciu, Gh Isvoranu, R Costache, CC Diaconu, OG Bratu. Vascular involvement in primary retroperitoneal tumors, Revista de Chimie, Vol 70, Nr 2/2019, p 445-448

35. Banaszkiewicz Z, Woda Ł, Tojek K, Jarmocik P, Jawień A. Colorectal cancer with intestinal perforation - a retrospective analysis of treatment outcomes. ContempOncol (Pozn). 2014;18(6):414–418.

36. Chiarugi M, Galatioto C, Panicucci S, Scassa F, Zocco G, Seccia M. Oncologic colon cancer resection in emergency: are we doing enough? SurgOncol.2007;16(Suppl 1):S73–7

37. Otani K, Kawai K, Hata K. Colon cancer with perforation. Surg Today 2019;49:15–20.

38. Yang XF, Pan K. Diagnosis and management of acute complications in patients with colon cancer: bleeding, obstruction, and perforation. Chin J Cancer Res. 2014;26(3):331–340.

39. Lee-Kong S, Lisle D. Surgical Management of Complicated Colon Cancer.Clin Colon Rectal Surg. 2015;28(4):228–233

40. Bratu OG, Cherciu AI, Bumbu A, Lupu S, Marcu DR, Ionita Radu F, Manea M, Furau C, Diaconu CC, Mischianu DLD. Retroperitoneal tumours - treatment and prognosis of tumour recurrence, Rev Chim. 70(1), 2019, 190-194.

41. Draghici T, Negreanu L, Bratu OG, Pantea Stoian A, Socea B, Neagu TP, Stanescu AMA, Manuc D, Diaconu CC. Paraneoplastic syndromes in digestive tumors: a review, Rom Biotechnol Lett. 24(5), 2019, 813-819.

42. Harish K., Narayanaswamy Y, Nirmala S. Treatment outcomes in locally advanced colorectal carcinoma.IntSeminSurgOncol 2004;1,8

43. Sugarbaker E D. Coincident removal of additional structures in resections for carcinoma of the colon and rectum.Ann Surg. 1946;123:1036–1046

44. Croner RS, Merkel S, Papadopoulos T, Schellerer V, Hohenberger W, Goehl J. Multivisceral resection for colon carcinoma. Dis Colon Rectum. 2009;52(8):1381–1386

45. Medina Villasenor E, Quezada Adame I, Martinez Macias R, Elvia Neyra Ortiz, Parra PAO, Cruz MR. Urgenciasgastrointestinales en el paciente con cancer. ActaMedicaGrupo Angeles 2011;9(3):136-142

46. Lopez J, Mariangel P, Natalia Cardenas, JohanneJahnsen, Daniela Massri, Werner A, Avendano R. Cancer colorectal complicado. Cuad. Cir. 2004;18:11-20

47. Lee YM, Law WL, Chu KW, Poon RTP. Emergency surgery for obstructing colorectal cancers: a comparison between right-sided and left-sided lesions. Journal of the American College of Surgeons, 2001;192(6):719–725

48. Zorcolo L, Covotta L, Carlomagno N, Bartolo DC Safety of primary anastomosis in emergency colo-rectal surgery. Colorectal Disease, 2003;5(3):262–269

49. Gainant A. Emergency management of acute colonic cancer obstruction. J Vis Surg. 2012;149(1):e3–e10

50. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, Editors.AJCC cancer staging manual. 7th ed. New York, NY: Springer; 2010:143–164

51. Tong GJ, Zhang GY, Liu J, Zheng ZZ, Chen Y, Niu PP, Xu XT. Comparison of the eighth version of the American Joint Committee on Cancer manual to the seventh version for colorectal cancer: A retrospective review of our data. World J ClinOncol. 2018;9(7):148–161.

52. Ronnekleiv-Kelly SM, Kennedy GD. Management of stage IV rectal cancer: palliative options. World J Gastroenterol. 2011;17(7):835–847.

53. Liang J, Church JM, Stocchi L, Fazio V, Kiran RP. Should bypass or stoma creation be undertaken for unresectable stage IV colorectal carcinoma?.ANZ J Surg. 2014 Apr;84(4):275-9

The article was received on January 23, 2020, and accepted for publishing on July 14, 2020.

ORIGINAL ARTICLES

Assessment of patient satisfaction with primary health care in a military setting: A cross-sectional study from Turkey

Alper Tunga Kokcu

Abstract: *Background and Aim: Information on patients' experiences with and evaluations of health care is considered an essential outcome indicator to assess the quality of health care. This study aims to evaluate patient satisfaction with primary health care in a military setting.*

Methods: This cross-sectional study was conducted at the primary health care center located in a military setting, in Ankara, Turkey. A total of 3080 military personnel who received primary care in the last 12 months formed the population of the study. Turkish version of the European task force on patient evaluations of general practice care (EUROPEP) questionnaire was administered to the participants.

Results: In the study, 2677 participants were reached with a response rate of 86.9%. The mean satisfaction rate (MSR) of clinical behaviour (69.3%) was higher than the MSR of the organization of care (58.4%). The MSR of the overall questionnaire was 67.1%. Significant differences were observed in the mean satisfaction scores of patients according to their descriptive characteristics including gender, age level, troop type, and the doctor providing the care.

Conclusions: This study highlights the low patient satisfaction levels, which may have resulted from the fact that the study population was young and relatively healthy, and that there was no possibility of choosing the general practitioner. The EUROPEP questionnaire, which is an internationally validated and standardized instrument, can also be used to improve primary health care in military settings.

Keywords: *doctor-patient relationship, military medicine, patient satisfaction, primary care, quality of care*

INTRODUCTION

The World Health Organisation's definition of quality of care is "the extent to which health care services provided to individuals and patient populations improve desired health outcomes. To achieve this, health care must be safe, effective, timely, efficient, equitable, and people-centered." [1]. There are various parameters or indicators to judge the quality of health care. The measurement of patient satisfaction is considered as an essential outcome indicator to evaluate health care quality. Questionnaires are the most widely used instruments to assess patient satisfaction [2,3]. Although there is a controversy about measuring patient satisfaction or patient experience of the quality of care, many authors hold that satisfaction is linked to patient expectations of ideal care and their real experience of care [4].

Corresponding author: Alper Tunga Kokcu
alpertungakokcu@comu.edu.tr

Gendarmerie and Coast Guard Academy, Primary Health Care Centre, Ankara, Turkey

In 1997, it was stated by the Council of Europe that the continuous improvement of quality of care is a key priority for all member states. According to this decision, information on the needs, priorities, and experiences of patients at all levels of care provision had to be gathered through appropriate methods ensuring the active participation of patients [5]. A valid and easy-to-use instrument to gather information on patients' experiences with and evaluations of general practice care was developed by the European working party on quality in general practice in 1999. The European task force on patient evaluations of general practice care (EUROPEP) instrument was designed to assess the quality of general practice and to provide relevant feedback to general practitioners, patients, and health care policymakers at different levels [6]. The EUROPEP questionnaire, which is an internationally validated and standardized instrument for patients' evaluations on general practice care, has been used in many European countries, including Turkey.

The objective of this study was to evaluate patient satisfaction with primary health care in a military setting by using the EUROPEP questionnaire. The impact of the differences in patient characteristics on their satisfaction was also investigated. Besides, comparisons were made between this study and other studies, especially those conducted with the EUROPEP questionnaire.

METHODS

This cross-sectional study was conducted at the primary health care center (PHCC) located in Gendarmerie and Coast Guard Academy, in Ankara, Turkey. A total of 3080 military personnel who received care from the PHCC in the last 12 months formed the population of the study. Since the whole population was included in the study, a sample was not chosen. The data were collected between August and October 2018.

Using a five-point answering scale with the extremes labeled as 'poorest' and 'excellent,' the EUROPEP questionnaire is a multidimensional instrument comprising 23 questions on evaluations by patients of specific aspects of general practice care. The questionnaire has two dimensions: clinical behavior (items 1-16), and organization of care (items 17-23). Through this questionnaire, patients are asked to rate the quality of care that they have received in the last 12 months from the general practitioner that they usually visit [6]. In 2002, Akturk et al adopted the English version of EUROPEP questionnaire into Turkish and demonstrated that the Turkish version of EUROPEP questionnaire is a valid and reliable instrument that can be used for the Turkish population [7]. Three items of organization of care (making an appointment and contacting PHCC or doctor by phone) not applicable in this study were removed from the EUROPEP questionnaire. In the study, the remaining 20 items of the Turkish EUROPEP questionnaire (items 1-16: clinical behavior; items 17-20: organization of care) were administered to the participants. Descriptive characteristics of the participants were also obtained through the questionnaire.

Participants who scored the two most positive answering categories (good and excellent) were considered as satisfied patients. The rate of satisfied patients was used for the description of patients' views for each item. For the overall questionnaire and each dimension, the mean satisfaction rate (MSR) was used to assess patient satisfaction. Additionally, each item was scored on a five-point answering scale, ranging from one (poorest) to five (excellent). The mean satisfaction score (MSS) and the standard deviation of mean were used for each item. For the overall questionnaire and each dimension, MSS was used to assess patient satisfaction according to descriptive characteristics.

The internal consistency was assessed by using Cronbach's alpha. The data analysis was performed using the SPSS 22.0 software package. As the dataset was neither distributed normally nor was homogeneous, non-parametric statistical tests were used in the analysis. Mann-Whitney U test and Kruskal-Wallis test were used to determine whether there was any difference in the answers of patients according to their descriptive characteristics. If the Kruskal–Wallis test was found to be statistically significant, Dunn-Bonferroni test was performed for pairwise comparisons. A value of $p<0.05$ was accepted as statistically significant. The descriptive tables including numbers, rates, and means are presented and the results are discussed at the end of the paper.

The necessary administrative permission was obtained from the command of the military setting before the study. The ethical approval for this study was provided by the relevant University Human Research Ethics Committee on 4 July 2018 (No:3304). The completion of the questionnaire was voluntary and anonymous. Consent forms were obtained from the participants before the administration of the questionnaire.

RESULTS

In the study, 2677 participants were reached with a response rate of 86.9%. In subgroups according to the descriptive characteristics of the participants, response rates ranged from 81.2% to 92.3%. All of the participants were military personnel of four different troops and received care from

PHCC at least one time over the last 12 months. General practice care was given by two doctors working in PHCC. Most of the patients were unmarried (n=2251; 84.1%) and male (n=2472; 92.3%). The mean age of patients was 24.8±2.5 and ranged from 18 to 40 years. The descriptive characteristics of the patients are summarized in Table 1.

In the study, all items of the questionnaire were aggregated into two dimensions: clinical behavior (items 1-16) and organization of care (items 17-20). The Cronbach's alpha ranged between 0.975 for "clinical behavior," and 0.883 for "organization of care." For the overall 20 items of the Turkish EUROPEP questionnaire, the Cronbach's alpha was 0.974.

Table 1: Descriptive characteristics of the patients (n=2677)

Characteristics	n	(%)
Gender		
Male	2472	(92.3)
Female	205	(7.7)
Marital status		
Unmarried	2251	(84.1)
Married	426	(15.9)
Age level		
18-20	158	(5.9)
21-25	1408	(52.6)
>25	1111	(41.5)
Troop type*		
A	1997	(74.6)
B	347	(13.0)
C	176	(6.6)
D	157	(5.8)
Visit number		
1-2	1663	(62.1)
3-4	637	(23.8)
>4	377	(14.1)
Dr. providing the care*		
Dr-A	1436	(53.6)
Dr-B	1241	(46.4)

**Names of the troops and doctors were encoded because of confidentiality*

For each item, the MSS and the rate of patients who scored the two most positive answering categories (good and excellent) are presented in Table 2. The highest satisfaction rate and MSS were observed for "keeping your records and data confidential" (81.2%; 4.15±0.86), "thoroughness" (75.9%; 4.06±0.97), and "listening to you" (75.9%; 4.04±0.96). The lowest satisfaction rate and MSS were found for "waiting time in the waiting room" (47.2%; 3.30±1.25), and "the helpfulness of the staff (other than the doctor)" (56.5%; 3.56±1.16). MSR of clinical behavior (69.3%) was higher than MSR of organization of care (58.4%). The MSR of the overall questionnaire was 67.1%. While the MSS of clinical behavior was 3.89±0.85, the MSS of organization of care was 3.60±1.00. For the overall general practice, the MSS was 3.84±0.84.

It was observed that there were significant differences in the MSSs of patients according to their descriptive characteristics including gender, age level, troop type, and the doctor providing the care. The MSS of female patients was lower than the MSS of male patients ($p<0.05$). The MSS of patients in the 18-20 age group was higher than those in the other age groups ($p<0.05$).

Regarding the overall questionnaire and each dimension, the patients from troop-A had lower MSS, compared to the patients from troop-C and troop-D ($p<0.05$). Regarding the dimension of clinical behaviour, the patients from troop-A also had lower MSS, compared to the patients from troop-B ($p<0.05$). Patients consulting Dr-A reported more satisfaction regarding the organization of care and overall general practice than the patients consulting Dr-B ($p<0.05$). However, there were no differences among other descriptive characteristics of patients such as marital status and the number of visits. The detailed results of comparisons of MSSs concerning the descriptive characteristics are given in Table 3 and Table 4.

DISCUSSION

It can be said that patient satisfaction is related to the physicians' adherence to the four principles of biomedical ethics including autonomy, beneficence, non-maleficence, and justice. Physicians' adherence to the principles of biomedical ethics, especially of autonomy, can be evaluated by using the instruments for assessing patient satisfaction. Most of the time, patients are not aware of the quality of health care delivered to them. Therefore, valid and reliable instruments are used to evaluate patients' experiences of health care.

In this study, the EUROPEP questionnaire was used for the assessment of patient satisfaction with primary health care in a military setting for the first time. Having this study conducted with the EUROPEP instrument allows us to make direct comparisons between the results of this study and the results of previous studies conducted with the same instrument. Similar to other studies, the current study revealed very high values for Cronbach's alpha for the EUROPEP questionnaire and its two dimensions [8-10]. For the overall questionnaire and each item, this study reported low patient satisfaction levels. Significant differences were observed in the MSSs of patients according to their descriptive characteristics including gender, age level, troop type, and the doctor providing the care. On the other hand,

no differences were determined among other descriptive characteristics of patients, such as marital status and the number of visits.

Consistent with the previous EUROPEP studies, the results of this study showed that the patients were more satisfied with "clinical behavior" compared to the "organization of care." [8,9,11-14]. Similar to other studies, the highest and lowest satisfaction rates were for the items ''keeping your records and data confidential'' (81.2%), and "waiting time in the waiting room" (47.2%) [8-10,12-14].

Table 2: Descriptive statistics for 20 items of the questionnaire (n=2677)

Questions	MSS (Mean±SD)*	Good or excellent response [n (%)]**	
Clinical behaviour			
1. Making you feel you had time during consultations	3.80±1.02	1768	(66.0)
2. Interest in your personal situation	3.85±0.99	1802	(67.3)
3. Making it easy for you to tell him or her about your problems	3.97±0.95	1953	(73.0)
4. Involving you in decisions about your medical care	3.82±0.99	1763	(65.9)
5. Listening to you	4.04±0.96	2032	(75.9)
6. Keeping your records and data confidential	4.15±0.86	2173	(81.2)
7. Quick relief of your symptoms	3.85±1.00	1809	(67.6)
8. Helping you to feel well so that you can perform your normal daily activities	3.89±0.97	1867	(69.7)
9. Thoroughness	4.06±0.97	2033	(75.9)
10. Physical examination of you	4.00±0.99	1942	(72.5)
11. Offering your services for preventing diseases	3.89±0.98	1823	(68.1)
12. Explaining the purpose of tests and treatments	3.80±1.05	1744	(65.1)
13. Telling you what you wanted to know about your symptoms and/or illness	3.87±1.01	1833	(68.5)
14. Helping you deal with emotional problems related to your health status	3.72±1.05	1646	(61.5)
15. Helping you understand the importance of following his or her advice	3.86±0.99	1810	(67.6)
16. Knowing what he or she had done or told you during contacts	3.75±1.06	1688	(63.1)
MSS and MSR (items 1-16)	3.89±0.85		(69.3)
Organization of care			
17. Preparing you for what to expect from a specialist or hospital care	3.83±1.05	1784	(66.6)
18. The helpfulness of the staff (other than the doctor)	3.56±1.16	1512	(56.5)
19. Waiting time in the waiting room	3.30±1.25	1264	(47.2)
20. Providing quick services for urgent health problems	3.71±1.17	1690	(63.1)
MSS and MSR (items 17-20)	3.60±1.00		(58.4)

MSS: Mean satisfaction score; MSR: Mean satisfaction rate; SD: Standard deviation.

**Items were scored on a five-point answering scale, ranging from 1 (poorest) to 5 (excellent).*

***Participants who scored the two most positive answering categories (good and excellent) were considered as satisfied patients.*

By using the EUROPEP instrument, Petek et al. conducted a study in eight European countries in 2009. The study aimed to describe evaluations of general practice care by patients with a chronic illness. The MSRs ranged from 82.1% to 93.0% in the European countries [15]. It may be questionable that the study was conducted with a single group of chronic care patients. While a study reported that better health status was associated with a more positive evaluation of care, another study showed that patients reporting a chronic condition were more positive in their assessment of the general practice than patients without a chronic condition [16,17]. However, conducted by Rosemann et al., a previous study utilizing the EUROPEP instrument revealed that patient satisfaction was not determined by the disease-specific quality of life, at least not in osteoarthritis patients [18]. The Turkish Ministry of Health conducted a study in 2010 that surveyed 34472 patients across Turkey. The study aimed to measure patient satisfaction with PHCCs. The MSR was found to be 77.8% with the EUROPEP instrument [19]. The MSR of the current study (67.1%) is lower than that of the previous studies conducted in European countries and Turkey with similar methodology.

In contrast to some other studies, this study found that

female patients' satisfaction levels were lower than those of the males [12, 16, 20]. On the other hand, the gender results of this study were consistent with the previous studies conducted in the military settings that found male patients to be more satisfied than female patients [21, 22].

Similar to the study conducted by Petek et al., no difference was found according to marital status in this study [15]. On the other hand, Baltaci et al. observed that the patient satisfaction level was higher for married patients than it was for the unmarried [20].

Table 3: Comparisons of mean satisfaction scores concerning the descriptive characteristics (n=2677)

Characteristics	n	(%)	MSSs (Mean±SD)** and p-values***					
			Clinical behaviour	p	Organization of care	p	Overall general practice	p
Gender								
Male	2472	(92.3)	3.91±0.84	0.000[a]	3.60±1.00	0.022[a]	3.85±0.84	0.000[a]
Female	205	(7.7)	3.68±0.87		3.49±0.83		3.64±0.83	
Marital status								
Unmarried	2251	(84.1)	3.89±0.84	0.679	3.60±0.99	0.308	3.83±0.84	0.897
Married	426	(15.9)	3.90±0.84		3.55±0.99		3.83±0.83	
Age level								
18-20	158	(5.9)	4.09±0.83	0.003[a]	3.81±0.99	0.008[a]	4.03±0.83	0.004[a]
21-25	1408	(52.6)	3.89±0.83		3.60±0.99		3.83±0.83	
>25	1111	(41.5)	3.85±0.85		3.56±0.99		3.80±0.84	
Troop type*								
A	1997	(74.6)	3.84±0.86	0.000[a]	3.55±1.00	0.000[a]	3.78±0.85	0.000[a]
B	347	(13.0)	3.98±0.79		3.66±0.97		3.91±0.79	
C	176	(6.6)	4.09±0.68		3.80±0.89		4.04±0.67	
D	157	(5.8)	4.07±0.85		3.77±1.00		4.01±0.84	
Visit number								
1-2	1663	(62.1)	3.89±0.79	0.149	3.63±0.95	0.254	3.84±0.79	0.441
3-4	637	(23.8)	3.87±0.89		3.53±1.05		3.80±0.88	
>4	377	(14.1)	3.92±0.96		3.55±1.07		3.84±0.94	
Dr. providing the care*								
Dr-A	1436	(53.6)	3.92±0.83	0.052	3.64±0.99	0.004[a]	3.87±0.83	0.035[a]
Dr-B	1241	(46.4)	3.85±0.86		3.54±0.99		3.79±0.85	

MSS: Mean satisfaction score; SD: Standard deviation.

**Names of the troops and doctors were encoded because of confidentiality.*

***Items were scored on a five-point answering scale, ranging from 1 (poorest) to 5 (excellent).*

****Mann-Whitney U test and Kruskal-Wallis test were performed ([a] p<0.05).*

In contrast to other studies, this study found that younger age was associated with higher levels of patient satisfaction. [15, 16]. However, it is worth bearing in mind that the participants in this study were aged 40 or under.

A previous study conducted in a military setting revealed that waiting times were significantly correlated to overall patient satisfaction [23]. The current study found a difference in the satisfaction levels according to the troops the patients belonged to. In the military setting where the current study was conducted, according to the rules, the patient should visit PHCC with the other patients of his/her troop at the same time in the morning, except for emergencies. As the number of patients in the troop increases, the waiting time in the PHCC extends, which may be the underlying reason for the low patient satisfaction level in crowded troops like troop-A.

The current study couldn't confirm the results of previous studies that there is a positive association between the number of visits and the level of patient satisfaction [15, 16]. A majority of the participants of this study (85.9%) had a low number of visits (≤4), and the mean number of visits was 2.6. In Turkey, the total number of visits per person to a general practitioner in 2017 was 2.9 [24].

In this study, it was observed that there was a difference in the satisfaction levels depending on the doctor providing the care. While Dr-A is a military general practitioner, Dr-B is a civilian general practitioner, which may be one of the reasons for the low satisfaction levels of patients evaluating Dr-B.

A strength of this study is that it was conducted with a large population sample. On the other hand, there are relatively several limitations to the study. Because the study was conducted in a military setting, participants were younger than 40 and most of the visits to PHCC were due to acute health disorders. Due to the limited number of general practitioners working in PHCC where the study was conducted, the participants were able to evaluate two doctors in terms of general practice care.

Table 4: Pairwise comparisons of multiple groups whose comparisons were found to be statistically significant

Pairwise groups	p-values**		
	Clinical behavior	Organization of care	Overall general practice
Age level			
18-20 and 21-25	0.009[a]	0.019[a]	0.010[a]
18-20 and >25	0.002[a]	0.005[a]	0.003[a]
21-25 and >25	1.000	1.000	1.000
Troop type*			
A and B	0.034[a]	0.413	0.062
A and C	0.004[a]	0.010[a]	0.005[a]
A and D	0.003[a]	0.035[a]	0.005[a]
B and C	1.000	0.777	1.000
B and D	1.000	1.000	1.000
C and D	1.000	1.000	1.000

Names of the troops were encoded because of confidentiality.

***Dunn-Bonferroni posthoc test was performed ([a] p<0.05).*

This study highlights the low patient satisfaction levels, which may have resulted from the fact that the study population was young and relatively healthy, and that there was no possibility of choosing the general practitioner and PHCC. However, according to the results obtained through the questionnaire, taking necessary actions to promote patient satisfaction will improve the quality of primary health care in this military setting.

The EUROPEP questionnaire, which is an internationally validated and standardized instrument for patients' evaluations on general practice care, provides feedback to general practitioners and policymakers. The results of a study conducted with this instrument can be directly compared with other studies conducted with the same instrument. These comparisons can shed light on the similarities and differences between various PHCCs. This instrument can also be used to improve primary health care in military settings.

Disclosure statement

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests: No potential conflict of interest was reported by the author.

Acknowledgments

Author contribution: ATK was responsible for study conception, the design of the study, recruitment of participants, analyzing data, and preparing the manuscript for publication.

Ethics approval: The ethical approval for this study was provided by the Atilim University Human Research Ethics Committee on 4 July 2018 (reference number 3304).

Patient consent: Consent forms were obtained from the participants before the administration of the questionnaire.

Disclaimer: The opinions expressed in this article are those of the author and do not reflect official military policy or position of the Gendarmerie and Coast Guard Academy.

References:

1. What is quality of care and why is it important? World Health Organisation [Internet]. 2016 [cited 2019 Nov 21]. Available from: https://www.who.int/maternal_child_adolescent/topics/quality-of-care/definition/en/

2. Gupta KS, Rokade V. Importance of quality in health care sector: A review. J Health Manag. 2016;18:84-94. doi:10.1177/0972063415625527

3. Cimas M, Ayala A, Garcia-Perez S, Sarria-Santamera A, Forjaz MJ. The patient satisfaction questionnaire of EUprimecare project: measurement properties. Int J Qual Health Care. 2016;28:275-80.

doi:10.1093/intqhc/mzw024

4. Keller AC, Bergman MM, Heinzmann C, Todorov A, Weber H, Heberer M. The relationship between hospital patients' ratings of quality of care and communication. Int J Qual Health Care. 2014;26:26-33. doi:10.1093/intqhc/mzt083

5. Recommendation No. R (97) 17 of the Committee of Ministers to Member States on the development and implementation of quality improvement systems (QIS) in health care. Strasbourg: Council of Europe [Internet].1997 [cited 2019 Nov 24]. Available from: https://rm.coe.int/CoERMPublicCommonSearchServices/DisplayDCTMContent?documentId=0900001680506e0d

6. Grol R, Wensing M. Patients evaluate general/family practice: The EUROPEP Instrument. Nijmegen: EQuiP, WONCA-Europe [Internet]. 2000 [cited 2019 Nov 29]. Available from: http://equip.woncaeurope.org/sites/equip/files/documents/publications/resources/grolwensing2000theeuropepinstrumentequipwonca.pdf

7. Akturk Z, Dagdeviren N, Sahin EM, et al. Patient evaluate physicians: The EUROPEP instrument. Journal of Dokuz Eylul University Medical Faculty. 2002;16:153-60.

8. Dimova R, Stoyanova R, Keskinova D. The EUROPEP questionnaire for patient's evaluation of general practice care: Bulgarian experience. Croat Med J. 2017;58:63-74. doi:10.3325%2Fcmj.2017.58.63

9. Goetz K, Hahn K, Steinhauser J. Psychometric properties of the Arabic version of the EUROPEP questionnaire. Patient Prefer Adherence. 2018;12:1123-28. doi:10.2147/PPA.S169355

10. Peltzer K, Phaswana-Mafuya N, Davids A. The use of EUROPEP in South Africa: An internationally standardised instrument to evaluate general practice. Journal of Psychology in Africa. 2010;20:113-6. doi:10.1080/14330237.2010.10820351

11. Bjertnaes OA, Lyngstad I, Malterud K, Garratt A. The Norwegian EUROPEP questionnaire for patient evaluation of general practice: Data quality, reliability and construct validity. Fam Pract. 2011;28:342-9. doi:10.1093/fampra/cmq098

12. Ali NS, Khuwaja AK, Kausar S, Nanji K. Patients' evaluations of family practice care and attributes of a good family physician. Qual Prim Care. 2012;20:375-83.

13. Baltaci D, Celesun T, Eroz R, et al. Evaluation of patient satisfaction with family physicians after implementation of family medicine in Turkey. HealthMED. 2012;6:469-75.

14. Akturk Z, Atesoglu D, Ciftci E. Patient satisfaction with family practice in Turkey: Three-year trend from 2010 to 2012. Eur J Gen Pract. 2015;21:238-45. doi:10.3109/13814788.2015.1048681

15. Petek D, Kunzi B, Kersnik J, Szecsenyi J, Wensing M. Patients' evaluations of European general practice - revisited after 11 years. Int J Qual Health Care. 2011;23:621-8. doi:10.1093/intqhc/mzr052

16. Heje HN, Vedsted P, Sokolowski I, Olesen F. Patient characteristics associated with differences in patients' evaluation of their general practitioner. BMC Health Serv Res. 2008;8:178. doi:10.1186/1472-6963-8-178

17. Milano M, Mola E, Collecchia G, et al. Validation of the Italian version of the EUROPEP instrument for patient evaluation of general practice care. Eur J Gen Pract. 2007;13:92-4. doi:10.1080/13814780701378990

18. Rosemann T, Wensing M, Szecsenyi J, Grol R. Satisfaction of osteoarthritis patients with provided care is not related to the disease-specific quality of life. J Eval Clin Pract. 2009;15:486-91. doi:10.1111/j.1365-2753.2008.01047.x

19. Mollahaliloğlu S, Kosdak M, Sanisoglu Y, Boz D, Bulut Demirok A. Patient satisfaction with primary health care services. Ankara: School of Public Health, Refik Saydam Hygiene Center Presidency, Ministry of Health of Turkey [Internet]. 2010 [cited 2019 Dec 12]. Available from: https://dosyaism.saglik.gov.tr/Eklenti/12293,2010-birinci-basamak-saglik-hizmetlerinde-hasta-memnuniyetipdf.pdf?0

20. Baltaci D, Eroz R, Ankarali H, Erdem O, Celer A, Korkut Y. Association between patients' sociodemographic characteristics and their satisfaction with primary health care services in Turkey. Kuwait Medical Journal. 2013;45:291-9.

21. Barido GT, Campbell-Gauthier GD, Mang-Lawson AM, Mangelsdorff AD, Finstuen K. Patient satisfaction in military medicine: Model refinement and assessment of continuity of care effects. Mil Med. 2008;173:641-6. doi:10.7205/milmed.173.7.641

22. Mangelsdorff AD, Finstuen K, Larsen SD, Weinberg EJ. Patient satisfaction in military medicine: Model refinement and assessment of Department of Defense effects. Mil Med. 2005;170:309-14. doi:10.7205/milmed.170.4.309

23. Leiba A, Weiss Y, Carroll JS, Benedek P, Bar-dayan Y. Waiting time is a major predictor of patient satisfaction in a primary military clinic. Mil Med. 2002;167:842-5.

24. Bora Basara B, Soytutan Caglar I, Aygun A, et al. Health statistics yearbook 2017. Ankara: General Directorate of Health Information Systems, Ministry of Health of Turkey [Internet]. 2018 [cited 2019 Dec 23]. Available from: https://dosyasb.saglik.gov.tr/Eklenti/30148,ingilizcesiydijiv1pdf.pdf?0

The article was received on July 10, 2020, and accepted for publishing on October 23, 2020.

ORIGINAL ARTICLES

Total knee arthroplasty radiographic evaluation via a Bayesian belief network. A pilot study

Catalin Cirstoiu[1,2], Bogdan Cretu[1,2], Bogdan Serban[1,2], Sergiu Iordache[1,2], Adrian Cursaru[1,2], Stefan Cristea[1,3], Anca I. Eremia[1,4], Silvia Nica[1,4]

Abstract: *In an attempt to standardize the X-ray analysis and to create relevant correlations between it and the functional results, we present a pilot model of an artificial neural network based on a Bayesian belief network (BNN) designed for the automatic analysis of anteroposterior X-ray of the knee following total knee arthroplasty and more precisely the analysis of the tibial component.*

A prospective analysis was conducted in which 30 patients were analyzed and two groups resulted: the first was made up of 12 cases considered "normal" by the examiners (optimal positioning and cementation) and the second one, which was considered "pathological" (incorrect positioning or cementation) and included 16 cases.

Based on 22 points established on the tibial component several geometric sizes (calculated parameters) were computed. Several parameters were compared and the results were up to 75% accuracy, 81.25% sensitivity, and 66.7% specificity.

BBNs can be a solution for X-ray evaluation of total knee arthroplasty and can improve the understanding of its evolution. It needs confirmation in time, its accuracy rising with the number of patients introduced in the analysis algorithm.

Keywords: *TKA; Bayesian method; ANN; X-ray analysis*

INTRODUCTION

Artificial Neural Networking (ANN) are computer systems that create connections, similar to those existing in the biological neural network [1]. Such systems are programmed to learn based on examples, without being programmed in advance to identify specific tasks [2]. For example, artificial neural imaging systems can identify an area of osteolysis, the area that has been previously set as osteolysis using a yes/no algorithm on other images. They can perform this task without having the ability to understand what an osteolysis area means.

ANN is made up of a mass of nodes connected by artificial neurons just like the component of a biological brain. Artificial neurons are interconnected by synapses and can send information between them.

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Department of Orthopedics and Traumatology, University Emergency Hospital, Bucharest, Romania
[3] Department of Orthopedics and Traumatology, Pantelimon Emergency Hospital, Bucharest, Romania
[4] Department of Emergency, University Emergency Hospital, Bucharest, Romania

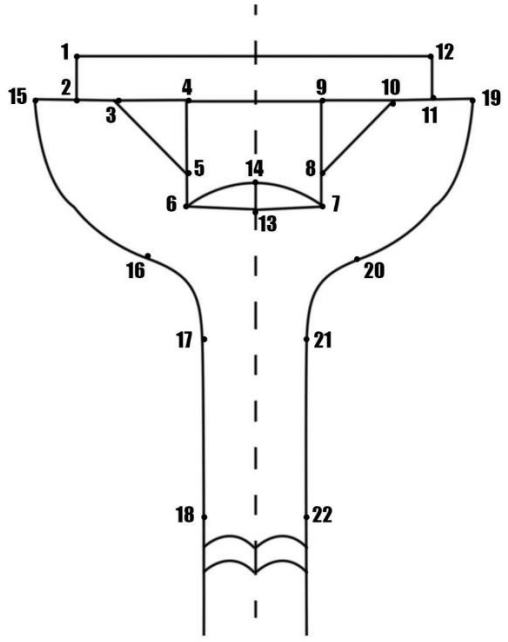
Corresponding author: Bogdan Cretu
jfrbogdan@yahoo.com

The initial purpose of these artificial neural networks was to create a replica of the human brain and the latter to be able to make decisions similar to those made by a human. Following their application in different fields, the initial purpose was forgotten. They are currently used for verbal recognition, translation, social networks, but most importantly in the medical diagnosis, such as total knee arthroplasty (TKA) [3, 4, 5, 6].

Thus, for patients with diseased knee or hip joints, total knee or hip arthroplasty (TKA/THA) is considered as one of the most effective procedures for relieving pain and improving joint function [7]. Improvements in joint arthroplasty procedures will routinely witness rapid recovery, faster functional recovery, lower postoperative discomfort, and higher patient satisfaction, which is a win-win for patients and surgeons [8].

The importance of the restoration of the biomechanical axis of the pelvic limb is emphasized in current studies [9]. Proper prosthetic positioning, mobility restoration, and pain disappearance are factors predicting the long-term survival of the prosthesis as well as the postoperative patient satisfaction [10].

Figure 1: Postoperative TKA image used for Bayesian evaluation



Radiological postoperative evaluation following total knee arthroplasty is essential to improve the quality of the surgical act. The standard procedure implies that two postoperative X-rays are performed, one anteroposterior, and one profile X-ray. They analyze the mechanical alignment of the knee, bone coverage by the prosthesis, femoral anterior and posterior offset, femoral flexion and extension, tibial slope (Figure 1).

Also, during the initial postoperative evaluation, any deficiencies in the cementation technique are identified. Ideally, it is sought to obtain a uniform cement coat for thickness and distribution.

In an attempt to standardize the X-ray analysis and to create relevant correlations between it and the functional results, we present a pilot model of an artificial neural network based on a Bayesian belief network (BNN) designed for the automatic analysis of anteroposterior X-ray of the knee following total knee arthroplasty and more precisely the analysis of the tibial component.

BNNs are frequently used in medicine, they provide the probability of an outcome based on creating intuitively relations between variables [11-15].

MATERIALS AND METHODS

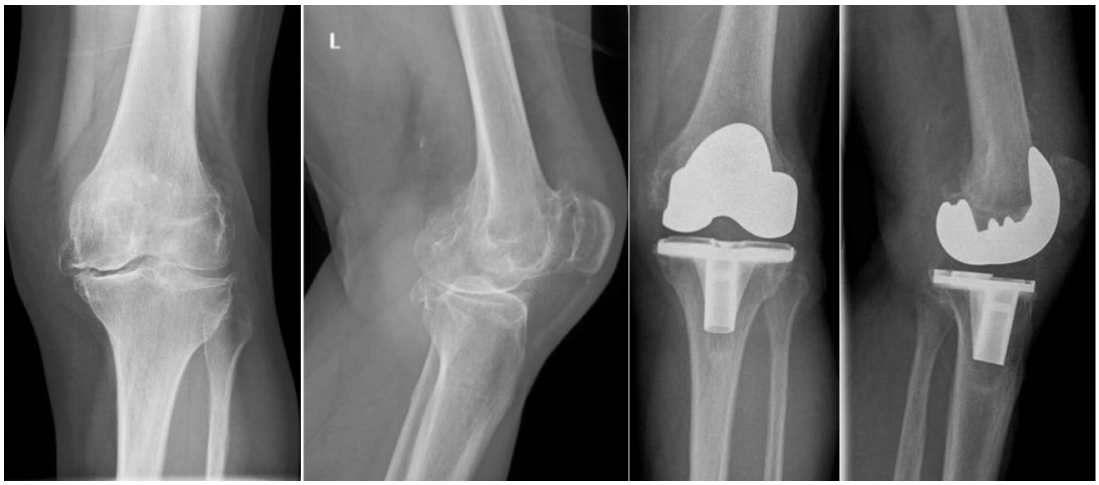
A prospective study in which two lots of patients were used. In both, patients with gonarthrosis were included, who were subjected to total knee arthroplasty, which was performed in the same center by the same surgical team. The inclusion criteria were patients over 65 years old, who were subjected to TKA, with underlying gonarthrosis disease. Exclusion criteria included inflammatory arthritis, post-traumatic gonarthrosis with major deformities, unicompartmental arthroplasty.

The two lots of patients were conceived following the X-ray analysis on day 0 postoperatively by an independent team of orthopedists. Standing AP, profile, and full leg X-rays of 30 patients were analyzed and two groups resulted: the first was made up of 12 cases considered “normal” by the examiners (optimal positioning and cementation) and the second one, which was considered “pathological” (incorrect positioning or cementation) and included 16 cases. 2 patients were excluded following the appearance of postoperative complications. The same patient groups were followed up at 1 month, 6 months, and 1 year postoperatively. The same set of X-rays was performed at each visit.

Following the constitution of the two groups of patients, it was decided to start the computer analysis of the postoperative X-rays from 6 months and 1 year. To test the validity/relevance of the automatic analysis, we decided that the initial analysis should be performed at the tibia level, on front-loading X-ray. 22 control points were established at the level of the tibial component (Figure 2) that corresponds to the placement of the prosthesis and the tibial bone, as

shown in the schematic picture, 14 points on the contour of the prosthesis and 8 points on the tibia.

Figure 2: 22 control points at the level of the tibial component



Using the identified points, several geometric sizes (calculated parameters) were computed:

1. The left-right rotation of the X-ray image, determined by the difference of the areas associated with the triangles determined by points 3 – 4 – 5 and 8 – 9 – 10 on the prosthesis.
2. Up-down rotation of the X-ray view, determined by the area associated with the ellipse determined by points 6 – 7 – 13 – 14 on the prosthesis.
3. The angle of vertical offset between the axis of the prosthesis (calculated as bisector of the angle formed by sides 4 – 5 – 6 and 7 – 8 – 9) and the axis of the bone, calculated as bisector of the angle formed by sides 17 – 18 and 21 – 22.
4. Horizontal offset angle between the base of the prosthesis (2 – 3 – 4 – 9 – 10 – 11) and the cut of the bone 15 – 19.
5. Percentage of coverage to the left of the prosthesis, determined by the part of the head bone not covered by the prosthesis at level 15 – 2.
6. Percentage of coverage to the right of the prosthesis, determined by the part of the head bone not covered by the prosthesis at level 11 – 19.
7. Variation of previously calculated parameters between postoperative images at 1 month and 6 months.

RESULTS

Following the schematic of the calculated parameters, a Bayes statistical model was applied.

DECISION 1: Normal-pathological differentiation tests at the level of individual X-rays

Of the many variants tested to make the decision, the best results were obtained based on measure 5 (percentage of coverage left of the prosthesis), with a threshold of 0.82 for differentiation (pathological > 0.82). Taking into account these conditions, the normal/ pathological decision correctly identified: 11 images from normal patients (out of the 24) and 26 images from pathological patients (out of the 32).

This led to the following sizes: 66.1% accuracy, 81.25% sensitivity, and 45.8% specificity.

DECISION 2: Normal-pathological differentiation tests at the level of the pair of individual postoperative X-rays at 1-6 months

Of the many variants tested to make the decision, the best results were obtained based on combined measures:

A. The decision according to a single parameter: the sum of parameter 1 (left-right rotation of the X-ray view) at 1 and 6 months, with a decision threshold of 0.47; pathological > 0.47). Taking into account these conditions, the normal/ pathological decision correctly identified: 9 pairs of images from normal patients (out of the 12) and 9 pairs of images from pathological patients (out of 16).

This led to the following sizes: 64.3% accuracy, 56.25% sensitivity, and 75% specificity.

B. The decision according to several parameters: the sum of parameter 1 (left-right rotation of the X-ray view) at 1 month and 6 months, with a decision threshold of 0.47, pathological > 0.47, or difference of parameter 3 (vertical offset angle between the axis of the prosthesis) at 1 month and 6 months, with a decision threshold of 0.75, pathological < 0.75 and difference of parameter 4 (horizontal offset angle between the axis of the prosthesis) at 1 month and 6

months, with a decision threshold of 1.8, pathological < 1.8.

Taking into account these conditions, the normal/ pathological decision correctly identified: 8 pairs of images from normal patients (out of 12) and 13 pairs of images from pathological patients (out of 16). This led to the following sizes: 75% accuracy, 81.25% sensitivity, and 66.7% specificity.

DISCUSSION

Artificial neural networks are increasingly present in classifications, group creation, pattern recognition, and prediction in many disciplines, medicine being among them. The huge potential is represented by speed, volume, and accuracy of data analysis.

The Bayesian system developed by us can recognize immediately and accurately any deficient positioning of the tibial prosthetic component. It can integrate this assessment into the clinical context and provide answers to a series of questions of patients with low satisfaction. It may be an optimal way of evaluating the series X-ray with results that are superimposed over those obtained by a CT scan.

Our model of X-ray analysis by BBN has several limitations. The number of patients is not large enough to obtain sufficiently conclusive results. X-ray analysis is performed only for the tibial component at present, a comprehensive X-ray analysis that also includes the femoral component is required. The registered data do not contain patient information: age, weight, degree of osteoarthritis, preoperative and postoperative mobility, pain scores, and so on.

CONCLUSIONS

BBNs can be a solution for X-ray evaluation of total knee arthroplasty and can improve the understanding of its evolution.

It needs confirmation in time, its accuracy rising with the number of patients introduced in the analysis algorithm.

It may provide an answer for low satisfaction rates of certain patients in whom the prosthetic components are optimally positioned and have no other postoperative complications.

References:

1. Greenwood D. An overview of neural networks. Behav Sci. 1991;36:1-33. Doi:10.1002/bs.383036102.

2. Terrin N, Schmid CH, Griffith JL, D'Agostino RB, Selker HP. External validity of predictive models: a comparison of logic regression, classification trees, and neural networks. J Clin Epidemiol. 2003;56:721-729. doi: 10.1016/S0895-4356(03)00120-3.

3. Rughani AI, Dumont TM, Lu Z, Bongard J, Horgan MA, Penar PL, et al. Use of an artificial neural network to predict head injury outcome. J Neurosurg. 2010;113:585–590. doi: 10.3171/ 2009.11.JNS09857.

4. Ongphiphadhanakul B, Rajatanavin R, Chailurkit L, Piaseu N, Teerarungsikul K, Sirisriro R, et al. Prediction of low bone mineral density in postmenopausal women by artificial neural network model compared to logistic regression model. J Med Assoc Thai. 1997;80:508–515.

5. Ottenbacher KJ, Linn RT, Smith PM, Illig SB, Mancuso M, Granger CV. Comparison of logistic regression and neural network analysis applied to predicting living setting after hip fracture. Ann Epidemiol. 2004;14:551–559. doi: 10.1016/ j.annepidem.2003.10.005.

6. Lin CC, Ou YK, Chen SH, Liu YC, Lin J. Comparison of artificial neural network and logistic regression models for predicting mortality in elderly patients with hip fracture. Injury. 2010;41:869–873. doi: 10.1016/j.injury.2010.04.023.

7. Bullens PH, van Loon CJ, de Waal Malefijt MC, Laan RF, Veth RP. Patient satisfaction after total knee arthroplasty: a comparison between subjective and objective outcome assessments. J Arthroplasty. 2001 Sep;16(6):740-7.

8. Rutherford RW, Jennings JM, Dennis DA. Enhancing Recovery After Total Knee Arthroplasty. Orthop Clin North Am. 2017 Oct;48(4):391-400. doi: 10.1016/j.ocl.2017.05.002. Epub 2017 Aug 8.

9. Khatib Y, Xia A, Naylor JM, Harris IA, Sorial RM. Different targets of mechanical alignment do not improve knee outcomes after TKA. Knee. 2019 Dec;26(6):1395-1402. doi: 10.1016/j.knee.2019.08.004. Epub 2019 Aug 30.

10. Lange T, Schmitt J, Kopkow C, Rataj E, Günther KP, Lützner J. What Do Patients Expect From Total Knee Arthroplasty? A Delphi Consensus Study on Patient Treatment Goals. J Arthroplasty. 2017 Jul;32(7):2093-2099.e1. doi: 10.1016/j.arth.2017.01.053. Epub 2017 Feb 7.

11. Caillet P, Klemm S, Ducher M, Aussem A, Schott AM. HIP fracture in the el- derly: a re-analysis of the Epidos study with causal Bayesian networks. PLoS One 2015;10:e0120125.

12. Takenaka S, Aono H. Prediction of postoperative clinical recovery of drop foot attributable to lumbar degenerative diseases, via a Bayesian network. Clin Orthop Relat Res 2017;475:872–80.

13. Stojadinovic A, Kyle Potter B, Eberhardt J, Shawen SB, Andersen RC, Forsberg JA, et al. Development of a prognostic naive bayesian classifier for successful treatment of nonunions. J Bone Jt Surg Am 2011;93:187–94.

14. Nandra R, Parry M, Forsberg J, Grimer R. an a Bayesian belief network be used to estimate 1-year survival in patients with bone sarcomas. Clin Orthop Relat Res 2017;475:1681–9.

15. Needham CJ, Bradford JR, Bulpitt AJ, Westhead D. A primer on learning in Bayesian networks for computational biology. PLoS Comput Biol 2007;3:e129.

The article was received on January 30, 2020, and accepted for publishing on July 23, 2020.

ORIGINAL ARTICLES

Prevalence of osteoarthritis disorders in Iranian chemical injured patients: A cross-sectional study using the COPCORD approaches

Abolfazl Shakibaee[1], Alireza Shahriary[2], Noushin Bayat[3], Soraya Shadmanfar[3], Zeynab Ebrahimpour[4], Eshagh Harsij[5], Ahmad Farhadi[5], Ahmad Reza Jamshidi[6], Mahmood Salesi[2], Seyed Reza Hosseini Zijoud[7], Gholam Hossein Alishiri[8]

Abstract: *Introduction: Osteoarthritis is considered as the most common joint disease. Sulfur mustard (SM) is a toxic compound, which was applied as a chemical warfare agent by Iraq against Iran veterans during 1980-1988. Chemical veterans suffer from chronic implications caused by sulfur mustard that not only adversely affect their quality of life, but also restrict their working abilities and their participation in social activities. This study aims to consider the prevalence of osteoarthritis disorders among Iranian SM-exposed veterans.*

Methods: In this cross-sectional study, 248 Iranian SM exposed patients were evaluated from 2013 to 2014. Veterans filled a special questionnaire for COPCORD studies and then general and specific rheumatology examinations were applied under the supervision of internists and rheumatologists. The obtained data from 245 filled questionnaires were analyzed by SPSS software and the results were reported as a percentage or mean ±SD.

Results: Bone and joint pain (72%), knee joint pain (52.5%), Joint stiffness (49.2%), and shoulder joint pain (45.8%) were the most common type of complications in these patients. Osteoarthritis in at least one joint was the most common type of osteoarthritis in veterans. 69.5% of veterans had osteoarthritis in at least one joint. Knee osteoarthritis was the second most common type of osteoarthritis, which has been found in 58.4% of all veterans. The prevalence of neck osteoarthritis in all veterans was 23.9%.

Conclusion: The total prevalence of musculoskeletal disorders among Iranian veterans was significantly higher than the average of society.

Keywords: *chemical warfare, osteoarthritis, prevalence, COPCORD*

[1] Exercise Physiology Research Center, Lifestyle Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3] Exercise Physiology Research Center, Lifestyle Institute, Department of Rheumatology, Baqiyatallah University of Medical Sciences, Tehran, Iran
[4] Department of Physical education, Tehran Shomal Branch, Islamic Azad University, Tehran, Iran
[5] Student research committee, Department of Internal Medicine, Faculty of Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran
[6] Rheumatology Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[7] Clinical Research Development Unit, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[8] Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Department of Rheumatology, Baqiyatallah Faculty of Medicine, University of Medical Sciences, Tehran, Iran

INTRODUCTION

Osteoarthritis (OA) is considered as the most common joint disease and its main pathologic indication at the tissue level is joint cartilage breakdown. This disease is classified into two main groups: (1) primary or idiopathic osteoarthritis in

Corresponding author: Gholam Hossein Alishiri
ghalishiri@gmail.com

which no underlying disease causes the disorder, and (2) secondary osteoarthritis in which an underlying predisposing factor imposes the disease locally or systemically [1]. However, another classification based on the number of involved joints is considered which includes generalized osteoarthritis in which more than 3 joints are involved and also localized osteoarthritis in which less than 3 joints are involved [2, 3]. Identification of predisposing factors gives better insights for the disease pathogenesis. There are various factors such as age, gender, race, genetic, bone density, sex hormones, nutritional status, and environmental factors that can affect the prevalence of OA. Age is the most important risk factor that is not controllable; as it increases, osteoarthritis prevalence rises [4, 5]. The type of joint involvement before 55 years is the same among both sexes; however, when age increases hand joint involvements more likely occur among females but hip joint involvements are more prevalent among men [6, 7]. The prevalence of OA can be increased along with aging and obesity. According to the United Nations, 130 million people will suffer from OA by 2050, of which 40 million will be severely disabled by the disease. The burden associated with OA includes costs for adaptive aids and devices, medicines, surgery, and time off at work. Osteoarthritis prevalence among black and white races is different [8]. The risk of osteoarthritis among individuals who have parents suffering from the disease is significantly higher [9]. Some studies have proposed a reverse relation between osteoporosis and osteoarthritis and some have suggested that bone density increscent is correlated to thigh and knee osteoarthritis but not hand osteoarthritis [10-12]. Endocrine or metabolic disorders such as diabetes, hyperparathyroidism, and acromegaly are in association with osteoarthritis [13]. Nutrition status and antioxidant materials in diets may prevent or postpone osteoarthritis. The damage caused by reactive oxygen species (ROS) is determined through the osteoarthritis trend [14]. Knee osteoarthritis progress among people suffering from vitamin C deficiency is significantly more than those consuming a high amount of this vitamin [15]. Obesity is one of the most important causes of osteoarthritis progress especially in the knee [16]. High pressure on joints due to sport or job, congenital disorders, and inflammatory or infectious diseases are the other affecting factors [16].

The chemical contamination from the wars is one of the main causes of various diseases in veterans. Sulfur mustard [17] is one of the warfare agents which has been utilized during various chemical wars and it was widely applied during the imposed war of Iraq against Iran (1980-88)[18]. The first report on the late implications of SM toxicity among 236 Iranian chemical veterans revealed 78% respiratory, 45% central nerve system, 41% skin, and 36% eye complications. These abnormalities were reported 2-28 months after SM exposure [19].

Chemical veterans are still suffering from the late effects of SM toxicity which negatively impacts their quality of life. More importantly, the progression of their disease restricts their working abilities and participation in social activities. There is little information about the prevalence of osteoarthritis or musculoskeletal disorders among chemical veterans. Since the status of nutrition, medicine, economy, mobility, and generally the lifestyle of the veterans are different from other parts of the society, low bone density or suffering from endocrine and metabolic disorders or chronic infectious disease is more likely to occur among this community [20]. Therefore, the purpose of this study was to evaluate the frequency of osteoarthritis disorders among Iranian chemical veterans who previously exposed to SM using the COPCORD approach.

METHODS

This cross-sectional study was conducted on Iranian chemical veterans in Tehran from 2013 to 2015. For sampling, the initial list of chemical veterans was provided from the lung clinic and medical commission of Baqiyatallah University of Medical Sciences, and individuals who fulfilled the inclusion criteria were entered into the study. Furthermore, according to the coordination of the Veterans and Martyrs Affair Foundation (VMAF), a list of patients who fulfilled the inclusion criteria were selected and invited to participate in the study. The Including criteria were as follows: having documented exposure to sulfur mustard (confirmed by related authorities), male gender, being over 40 years old, moderate and negligible involvement of lungs, and giving consent for participating in the study.

The special questionnaire for COPCORD studies was filled by veterans and the general and specific rheumatology examinations were applied under the supervision of internists and rheumatologists. This questionnaire consisted of demographic questions, complaints about osteoarthritis in the past 7 days, questions about the restrictions, accidents, damages, and external joint symptoms related to musculoskeletal diseases, and also questions in the scope of the treatment detailed examination by specialists and assessing medical histories elucidated the prevalence of different osteoarthritis complications for the mentioned population.

The final part of the questionnaire contained the recorded probable and final diagnosis of the patients who complained about at least one joint (pain, inflation, and stiffness) or

external joint pain. If the patient needed more examinations such as radiology in the opinion of the physician, this information was obtained and attached to the questionnaire. Finally, the filled questionnaires were analyzed and the obtained data were revised and after excluding the defaced cases, the questionnaires data were entered into the SPSS software version .20 and the results were described as percentages and mean. The confidentiality of the information of the subjects studied by researchers and project implementers were considered as the ethical considerations of this study. The COPCORD questionnaire used in this study was provided by the Rheumatology Research Center at COPCORD website.

RESULTS

In this study, 245 subjects were evaluated in which 97 patients lived in Tehran and 148 subjects lived in Alborz Provinces. The mean age of the studied population was 51.1 years. Data on demographic information and smoking status can be seen in Tables 1 and 2, respectively.

Table 1: The frequency distribution of studied veterans based on demographic variable

Variable		Number (%)
Marriage status	Single	1 (0.4)
	Married	237 (98.8)
	Spouse dead	1 (0.4)
	Separated or divorced	1 (0.4)
Race	Fars	149 (62.1)
	Azeri	67 (27.9)
	Kurd	11 (4.6)
	Lor	7 (2.9)
	Other	6 (2.5)
Occupation status	Employee	76 (34.1)
	Worker	6 (2.7)
	Retired	76 (34.1)
	Self-employed	49 (22)
	Unemployed	15 (6.7)
	Disabled	1 (0.4)

Table 2: The smoking status of studied veterans

Smocking	Frequency	Percentage	Use average daily	Average of Time (year)
Never	178	75.4	--	--
I am smoking	23	9.7	10.9	19.9
I used to	35	14.8	12.7	6.8

The prevalence of bone and joint complaints in each age group is presented in Table 5. There was no significant difference in the percentage of bone and joint complaints between different age groups. Overall, bone and joint complain (78.4%), bone and joint pain (72%), knee joint pain (52.5%), Joint stiffness (49.2%), and shoulder joint pain (45.8%) were the most common types of bone and joint complains in studied patients.

The percentage of disease intensity and restriction following pain is summarized in Table 3. Most veterans have complained about the intensity of annoying and intolerable pain (73.9%). Furthermore, musculoskeletal pain is getting worse in 66.9% of veterans during activities. Approximately 68.8% of veterans wake up due to musculoskeletal pain.

Table 3: Prevalence of intensity and restriction following pain for complaining veterans

Variable	Percentage
Musculoskeletal pain going worse in the morning	54.1
Musculoskeletal pain going worse during activities	66.9
Waking up because of musculoskeletal pain	68.8
The intensity of annoying and intolerable pain	73.9
Restrictions due to the type or the number of activities in the present or past because of pain, sensitivity, etc.	55.7
Perfect adaptations with problems (pain, sensitivity, etc.)	55.2

Table 4: The relative prevalence of osteoarthritis based on different age groups

Type of the Disease	Age Group (year)			Total
	40-49	50-59	≥ 60	
osteoarthritis at least in one joint (%)	82(69.5%)	72(69.2%)	15(71.4%)	169(69.5%)
dorsal dick osteoarthritis	1(0.8%)	0(0%)	0(0%)	1(0.4%)
spinal osteoarthritis	2(1.7%)	2(1.9%)	0(0%)	4(1.6%)
shoulder osteoarthritis	1(0.8%)	1(0.8%)	0(0%)	2(0.8%)
wrist osteoarthritis	0(0%)	2(1.9%)	0(0%)	2(0.8%)
foot osteoarthritis	1(0.8%)	0(0%)	0(0%)	1(0.4%)
neck osteoarthritis	23(19.5%)	30(28.8%)	5(23.8%)	58(23.9%)
hand osteoarthritis	0(0%)	1(0.8%)	0(0%)	1(0.4%)
hip osteoarthritis	1(0.8%)	3(2.9%)	0(0%)	4(1.6%)
knee osteoarthritis	70(59.3%)	57(54.8%)	15(71.4%)	142(58.4%)

The relative prevalence of osteoarthritis based on different age groups is shown in Table 4. Osteoarthritis in at least one joint was the most common type of osteoarthritis in each age group. 69.5% of veterans had osteoarthritis in at least one joint. Knee osteoarthritis was the second most common type of osteoarthritis in each group. It has been found in 58.4% of all veterans. The prevalence of neck osteoarthritis

in all veterans was 23.9%.

The prevalence of osteoarthritis is also considered in men with different age groups (Table 6). Similarly, osteoarthritis in at least one joint was the most common type of osteoarthritis in each age group. Knee osteoarthritis was the second most common type of osteoarthritis in each group.

Table 5: The prevalence of bone and joint complaints in the last 7 days based on the age group.

Type of implication	Percentage in age groups			Total
	40-49 years	50-59 years	≥60 years	
Bone and joint complain	77.1	81	72.2	78.4
Bone and joint pain	73.7	72	61.1	72
Joint inflation	28.8	32	27.8	30.1
Joint stiffness	47.5	50	55.6	49.2
Shoulder joint pain	46.6	47	33.3	45.8
Shoulder joint stiffness	21.2	26	16.7	22.9
Pain due to pressure in the shoulder	30.5	29	16.7	28.8
Elbow joint pain	26.3	22	22.2	24.2
Elbow joint inflation	6.8	8	5.6	7.2
Elbow joint stiffness	10.2	12	11.1	11
Pain due to pressure in Elbow	12.7	17	22.2	15.3
Wrist joint pain	24.6	27	27.8	25.8
Wrist joint inflation	7.6	10	11.1	8.9
Wrist joint stiffness	8.5	14	22.2	11.9
Pain due to pressure in the wrist	14.4	20	16.7	16.9
Pain in the hands and fingers joints	23.7	25	16.7	23.7
Inflation in the hands and fingers joints	12.7	6	11.1	9.7
Stiffness in the hands and fingers joints	9.3	14	11.1	11.4
Pain caused by pressure in the hands and fingers joints	13.6	17	16.7	15.3
Pelvic joint pain	33.1	28	16.7	29.7
Pelvic joint stiffness	11.9	19	11.1	14.8
Pain caused by pressure in the pelvic	19.5	28	22.2	23.3
Knee joint pain	50.8	55	50	52.5
Knee joint inflation	18.6	22	27.8	20.8
Knee joint stiffness	16.9	29	38.9	23.7
Pain due to pressure in the knee	28	34	33.3	30.9
Ankle joint pain	22.9	25	22.2	23.7
Ankle joint inflation	11.9	14	16.7	13.1
Ankle joint stiffness	10.2	18	22.2	14.4
Pain due to pressure in the ankle	15.3	22	16.7	18.2
Toes joint pain	16.9	21	16.7	18.6
Toes joint inflation	5.1	8	16.7	7.2
Toes joint stiffness	5.1	12	16.7	8.9
Pain due to pressure in the toes	12	18	27.8	15.7
Neck joint pain	37.3	39	16.7	36.4
Neck joint stiffness	18.6	21	16.7	19.5
Pain due to pressure in the neck	20.3	29	16.7	23.7
Spine joint pain	47.5	46	27.8	45.3
Spine joint stiffness	22	21	16.7	21.2
Pain due to pressure in the spine	29.7	32	16.7	29.7

DISCUSSION

Musculoskeletal implications negatively affect individuals' health, sanitary, and treatment systems [21]. In a previous study by Joshi and Chopra (2009), they considered the prevalence of osteoarthritis types in 8145 adult subjects in the Pune area located in India. Their results revealed that musculoskeletal pain was the most prevalent type of osteoarthritis in these individuals [22]. The results of the current study demonstrated that the prevalence of musculoskeletal complaints during the past 7 days among veterans is significantly high (78.4%). The most prevalent complaints from the veterans were related to Bone and joint pain, Knee, shoulder joint pains, and joint stiffness. The results of previous studies from different parts of Iran showed that the prevalence of joint complaints in the past 7 days is 54.13%, 41.9%, 42.8%, and 44.7% [23-26]. The comparison of the approached global studies indicated that the prevalence of musculoskeletal complaints in Iran is generally higher than in other Asian countries [27].

Table 6: Prevalence of osteoarthritis among men (Tehran COPCORD results)

Type of the Disease	Age Group (Year)		
	40-49	50-59	≥ 60
osteoarthritis at least in one joint (%)	39%	27%	16.6%
neck osteoarthritis	3.35%	2.41%	1.14%
hand osteoarthritis	7.14%	1.39%	0.5%
hip osteoarthritis	1.99%	0%	0.14%
knee osteoarthritis	36.32%	24.46%	14.49%

Based on the obtained results and final diagnosis of the following study, osteoarthritis, back pain, and pre-arthritis (69.9%, 30.5%, and 27.2%) had the highest frequency of the musculoskeletal diseases among the studied population. This finding confirmed the results of Tehran's study [27]. The results of a previous study on the rural population in Iran showed that approximately 20% of individuals suffered from osteoarthritis in at least one joint. The comparison of COPCPRD results in 17 countries revealed that Iran is second place in regards to osteoarthritis complications (with a frequency of 16.9%) [26[.

The results of this study demonstrated that the most prevalent type of osteoarthritis among veterans is knee (58.4%) and neck osteoarthritis (23.9%), respectively. Interestingly, knee osteoarthritis has been reported as one of the most prevalent rheumatic disorders among the Asian-Oceanic population [23]. The prevalence of knee osteoarthritis was previously calculated to be 5.8% in the rural areas of India, 22-28% in the urban areas of India, 25% in the rural populations in the north of Pakistan, 7.5, 9.2 and 10.6 in the rural, urban slumps and developed urban areas of Bangladesh, and 7.5% in China respectively [28-31]. The results of other studies on the Iranian population demonstrated that the prevalence of knee osteoarthritis in the southeast areas, rural areas, Sanandaj, and the whole country is 18.66%, 19.34%, 26.3%, and 15.5%, respectively [24-26, 28]. Recent studies have indicated that Iran is r ranked third for knee pain among 17 investigated countries [25]. According to previously accomplished data and results of the current research, the incidence of knee pain in veterans is significantly higher than that in the general population of Iran.

In this research, the prevalence of Gout arthritis in veterans was 0.4%. In previous studies, the prevalence of gout arthritis among individuals who lived in Tehran and Sanandaj was 0.13% and 0.12%, respectively [27, 32]. Dawatchi et al. indicated that Iran is ranked 11 among 17 countries regarding the prevalence of rheumatic diseases [25]. Further statistical analysis revealed that Indonesia (1.6%) and Australia (1.5%) had the highest frequency for this disease [25].

CONCLUSIONS

The results of this study described the frequency of musculoskeletal disorders and associated complaints among Iranian chemical veterans. Our data have revealed that the total prevalence of musculoskeletal disorders among Iranian veterans is significantly higher than the average of society. Due to the restrictions of these individuals and specific treatment needs, periodic screening tests, effective and proper nutrition, athletic and therapeutic interventions are strongly suggested to improve musculoskeletal disorders among chemical veterans.

Acknowledgments

The authors would like to acknowledge all members and staff who helped us with sample collection and technical supports. This work was supported by a grant provided by the Baqiyatallah University of Medical Science, Tehran-Iran (2015/2016).

Declaration of interest

No competing interest was declared by any of the authors.

References:

1. Samson DJ, Grant MD, Ratko TA, Bonnell CJ, Ziegler KM, Aronson N. Treatment of primary and secondary osteoarthritis of the knee. Evid Rep Technol Assess (Full Rep). 2007;157:1-157.

2. Nelson AE, Smith MW, Golightly YM, Jordan JM, editors. "Generalized osteoarthritis": a systematic review. Seminars in arthritis and rheumatism; 2014: Elsevier.

3. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis & Rheumatism. 1986;29(8):1039-49.

4. Buckwalter JA, Lane NE. Aging, Sports, and Osteoarthritis. Sports Medicine and Arthroscopy Review. 1996;4(3):276-87.

5. Panahi Y, Alishiri GH, Bayat N, Hosseini SM, Sahebkar A. Efficacy of Elaeagnus Angustifolia extract in the treatment of knee osteoarthritis: a randomized controlled trial. EXCLI journal. 2016;15:203.

6. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. Arthritis & Rheumatism. 1995;38(8):1134-41.

7. Srikanth VK, Fryer JL, Zhai G, Winzenberg TM, Hosmer D, Jones G. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. Osteoarthritis and cartilage. 2005;13(9):769-81.

8. Walker J, Campbell C, Buenaver L, Hand M, Edwards R, Smith M. (537) Race, pain and pain catastrophizing among African Americans and non-Hispanic Whites with osteoarthritis pain. The Journal of Pain. 2016;17(4):S108-S9.

9. Kerkhof H, Bierma-Zeinstra S, Arden N, Metrustry S, Castano-Betancourt M, Hart D, et al. Prediction model for knee osteoarthritis incidence, including clinical, genetic and biochemical risk factors. Annals of the rheumatic diseases. 2014;73(12):2116-21.

10. Lee JY, Harvey WF, Price LL, Paulus JK, Dawson-Hughes B, McAlindon TE. Relationship of bone mineral density to progression of knee osteoarthritis. Arthritis & Rheumatism. 2013;65(6):1541-6.

11. Bae KJ, Gong HS, Kim KW, Kim TK, Chang CB, Jang HC, et al. Evaluation of femoral neck bone mineral density and radiographic hand and knee osteoarthritis in a Korean elderly population. Clinics in orthopedic surgery. 2014;6(3):343-9.

12. Hussain SM, Cicuttini FM, Bell RJ, Robinson PJ, Davis SR, Giles GG, et al. Incidence of total knee and hip replacement for osteoarthritis in relation to circulating sex steroid hormone concentrations in women. Arthritis & Rheumatology. 2014;66(8):2144-51.

13. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. Nature Reviews Rheumatology. 2012;8(12):729-37.

14. Xie L, Lin AS, Kundu K, Levenston ME, Murthy N, Guldberg RE. Quantitative imaging of cartilage and bone morphology, reactive oxygen species, and vascularization in a rodent model of osteoarthritis. Arthritis & Rheumatism. 2012;64(6):1899-908.

15. Peregoy J, Wilder FV. The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. Public health nutrition. 2011;14(04):709-15.

16. Marks R. Knee Osteoarthritis, Obesity and Exercise Therapy-A Complex Issue. J Obes Eat Disord 2: 2. doi: h ttp. dx doi org/104172/2471-8203100007. 2016.

17. Somani S, Babu S. Toxicodynamics of sulfur mustard. International journal of clinical pharmacology, therapy, and toxicology. 1989;27(9):419-35.

18. Kehe K, Steinritz D, Balszuweit F, Thiermann H. Long-Term Effects of the Chemical Warfare Agent Sulfur Mustard. Chemical Warfare Toxicology2016. p. 179-90.

19. Balali-Mood M, Hefazi M. Comparison of early and late toxic effects of sulfur mustard in Iranian veterans. Basic & clinical pharmacology & toxicology. 2006;99(4):273-82.

20. Haskell SG, Ning Y, Krebs E, Goulet J, Mattocks K, Kerns R, et al. Prevalence of painful musculoskeletal conditions in female and male veterans in 7 years after return from deployment in Operation Enduring Freedom/Operation Iraqi Freedom. The Clinical journal of pain. 2012;28(2):163-7.

21. Mathew AJ, Chopra A, Thekkemuriyil DV, George E, Goyal V, Nair JB, et al. Impact of musculoskeletal pain on physical function and health-related quality of life in a rural community in south India: A WHO-ILAR-COPCORD-BJD India Study. Clinical rheumatology. 2011;30(11):1491-7.

22. Joshi VL, Chopra A. Is there an urban-rural divide? Population surveys of rheumatic musculoskeletal disorders in the Pune region of India using the COPCORD Bhigwan model. The Journal of rheumatology. 2009;36(3):614-22.

23. Haq SA, Davatchi F, Dahaghin S, Islam N, Ghose A, Darmawan J, et al. Development of a questionnaire for identification of the risk factors for osteoarthritis of the knees in developing countries. A pilot study in Iran and Bangladesh. An ILAR–COPCORD phase III study. International journal of rheumatic diseases. 2010;13(3):203-14.

24. Sandoughi M, Zakeri Z, Tehrani Banihashemi A, Davatchi F, Narouie B, Shikhzadeh A, et al. Prevalence of musculoskeletal disorders in southeastern Iran: a WHO-ILAR COPCORD study (stage 1, urban study). International journal of rheumatic diseases. 2013;16(5):509-17.

25. Davatchi F, Sandoughi M, Moghimi N, Jamshidi AR, Tehrani Banihashemi A, Zakeri Z, et al. Epidemiology of rheumatic diseases in Iran from analysis of four COPCORD studies. International journal of rheumatic diseases. 2015.

26. Tehrani-Banihashemi A, Davatchi F, Jamshidi AR, Faezi T, Paragomi P, Barghamdi M. Prevalence of osteoarthritis in rural areas of Iran: a WHO-ILAR COPCORD study. International journal of rheumatic diseases. 2014;17(4):384-8.

27. Davatchi F, Jamshidi A-R, Banihashemi AT, Gholami J, Forouzanfar MH, Akhlaghi M, et al. WHO-ILAR COPCORD study (stage 1, urban study) in Iran. The Journal of rheumatology. 2008;35(7):1384-90.

28. Davatchi F, Tehrani-Banihashemi A, Jamshidi A-R, Chams-Davatchi C, Gholami J, Moradi M, et al. The prevalence of oral aphthosis in a normal population in Iran: a WHO-ILAR COPCORD study. Arch Iran Med. 2008;11(2):207-9.

29. Chopra A, Patil J, Billempelly V, Relwani J, Tandle H. Prevalence of rheumatic diseases in a rural population in western India: a WHO-ILAR COPCORD Study. The Journal of the Association of Physicians of India. 2001;49:240-6.

30. Fransen M, Bridgett L, March L, Hoy D, Penserga E, Brooks P. The epidemiology of osteoarthritis in Asia. International journal of rheumatic diseases. 2011;14(2):113-21.

31. Farooqi A, Gibson T. Prevalence of the major rheumatic disorders in the adult population of north Pakistan. Rheumatology. 1998;37(5):491-5.

32. Moghimi N, Davatchi F, Rahimi E, Saidi A, Rashadmanesh N, Moghimi S, et al. WHO-ILAR COPCORD study (stage 1, urban study) in Sanandaj, Iran. Clinical rheumatology. 2015;34(3):535-43.

The article was received on june 2, 2020, and accepted for publishing on September 23, 2020.

ORIGINAL ARTICLES

CoViD-19 disease, Romanian health system response to outbreak and economic impact

Laura Bostangiu (Petcu)[1], Alexandru I. Iordache[2], Nicolae D. Garofil[3], Raluca S. Costache[3]

Abstract: *The pandemic called COVID-19 disease has an exponential course since the first cases were reported showing in 9th of May, 2020, more than 4 million cases of COVID-19. United States and European Council (EC), together with other European Union institutions, were closely monitoring the situation in order to take quick action.*

Objective: The aim of this article is to analyze the response to COVID 19 pandemic outbreak in term of strategy and money flow of Romanian health system in order to identify the strength and weakness and prepare for other similar provocative challenges.

Global and national strategy: United States Government is delivering a comprehensive package of services to support international partners around the world in combatting this disease adding American expertise for global benefit, saving lives by improving international partners abilities to respond to the COVID-19, and reducing secondary impacts. Meanwhile European Union is focused on 6 major coordinates limit the spread of the virus, ensure and provide medical supplies, decrease negative economic impact, support jobs, promoting research and help European citizens to repatriate. Despite all negative elements a proper and relatively quick response of Romanian Public Health System was noticed and the taken measures were harmonized and synchronized with the European coordinates, prioritize initiatives, build an action plan, establish a communication plan, workforce optimization and management strategy.

Conclusion: Global shock needs global response, with little or no government interventions, economic costs will be huge.

Keywords: *COVID-19, SARS-CoV-2, Coronavirus, pandemic financial impact, hospitalization cost*

BACKGROUND

COVID-19, coronavirus disease, is caused by a new type of coronavirus (SARS-CoV-2) and it was first identified in China in December 2019 when an outbreak in the municipality of Wuhan was described as quickly spreading to other regions of China and worldwide [1, 2]. By 7 of January 2020, isolated cases had appeared in some European Union (EU) member states. At the end of February 2020, Italy reported a significant increase of coronavirus disease (COVID-19) cases concentrated in two of the northern regions of the country [3]. By March 2020, all European Union (EU) member states had reported an exponential increase of COVID-19 cases. European Council (EC), together with other EU institutions, is closely monitoring the situation in order to take quick action [3]. This includes approving of relevant European

[1] The Bucharest University of Economic Studies, Romania
[2] Fundeni Clinical Institute, Bucharest, Romania
[3] Carol Davila University of Medicine and Farmacy, Bucharest, Romania

Corresponding author: Laura Petcu
laurabostangiu@yahoo.com

Union legislation and ongoing coordination with member states to share information, assess needs and ensure a coherent European Union wide response under direct coordination of The World Health Organization (WHO) [3]. On 11 March 2020, the World Health Organization (WHO) declare COVID-19 as global pandemic with an important issue: in this declaration they were talking about geographic spread, and not about the severity of the disease [4].

The pandemic called COVID-19 disease has an exponential course since the first cases were reported showing in 9th of May, 2020, more than 4 million cases. Disease caused by the new coronavirus that was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, COVID-19, have been reported globally with more than 286,000 deaths in 180 countries, including all United States with 1,4 million persons recovered [3, 5].

As epidemiological pattern, all groups of ages are at risk for infection including here severe form of disease, even death. However, seems that the probability of fatal disease is highest in people aged more than 65 years, those with comorbidity and those living in a nursing home or long-term care facility [6, 7, 8]. Of underlying condition, especially when those are not controlled is appropriate to mention as major risk factor for severe or critical COVID-19 disease [3-7]: Hypertension, Obesity, Chronic respiratory disease, Cardiovascular disease, Cancer, Renal disease, Diabetes [9]. As for diagnose WHO recommends as gold standard nasopharynx samples to be used in order to detect SARS-CoV-2. Nasal swabs or oropharyngeal swabs may be acceptable alternatives [9]. Lower respiratory tract samples have a demonstrated higher sensibility than upper tract samples, but WHO recommend not to obtain because of concerns about aerosolization of virus during collection procedures. Regarding treatment, no drug has been proven to be safe and effective for treating COVID-19. There are no Food and Drug Administration (FDA) or EMEA -approved drugs specifically to treat patients with COVID-19. In the medical literature, reports have appeared claiming or promoting successful treatment of patients with COVID-19 using a variety of agents [6, 8, 9]. A single conclusion has emerging: definitive clinical trial data are needed to identify optimal treatments for this disease. General clinical management of patients with COVID-19 includes infection prevention, control measures and supportive care, including supplemental oxygen and mechanical ventilatory when indicated. In is also compulsory to mention that as in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider [6, 7, 9, 10, 11, 12].

Behind the medical challenge generated by COVID-19 pandemic and all concerns, analyst anticipate an economic crisis. That is why worldwide governments are involved in generate measures in order to decrease negative economic impact.

OBJECTIVE

The aim of this article is to analyze the response to COVID 19 pandemic outbreak in term of strategy and money flow of Romanian health system in order to identify the strength and weakness and prepare for other similar provocative challenges.

GLOBAL ANALYSIS AND DISCUSSION

If we have to define the concept of support, probably in the last 50 years the United States (U.S.) will fit perfectly since they have been the largest contributor to global health security [4]. US built the foundation upon which the global health system is based, contributing more than $140 billion in global health assistance only in the last century and nowadays demonstrate leadership in fight to COVID-19 pandemic. From the beginning of the outbreak of COVID-19, the United States government provided more than $500 million in assistance specifically aimed to support anti-pandemic measures [3, 4, 13, 14].

But this is not all, US Government is delivering a comprehensive package of services to support international partners around the world in combatting this disease. The program should add American expertise for global benefit, saving lives by improving international partners abilities to respond to the COVID-19, and reducing secondary impacts [13, 14].

The strategy mentioned is focus to: Save lives by increasing international partners ability to respond to the pandemic; Reduce secondary impacts of the disease; Promote U.S. leadership for global benefit [13].

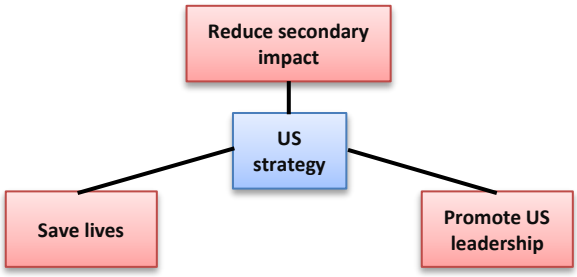


Figure 1: US Strategy for COVID-19 [13, 14]

The United States (US) was delivering a SAFE and more secure world from COVID-19 program as is state in the

following table [13,14].

The European Union's (EU) response to COVID-19 outbreak focuses on 6 major coordinates as they are mentioned above [15,16].

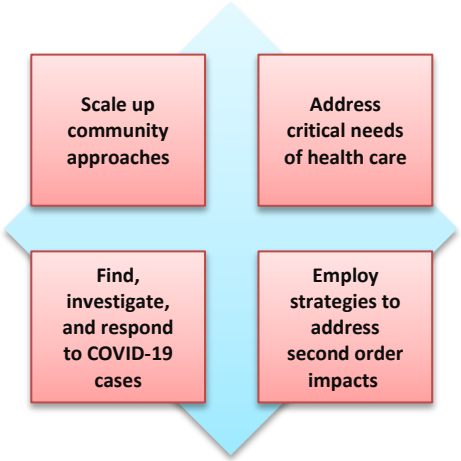


Figure 2: US program SAFE for a safer and more secure world from COVID -19

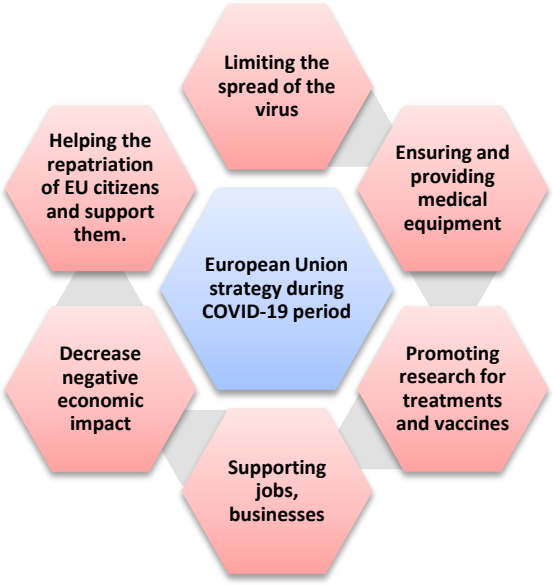


Figure 3: European Union strategy for COVID-19 disease [15, 16]

In order to slow down the transmission of the virus, European Union (EU) leaders agreed on a coordinated temporary restriction of non-essential travel to the EU for 30 days. The travel of European citizens outside the EU acquires negative recommendation. To coordinate the EU response to the COVID-19 outbreak the following measures were taken [15, 16, 17]:

- The Council activated the EU an integrated political crisis response (IPCR) with mandatory weekly roundtables gathering EU institutions, EU agencies experts and representatives of member states

- European Commission and the Council are gathering contact and coordination between relevant national ministries

- The European Centre for Disease Control (ECDC) quantify daily risk assessments and epidemiological updates for the EU population.

By using the union civil protection mechanism, the EU has: coordinated the deployment of medical teams to most affected areas, facilitated the sourcing for additional protective equipment, especially medical masks, activated the Emergency Response Coordination Centre, to coordinate support 24/7, created a new common European reserve of emergency medical equipment including also ventilators and lab supplies. More than €300 million was allocated for research and support initiatives in medical field and a European COVID-19 data portal was launched to ensure the rapid collection and sharing of available research data [15, 16, 18, 19].

The EU and its member states are taking action to minimize the negative impact of outbreak on the economy. On 9 April 2020, the Eurogroup generated, three immediate safety nets, worth €540 billion for: protect and generate new jobs and businesses in member states. The EU is putting forward temporary support to mitigate unemployment risks in an emergency (SURE) to help people keep their job during the crisis. The scheme consists of loans to member states of up to €100 billion to cover the costs related to the creation or extension of national short-time work schemes. European Investment Bank (EIB) Group to create a pan-European guarantee fund providing that way loans up to €200 billion for companies with a focus on small and medium-sized enterprises (SMEs) throughout the EU [15, 17, 18, 19].

European Stability Mechanism set up Pandemic Crisis Support based on an existing credit line, which will include loans available to all euro area member states up to 2% of their internal product estimated at €240 billion. The EU also has increased its budget for 2020, with €3.1 billion as response to the COVID-19 crisis [18, 19]. This additional fund will be used to purchase and distribute medical supplies, including protective gear and ventilators, boost the production of testing kits, build mobile hospitals, transfer patients for treatment in between member states, repatriate EU citizens stranded abroad [19].

The EU has also adopted measures to ensure additional flexibility in the use of structural funds. On behalf of

Coronavirus Response Investment Initiative Plus member states can transfer money between different capital lines in order to meet their needs, resources can be redirected to the most affected regions and the opportunity request up to 100% financing from the EU budget between 1 July 2020 and 30 June 2021 for programs involving measures with impact in the COVID-19 pandemic [15, 16]. The EU and its member states were working to repatriate more than 650.000 EU citizens stranded abroad. EU countries and EU delegations provide consular assistance to help EU citizens return home, providing 75% of the costs of the return flights and add measures in order to help them to cross EU borders [16].

Although Li at all [10] estimate that 86% of all infections were undocumented prior to 23 January 2020, when travel restrictions were beginning per person, the transmission rate of undocumented infections was 55% from all of documented cases. Due to their increasing factor, undocumented patients were the source for 79% of documented cases [12]. They conclude that two favorable condition are rising: existing estimates of case-fatality rates might be over-estimate and a grade of immunity is present in the system [12]. But they underline also that probably when interventions started in Europe and US the virus was already widely spread and simulation regarding on how measures of suppression will flatten the curve in the short period may be over-optimistic [12].

NATIONAL STRATEGY AND HEALTH ECONOMIC IMPACT

Geopolitical context

Romania is one of the countries that has to face the infection of the population with the new coronavirus. The most recent statistics shows that Romania has around 4.7 mil people that lives outside the country and they are spread all over the world [3, 19, 20].

According to statistics reported by the Ministry of Foreign Affairs from the total number of the Romanians that lives outside the borders in Italy lives 1.206.938 people which means that around 25% are located in the country that has the largest outbreak of the pandemic, and around 19% lives and works in Spain. This is the reason why Spain has become the second deadliest hotspot for COVID-19 after Italy with 27.967 cases and its death toll reached 24.824 on 1st of May 2020 [19, 20].

Having Italy as a "model "of how fast the virus spread among the citizens, medical stuff and hospitals and that no real actions were made until the spread was out of control, Romania introduced lockdown measures at an early stage in the outbreak: cancelled almost all flights in and out of the country, starting with the ones from the red zone, authorities were also quick to close bars, restaurants, cinemas and schools. Police were urging people to stay at home [19, 20].

The representatives of the Intersectoral Committee for the Prevention and Limitation of Diseases with the New Coronavirus (COVID-19), together with the representatives of the authorities responsible for this field, held a teleconference on the evening of February 22, 2020, taking into account the evolution of cases in Italy areas where many Romanian citizens are or traveling from [19].

After this point the public health authorities included persons arriving in Romania from the affected localities in the Veneto region and the province of Lodi / Lombardy or who have traveled to these localities in the last 14 days, in the category of those who must stay in quarantine for 14 days after entering the country. These measures were similar to those applied by the Italian authorities. At the same time, upon arrival in Romania, all asymptomatic passengers from the affected areas, respectively Hubei (China) or from 11 regions of Italy will be sent to quarantine for a period of 14 days [1, 2, 19].

New measures were sent by the Ministry of Health to the health units and family doctors, through the county and Bucharest public health directorates which included [21]:

- measures to control and prevent infection with the new coronavirus at land, sea / river and air border crossings. The Ministry of Health provided the necessary medical staff at the border crossing points, with specialists from the public health directorates, including by secondment from other counties and health units;

- all persons, who fall within the definition of a suspicious case, should be reported immediately by all health units where they appear (emergency units, hospitals, family doctors) to the public health departments and the Monitoring Service within Emergency Situation Department (DSU);

- Ministry of Health completed the legislative framework with necessary measures for quarantine and for the management of suspected and confirmed cases of coronavirus infection (COVID-19);

- public information campaign on the new coronavirus infection;

- individual and collective prevention measures were taken and extended with a daily information bulletin on the evolution of the situation at international level and any additional measures taken by the Romanian authorities;

Also, on March 10, 2020 the Ministry of Health

operationalized the Operational Coordination Center, a unit that establishes in operational time the connection with the public health directorates and health units under the Ministry of Health subordination, to identify in real time the risk situations associated with COVID 19 infection and to establish measures that are required [20, 21].

The Operational Center had to provide up-to-date information and all the useful and vital information to establish the correct measures for the epidemic phases, real time stocks of medicines, medical equipment and disinfectants existing at national level in hospital units, the number of medical staff involved in the actions in order to limit the spread of infection, the number of free beds in infectious disease departments and Intesive Care Units [21].

Other important measure was to limit the scheduled hospitalizations in the hospitals coordinated by the Ministry of Health, in relation to the degree of bed occupancy (including ICU beds) and the local epidemiological evolution corroborated with daily report the situation of bed occupancy of the hospitals in the centralized electronic system of the Coordination Center. This measure was necessary both to ensure the capacity of hospitals to take over cases and to manage material and human resources correctly and efficiently [21].

Adequate public communication was ensured so that, during this period, the public could turn to hospitals only for emergencies. The aim was to avoid congestion in the sanitary units [21]. At that point was established a support network for infectious disease hospitals depending on the contagiousness of non-coronavirus cases. These hospitals are going to be support hospitals, in which patients will be transferred from the Infectious Diseases Hospital. In a first phase, was recommended that the support hospitals not be represented by the important emergency hospitals in the area, which can provide medical assistance for the other medical-surgical emergencies [21].

The Ministry of Health Plan also provides measures in case of extend of the crisis and in case of capacity exceed of Infectious Diseases Hospitals, as well regulations on the use of protective equipment [21].

On March 11, 2020 at the proposal of the Ministry of Health, the National Committee for Special Emergency Situations issued an order for including the temporary suspension, for a period of 6 months, of distribution, outside Romania, of medicines, medical devices and sanitary materials essential in prevention and treatment conditions associated with COVID-19 infection [21].

This measure is part of the action plan of the Ministry of Health which aims to provide adequate and continuous stocks of medicines, medical devices and essential medical materials in this situation. The list was going to be established together with the experts from the specialized commissions of the ministry, taking into account in particular, medicines such as: antivirals, anti-inflammatory, antibiotics, antipyretics, antifungals, anesthetics, sedatives, as well as other medicines considered necessary in the treatment of cases of COVID-19 and their complications [21].

The list also included medical supplies and medical devices such as overalls, gloves, syringes, masks, goggles, disinfectant solutions, as well as other medical supplies and devices identified as necessary for the management of COVID-19 cases [21].

The Centre for Supervision and Control of Transmissible Diseases issued recommendations which were published on 12 March 2020 [21].

• The preventive measures considered as most effective include: frequent hygiene of the hands with hydro-alcoholic substances through friction if hands are not visibly dirty, or with water and soap if the hands are dirty; avoid touching eyes, nose and mouth; practice respiratory hygiene by coughing or sneezing in the elbow, or use napkin/tissues and throw it away immediately; wearing a mask if the person has respiratory symptoms and ensuring in such case the hygiene of the hands after removing the mask; maintain the social distance of minimum 1 meter from the persons with respiratory diseases.

• Protective Personal Equipment (PPE) must be used based on exposure risk and based on the dynamic of transmitting the pathogen agent. The overall use of PPE will have a supplementary impact on the lack of supplies of PPE.

• The state office mentions that for the people with no symptoms, it is not recommended to use masks of any type. The wearing of the masks when it is not recommended can cause useless costs, a burden on purchases and can create a false feeling of security that can lead to the neglect of other essential prevention measures.

Threats and weaknesses

In order to analyze the response to COVID-19 outbreak, we identify a panel of weaknesses which conduct in early stage to quick spread of the virus and generate uncontrolled local outbreaks:

A panel of negative elements should be considered when we analyze the Romanian Health System response to outbreak.

• Low infrastructure in term of hospitals, circuits, Intensive Care Units and number of available PPE for health workers

• Administrative human resources with lack of management skills, unable to generate procedures and coordinates the Public Health Departments

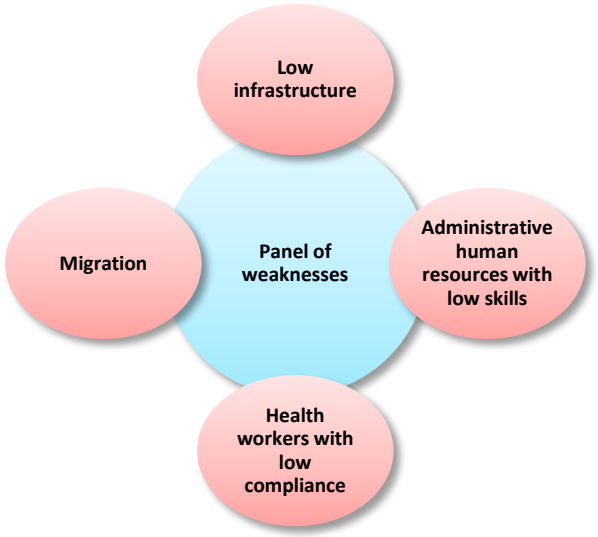


Figure 5: Panel of weaknesses regarding response to COVID-19 outbreak

• Health workers with low compliance at medical information and epidemiologic resources, unwilling in many situations to respect the new statement measures and legislation provided by Ministry of Health and National Health Institute

• Not as a last item, migration, the return of Romanian citizens from pandemic areas of Europe crossing the borders using in many situations false document of false declaration and being extremely low compliant of rules and measures, regarding quarantine or in self isolation

Ministry of Health strategy

Despite those negative elements a proper and relatively quick response of Public Health System and it could say that the taken measures were harmonize and synchronize with the European coordinates. Romanian Government through Ministry of Health established 5 directions as a strategy which enhanced the national response to COVID-19 disease.

When "everything is vital and important", Ministry of Health and the other public institution involved in fighting the pandemic had to prioritize the initiatives. In order to do that a Plan of measures for the preparation of hospitals in the context of the COVID-19 Coronavirus epidemic was approved. This plan was the base of the strategy framework regarding the hospitals that can treat patients infected with COVID19. In collaboration with the local public administration authorities, based on the local analysis of patient care capacities, was generated and approved the List of support hospitals for COVID - 19 positive patients requiring treatment for specific pathologies (eg heart disease, orthopedics, etc.)

Thus, a number of 57 hospitals/outpatient departments/ buildings, 44 maternity hospitals, 60 hospitals and centers for performing dialysis procedures in all counties of the country and Bucharest were identified and designated as support units.

Supportive cases of COVID 19 that require medical care for other pathologies are also treated in support hospitals.

As a first step, designated support hospitals are non-emergency medical units that can provide medical care for other medical and surgical emergencies. Included in the network of support hospitals, municipal/city units and hospitals in other counties mainly those with Infectious Diseases departments, as well as hospitals in other networks than the Ministry of Health (Ministry of Transport, Ministry of National Defense, private health units).

Figure 6: Romanian Ministry of Health direction strategy

"The plan of measures for the preparation of the hospitals was elaborated by the specialists within the specialized commissions ICU, infectious diseases and specialists within the Ministry of Health, based on the recommendations of the WHO and EC. I asked the managers of the health units, but also the public health departments, the ambulance services to inform the medical and auxiliary staff, repeatedly, the procedures to be followed in this crisis situation, all the existing measures in the plan of measures, especially the

regulations. regarding the prevention measures and the correct use, depending on the exposure, of the medical staff, but also of the auxiliary" [21].

Also, all health units from public and private system have the obligation to ensure the provision of medical care to all patients, in accordance with the disposition of the approved plan of measures. Any refusal to ensure the provision of medical care according to the specific attributions it's going to be sanctioned according to the legal disposals [21].

Develop an action plan

In order to be able to control and establish the right measures Ministry of Health with the help of the Operational Center were able to collect in real time the stocks of medicines, medical equipment and disinfectants existing at national level from the hospitals, the number of medical staff involved and the number of free beds in infectious disease departments and Intensive Care Units.

As we could see the plan is to deliver the equipment or medication where is most needed, or to purchase the equipment or medication where is most needed.

In order to simplify the Purchases of materials, medicines and equipment necessary to combat the COVID-19 pandemic, during the state of emergency, are made directly by the central and local public authorities, the legal entities in which the state is the majority shareholder, the public health directorates, the health units, as well as the National Administration of Penitentiaries and the units subordinated based on the obligation to draw up a note justifying the necessity of the acquisition.

Regulations have been approved on the use of personal protective equipment (PPE) at the level of the health unit, rationally and correctly, depending on the department, staff and type of activity. Thus, in the context of COVID-19, personal protective equipment should be used based on the risk of exposure (eg type of activity) and the transmission dynamics of the pathogen (eg contact, drops or aerosols).

The type of PPE used when caring for patients with COVID-19 will vary depending on the situation, healthcare staff and work carried out. Medical personnel involved in the direct care of patients should use the following PPE: gowns, gloves, mask and eye protection (goggles or face shield).

Specifically, for aerosol-generating procedures for patients with COVID-19 (eg: intubation, noninvasive ventilation, tracheostomy, cardiopulmonary resuscitation, manual ventilation before intubation, bronchoscopy, gastroscopy, and COVID PCR testing) medical personnel should use as protection, gloves, gowns, masks FFP2 and FFP3; waterproof aprons will also be used if overalls/gowns are not waterproof.

Build a communication plan

Creating a communication plan to collect key information from stakeholders regarding the planned initiatives and the capacity building was an important step in order to manage media coverage of the topics related to the new coronavirus infection.

Therefore, by the Decision of the National Committee for Special Emergency Situations no. 2 from February 24 2020 The Strategic Communication Group was established and it consists experts from several institutions like Ministry of Health, Ministry of Defense, Emergency Situation Department, National Institute of Public Health, General Inspectorate for Emergency Situations.

In order to support the population a Free Direct Line (Telverde) has become operational for coronavirus information in coordination of National Institute of Public Health and people can request information on how the virus manifests itself, how to prevent the disease and other details related to preventive behavior. However, the experts informed the populations that if they have any health problems or suspect that you may be infected, to continue to call the emergency number.

Workforce optimizations strategies

The evolution of the epidemiological situation determined by the spread of coronavirus on the Romanian territory, as well as the declaration of the pandemic by the World Health Organization determined the public health risk assessment for the next period as a result of the increased number of active surveillance, early detection , isolation and treatment of positive COVID 19 cases, follow-up of contacts and prevention of the continuous spread of the infection which imposes the need for additional staff involved in these activities [3, 20].

Therefore, at the proposal of the Ministry of Health, the Government of Romania approved the supplementation with 2000 positions within the county public health directorates and county ambulance services for a determined period of 6 months with 2000 positions [21].

In the current situation, the operative crews of the ambulance services are involved both in the transport of patients confirmed with COVID-19, and in the collection of samples from people in quarantine or home isolation.

Also, the staff of the public health directorates ensures the epidemiological triage from the border crossing points, monitors the self-isolated persons at home, monitors the

quarantined persons, collects field samples from the persons corresponding to the case definition for testing for COVID-19.

Currently, the number of posts allocated and fully distributed by ministerial order for the county and Bucharest public health departments is 3.862, and for the county ambulance services and the Bucharest-Ilfov Ambulance Service is 11.733 posts [21].

In order to prepare the health units and the health system and the emergency system to cope in case of an exponential increase of the cases with COVID and in case of signaling a personnel deficit in some areas it was necessary to detach the health personnel to cover the needs in the area. Therefore, specialized medical staff, primary care physicians, specialists or residents, medical staff, health auxiliaries and medical staff with higher education (chemists, biologists, biochemists, physicists, pharmacists and balneo-physiotherapists) employees of public health units are about to be seconded or delegated to other public health units that have a major staff shortage.

Management strategies

The socks which make up the pandemic cause a sharp drop in consumption and investment all over the world. With the previous experiences of pandemics, governments across the world have exercised a stronger caution towards outbreak by taking early measures, such as straitening the health infrastructure to prevent the outbreak.

With the measures taken by MoH regarding the fact that many hospitals were force to close outpatient departments and postponing or canceling elective visits and procedures, it's most likely that the financial viability to be threatened, especially for those with preexisting financial challenges and those heavily reliant on revenue from outpatient and elective services.

A 2018 report from the Agency for Healthcare Research and Quality suggested that elective admissions accounted for more than 30% of total inpatient hospital revenue [22]. Elective procedures, especially orthopedic and cardiac surgical procedures, are among the most profitable services for hospitals[23]. By one estimate, hospitals earn $700 more for elective admissions than for admissions through the emergency department [24]. Furthermore, for many hospitals, outpatient revenue now equals inpatient revenue, elective or otherwise [25].

Also in Romania though reduced outpatient and elective revenue may be partially offset by higher hospital and intensive care unit occupancy during the COVID-19 pandemic, and by an increase in services after the pandemic ends, this may not mitigate losses (particularly given the need for surge personnel and resources) or be evenly distributed across hospitals.

The COVID-19 pandemic represents an unprecedented medical and economic challenge for the Romanian health care system. In the absence of robust and sustained governmental support, almost all hospitals will experience financial difficulties.

But hospitals that are smaller, independent, rural, and have critical access status are particularly at risk. Policymakers provided dedicated support to these hospitals to access funds and allocated additional funding to them during the COVID-19 pandemic.

Table 1: Global Healthcare Systems Data

Country	Australia	New Zealand	Germany	UK	US	Romania
Healthcare expenditures per capita	AU $7845 ($5,612)	NZ $5,892 ($4,015)	€4,544 ($4,924)	£2,989 ($2332)	$10,612	€1,029 ($1,115)
Medical practitioners per 1,000 people	3,94	3,35	4,3	2,8	2,6	2,8
Beds per 1,000 people	3,9	2,6	6	2,5	2,8	6,8
Population aged +60 (%)	21,4	21,3	28,2	23,8	17	22,6

Source: https://insse.ro/cms/files/publicatii/Romania_in_cifre_breviar_statistic_2018.pdf, https://www.ibisworld.com/industry-insider/coronavirus-insights/effects-of-covid-19-on-global-healthcare-systems/ [26]

According to the Medical Group Management Association, 97% of medical group practices have experienced a negative financial impact directly or indirectly related to COVID-19. On average, these practices report a 55% decrease in revenue and a 60% decrease in patient volume since the start of the COVID-19 public health emergency [20, 24, 25].

In order to evaluate if Romania can face the expenditures due to COVID-19 outbreak we tried to compare data from different global healthcare system in their heroic and unprecedented ways to meet the challenges of COVID-19.

Hospitals and health systems face catastrophic financial challenges in light of the COVID-19 pandemic. We undertook four analyses to better understand and quantify these financial challenges.

Including:

• the effect of COVID-19 hospitalizations on hospital costs;

• the effect of cancelled and forgone services, caused by COVID-19, on hospital revenue;

• the additional costs associated with purchasing needed personal protective equipment (PPE); and

• the costs of the additional support some hospitals are providing to their workers.

a) Net Financial Impact of COVID-19 Hospitalizations

At this time there are no official estimates of the net financial impact of COVID-19 hospitalizations but for the over 6,800 patients tested positive until end of April, an expense of over 77 million lei (approximate 15 million euros) is estimated by the Ministry of Health [21, 26].

Table 2: Expenditure on protective equipment against COVID-19

Equipment	LEI	Euro
Protective coveralls	50,5 mil	10,4 mil
Disposable gown	15,2 mil	3,1 mil
Disposable caps	876,000	180,000
Disposable boots	3,1 mil	653,000
Disposable sort	732,000	150,000
Disposable gloves	7,7 mil	1,6 mil
Protective eyewear	2,2 mil	453,000
Protective visors	3,1 mil	640,000
FFP2 Mask	19,4 mil	4,1 mil
FFP3 Mask	2,4 mil	510,000
Surgical Mask	36,9 mil	7,6 mil
Disinfectant	21,8 mil	3,1 mil
Total	**153,9 mil**	**32,5 mil**

Source: Ministry of Health data collection from territory 30 April, 2020[27]

b) Total Revenue Losses from Cancelled Surgeries and Other Services

As a result of cancelled hospital services due to the COVID-19 pandemic, hospitals stand to lose approximately $200 million lei (approximate 40 million euros) in revenue over a period of four months, from March to end of April 2020. This includes cancelled surgeries, various levels of cancelled non-elective surgeries and outpatient treatment, and reduced emergency department services [26].

c) Additional Costs Associated with Purchasing Needed PPE

In order to estimate future expenditures and budget allocation Ministry of Health is collecting regularly data from territory regarding the consumption and demand for equipment and supplies, such as PPE, which considerably increased as a result of the COVID-19 pandemic. Hospitals have incurred additional costs as they struggle to acquire additional supplies to meet the needs of their patients and staff. Moreover, current guidelines require all hospital workers to wear some PPE, regardless of whether they are in direct contact with COVID-19 patients. These guidelines increase the need and expense for PPE relative to normal operations.

d) Costs of Additional Support Some Hospitals are Providing to their Front-line Workers

The govern could not yet estimate the cost of support for front-line hospital workers in COVID-19 hotspots for costs of providing child care, housing, transportation, and medical screening and treatment for COVID-19 for front-line workers but measures were taken to provide such services for them [27].

This report attempts to quantify these effects over the short-term, which are limited to the impacts over a two-month period from March 1, 2020 to April 30, 2020.

Although the government moved quickly to provide relief and the budget expenditures was increase by 2,5 billion euros in order to fight the financial impact, more help is needed [26, 27].

This includes:

• 120 million euros were added in staff costs, and this includes the payment of the risk incentive of 500 euros gross per month for doctors, medical staff, paramedical staff, including auxiliary staff directly involved during the emergency.

• Social security expenditures from National House increased by over 1,4 billion euros (technical unemployment and other health expenditures).

• Expenditures on the reserve fund increase by 3 billion lei.

• The Ministry of Labor also receives 1,6 billion euros and the Ministry of Health 785 million euros.

Following the immediate measures and reallocations of the government, the Ministry of European Funds obtained following the negotiations with the European Commission, a package worth 1.16 billion euros, European funds that will be injected urgently into the Romanian medical system to contribute to the socio-economic measures taken by the Government during this period [15, 16, 26, 27].

The allocation is going to cover expenditures as following [15, 16, 26, 27]:

• 100 million euros reimbursement of the risk incentive of 500 euros gross per month for doctors, medical staff, paramedical staff, including auxiliary staff directly involved during the emergency;

• 350 million euros for reimbursements of the purchases of medical equipment (ventilators, injectors, COVID-19 tests, etc.) and protective equipment (masks, gloves, coveralls, etc.), with the possibility of increasing the allocation to 500 million.

• 682 million euros for the purchase of medical equipment and equipment for the coordination system of the national emergency system, by financing an IGSU project.

The World Bank has allocated more than $1.4 billion to support the efforts of European and Central Asian countries to combat the effects of the COVID-19 pandemic. As of April 2, 2020, it has been approved to allocate approximately $ 490 million to be distributed for new emergency response programs [15,16]. In addition, it was decided to reallocate approximately $ 925 million, which will be redistributed from existing projects and loans, as well as additional funding, to support countries working to combat the effects of the COVID-19 pandemic [15]. Ministry of Health has purchased equipment for medical protection and treatment to fight against COVID worth 29 million euros from projects financed by the World Bank in Romania [27].

CONCLUSIONS

Global shock needs global response, with little or no government interventions, economic costs will be huge. For decrease negative impact, Government spending should be as large as the predicted economic costs, focusing directly on cash disbursement to firms and households. Central banks should support financial the government, not just through their own reserves but also by printing money if necessary. It is clear state that no country has fiscal capacity to stand alone [28].

Government priority should be on health expenditure but as the specialist anticipated is mandatory to generate a strategy to flatten the contagion curve that may rise back in the end of 2020. The tasks of test 'at random' representative samples of the population to identify the most contagious groups and isolate immediately the more vulnerable (e.g. the old) should be in front of strategy. A global expand of intensive care capacity (both beds and equipment) by building new units or convert available other type of buildings (e.g. hotel, barracks, etc.) is needed. Another imperative measures is to relocate patient who need intensive care to non COVID hospitals in order to increase capacity of that one placed in concentrated aria of contagion in terms of human resources and infrastructure.

Romania has harmonized with WHO and European Union requirements regarding preventive measures and legislation for COVID-19 disease and show a major and continuous concern in increasing testing capacity although the number of experts in that field was decreasing year by year. Despite the major weaknesses Ministry of Health adopted the best measures in order to combat the negative impact of pandemic. A perfect management strategy was setup in local outbreaks areas, introducing military management in hospitals in which wrong management decision were taken in early stage of COVID-19 disease.

Ministry of Health registered an extremely rapid reaction in support healthcare workers, purchase medical equipment and ventilators challenging the other health systems that faced with the same health problem forcing in a positive manner Public Health System for a simultaneous high inflow of SARS-CoV-2 positive patient in terms of human resources and infrastructure (mobile hospitals for patient with no and mild symptomatology, intensive care units etc.).

As part of European Nation, Romanian Government realized the harmonization of institution using emergency state providing this way an outstanding panel of experts in critical domains which initiate the best decision in a proper time, find the measures and optimal solutions for access to European available funds, cover the huge economic cost, helping Health System to fight against a complete new disease and providing the support for return of citizens in respect of European laws and Human Rights Declaration.

***Aknowledgement**: This paper was co-financed by The Bucharest University of Economic Studies during the PhD program. Ministry of Health and the National Institute of Public Health support the research by providing the relevant data.*

All mentioned authors equally contributed.

JEL Classification: H51, I15, I18, I28

References:

1. Guan WJ, Ni ZY, Hu Y, et al. Characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32109013.

2. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167524.

3. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed April 9, 2020.

4. Washington Post "WHO declares a pandemic of coronavirus disease covid-19

5. https://www.worldometers.info/coronavirus/

6. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): cases in U.S. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html. Accessed April 9, 2020.

7. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): People who are at higher risk for severe illness. 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html. Accessed April 8, 2020.

8. Cai Q, Chen F, Luo F, et al. Obesity and COVID-19 severity in a designated hospital in Shenzhen, China. Preprints with the Lancet. 2020;[Preprint]. Available at: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3556658

9. Garg S, Kim L, Whitaker M, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019 - COVID-NET, 14 states, March 1-30, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):458-464.

10. Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020. Available at: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html. Accessed April 8, 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298251

11. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons for coronavirus disease 2019 (COVID-19). 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Accessed April 8, 2020

12. Ruiyun Li et al. (2020), Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2), Science, 16 March 2020, DOI: 10.1126/science. abb3221

13. https://www.usaid.gov/coronavirus

14. https://www.defense.gov/Explore/Spotlight/Coronavirus/

15. Coronavirus: European roadmap shows path towards common lifting of containment measures Brussels, 15 April 2020

16. Communication from the Commission – Temporary Framework for assessing antitrust issues related to business cooperation in response to situations of urgency stemming from the current COVID-19 outbreak C(2020) 3200 (OJ C 116 I, 8.4.2020, p. 7)

17. Rapid risk assessment: Coronavirus disease 2019 (COVID-19) pandemic: increased transmission in the EU/EEA and the UK – eighth update https://www.ecdc.europa.eu/en/publications-data/rapid-risk-assessment-coronavirus-disease-2019-covid-19-pandemic-eighth-update

18. guidelines on the optimal and rational supply of medicines to avoid shortages during the COVID-19 outbreak (C (2020) 2272 final)

19. Guidance on EU Emergency Assistance on Cross-Border Cooperation in Healthcare (C (2020) 2153 final).

20. World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak. Geneva: WHO; [1 March 2020]

21. Delaration of Minister of Health in local Press. http://www.ms.ro/comunicate/

22. Weiss AJ, Elixhauser A, Andrews RM. Characteristics of operating room procedures in US hospitals, 2011. Accessed April 4, 2020. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb170-Operating-Room-Procedures-United-States-2011.jsp

23. Merritt Hawkins. 2019 Physician inpatient/outpatient revenue survey. Accessed April 4, 2020. https://www.merritthawkins.com/uploadedFiles/MerrittHawkins_RevenueSurvey_2019.pdf

24. McHugh M, Regenstein M, Siegel B. The profitability of Medicare admissions based on source of admission. Acad Emerg Med. 2008;15(10):900-907. doi:10.1111/j.1553-2712.2008.00238.xPubMedGoogle ScholarCrossref

25. American Hospital Association. AHA Hospital Statistics. Accessed April 4, 2020. https://www.ahadata.com/aha-hospital-statistics/

26. https://insse.ro/cms/files/publicatii/Romania_in_cifre_breviar_statistic_2018.pdf, https://www.ibisworld.com/industry-insider/coronavirus-insights/effects-of-covid-19-on-global-healthcare-systems/

27. Ministry of Health data collection from territory 30 April, 2020

28. Dobrin C., Dinulescu R., Costache R., Voicu L. One management method, two countries. Lean method applied in Romania and France, Proceedings of the 11th International Management Conference, 2015

The article was received on December 20, 2019, and accepted for publishing on March 23, 2020.

CLINICAL PRACTICE

Therapeutic and diagnostic considerations in multiple eruptive clear cell acanthoma

Florica Șandru[1,2], Cezara Teodorescu[3], Maria M. Constantin[1,4], Mihai C. Dumitrașcu[1,5], Raluca G. Miulescu[2], Adelina Popa[2]

Abstract: *Clear cell acanthoma represent a benign solitary epidermal tumor of the clear glycogen containing epithelial cells, which is quite common in dermatologic practice. The etiology of this tumor formation is not known exactly at the moment. Clinically, the lesion appears as a single reddish papule or papule-nodule and the characteristic of this lesion is represented by a peripheral scaling collarette. Although solitary lesions represent the most common form of presentation of the acanthoma with clear cells, less than thirtieth cases of multiple clear cell acanthoma, from two up to four hundred lesions, have been described in the medical literature to date. The diagnosis based on clinical features frequently needs to be supported using a dermoscopy exam and, in most cases, a histopathology exam is required. The treatment consists is complete removal (standard surgical excision, cryotherapy, electrofulguration alone, carbon dioxide laser or shave removal or curettage followed by electrofulguration). For the cases with multiple lesions, cryotherapy, or topical 5-fluorouracil are preferred.*

We present the case of a 62-year-old male patient, presented to our Dermatology Department for multiple asymptomatic rounded papules and multiple exophytic nodular tumor formations (approximate fifteen), on the lower extremities, which had occurred approximately two years previously and gradually increased in number.

Keywords: *multiple clear cell acanthoma, glycogen containing epithelial cells, surgical excision, cryotherapy*

INTRODUCTION

Clear cell acanthoma represents a benign solitary epidermal tumor of the clear glycogen containing epithelial cells, which is quite common in dermatologic practice. The clear cell acanthoma was first described in 1962 by Dr. Degos et al. [1].

The etiology of this tumor formation is not known exactly at the moment. Clinically, the most frequent part of the body at which level the tumor can appear is represented by the lower limbs, although other portions of the body at which this lesion can develop are represented by the inguinal region or scrotum, scalp, face, vermilion mucosa, far palm, nipple, buttock, trunk, forearm, head and toe [2, 3]. The period with the highest incidence of this condition is represented by the middle-age, with a peak incidence

Corresponding author: Mihai C. Dumitrascu
drdumitrascu@yahoo.com

[1] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[2] Department of Dermatology, "Elias" University Emergency Hospital, Bucharest, Romania
[3] Department of Dermatology, Valcea Emergency Hospital, Ramnicu Valcea, Romania
[4] Department of Dermatology, Colentina Clinical Hospital, Bucharest, Romania
[5] Department of Obstetrics and Gynecology, University Emergency Hospital, Bucharest, Romania

between 50 and 60 years, and does not appear to occur in children. The studies did not show any sex predominance and there is no racial predilection.

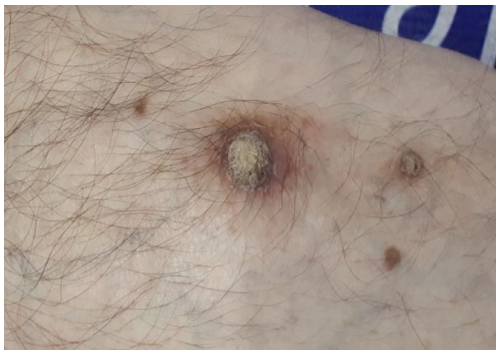
Clinically, the lesion appears as a single reddish papule or papule-nodule and the characteristic of this lesion is represented by a peripheral scaling collarette, but this sign is not always present [4]. Some of the nodules are covered with a thin crust rather than a keratinous layer and quite often they are exuding slight moisture [1,3]. Other features that can be representative of clear cell acanthoma include vascular blush and stuck-on appearance [5]. The lesions usually reach a diameter between 1mm and 4 mm until a few centimeters, but a giant tumor has been described by Duperrat et al. [1].

The lesions with this pattern, located at the level of an extremity, the unequivocal differentiation from Bowen's disease can be really difficult if is based only on clinical and dermoscopic features alone and is required a biopsy for the histological exam. The reflectance confocal microscopy has been used for the examination of the non-melanocytic neoplasms. The exam is usually showing microscopic findings similar to the optical histology.

CASE REPORT

We present the case of a 62-year-old male patient, from the urban area, non-smoking, presented to our Dermatology Department for multiple asymptomatic rounded papules and multiple exophytic nodular tumor formations (approximate fifteen), on the lower extremities, which had occurred approximately two years previously and gradually increased in number. On dermatological examination, the exophytic nodular tumor formations were well delimited on palpation with the diameter between 3mm and 15mm, some of them with exudative surface and reddish-brown nipples (Figure 2), while the other of the tumor formations had a dry surface, with a squamous and hyperkeratotic consistency (Figure 1 and Figure 3).

Figure 1: Nodular tumor formations



From his medical history, we found out that our patient is suffering from an HTA II degree and chronic venous insufficiency CEAP III; no history of drug ingestion was suspected. No other abnormal physical signs were found. Routine blood examination was in normal limits.

Figure 2: Nodular tumor formations

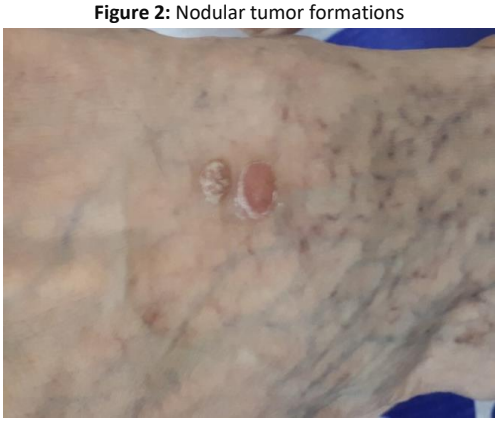
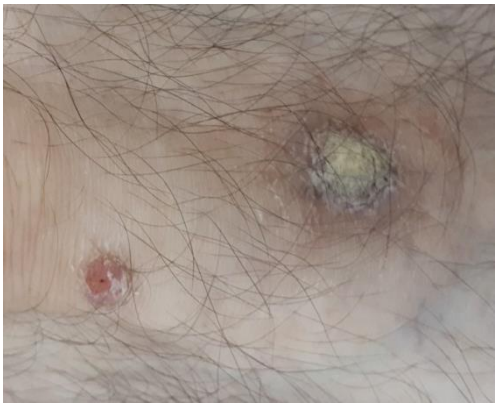


Figure 3: Nodular tumor formations with a dry surface and squamous and hyperkeratotic consistency.



Dermoscopy showed glomerular and punctiform vessels with a “pearl necklace” distribution. This image is highly characteristic of clear cell acanthoma (Figures 4 and 5).

Figure 4: Dermoscopy

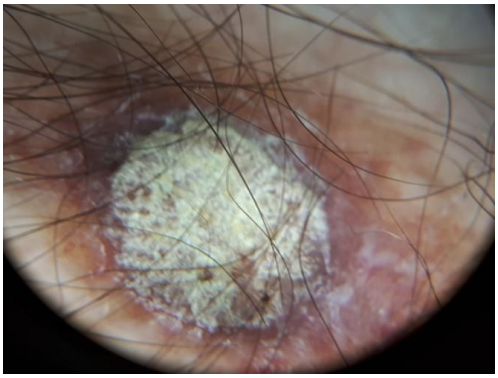
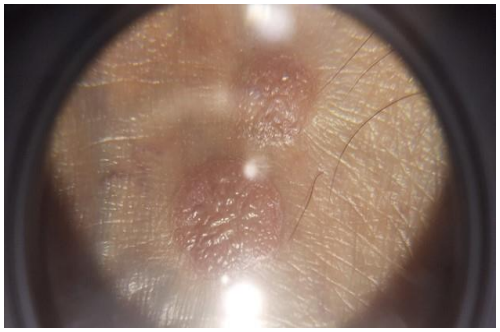


Figure 5: Dermoscopy



An excisional biopsy of one lesion followed by histopathological examination was performed. The histopathological examination showed psoriasiform elongation of plump and interconnected rete ridges, parchetosis and vascular ectasia in the papillary dermis (Figure 6), acanthosis, agranulosis, parakeratosis, and increased number of vessels in the papillary dermis (Figure 7); a periodic acid-Schiff reaction (PAS stain) demonstrated clear keratinocyte with pale cytoplasm, containing a large amount of glycogen (Figure 8).

Figure 6: Histopathological exam – psoriasiform elongation of plump and interconnected rete ridges, parchetosis, and vascular ectasia in the papillary dermis, HE stain x40.

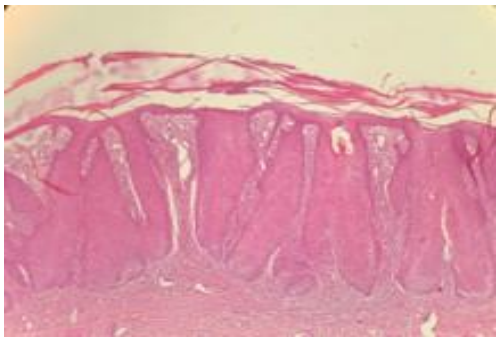
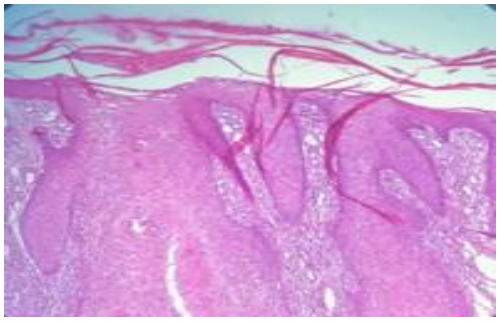
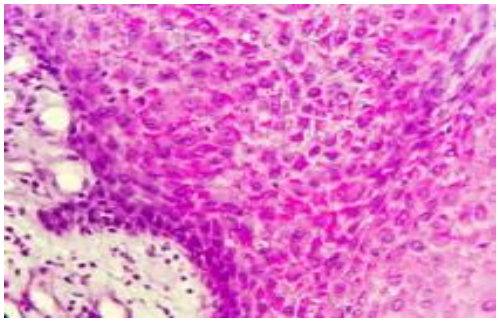


Figure 7: Histopathological exam – acanthosis, agranulosis, parakeratosis, an increased number of vessels in the papillary dermis, HE stainx100.



After establishing the diagnosis using the histopathological examination, the surgical excision of the larger tumor formations was decided, under local anesthetics with Xilina 1%, with the suture per-primam with non-absorbable suture threads and local dressing with Baneocin powder, and the others smaller lesions were treated by cryotherapy, using liquid nitrogen and a cotton wool swab, applied for fifteen seconds and repeated after one minute. All lesions were resolved with minimal residual scarring with no relapse at five months of dermatologic follow-up.

Figure 8: Histopathological exam – Clear keratinocyte with pale cytoplasm, containing a large amount of glycogen, demonstrated with a periodic acid-Schiff reaction, PAS stainx200.



DISCUSSION

Although solitary lesions represent the most common form of presentation of the acanthoma with clear cells, less than thirtieth cases of multiple clear cell acanthoma, from two up to four hundred lesions, have been described in the medical literature to date [6]. The diagnosis based on clinical features frequently needs to be supported using a dermoscopy exam and, in most cases, a histopathology exam is required. Dermoscopy can show dotted or globular vessels, similar to those that can be seen in Bowen disease and psoriasis [7,8]. Also, research has shown an association between clear cell acanthomas and some other conditions including arthropod bites, viral infections, seborrheic keratosis, xerosis, hyttiosis, stasis dermatitis, and varicose veins [9].

The etiology of clear cell acanthoma is not well understood and is no evidence that trauma toxic, drugs, or substances lead to the onset of tumors. In clear cell acanthoma, exist a metabolic enzyme defect, an enzyme that has an important role in the synthesis of keratin [6]. Some authors consider that is an inter-relation with the output of melanocytes and the interaction between melanocyte and keratinocyte. Some of the authors consider that lesions are benign epithelial neoplasm, while others stand up the hypothesis that the origin of this tumor formation is an inflammatory one [7]. Some authors that clear cell acanthoma represent a variant of seborrheic keratosis with the keratinocytes containing abundant amounts of glycogen [10]. In the medical literature, have been reported neither spontaneous

regression nor malignant transformation to data.

The most characteristic histopathologic features of clear cell acanthoma are the clear cells with acanthotic epidermis composed of a high composition of glycogen that can be highlighted by positive PAS-Periodic acid-Schiff-staining and the removal of the staining after the diastase digestion. The epidermis is in most cases infiltrated with an abundant number of neutrophils, which may lead to micro-abscesses in the corneum parakeratotic stratum. The Malpighian layer includes slight spongiosis or several pyknotic neutrophils in the intercellular spaces. The papillary dermal layer includes mixed cellular infiltrate and ectasia. A well definite line of demarcation limits the tumor. This line is produced by epidermal cells, which are increased in size, except those in the basal layer. The histochemical examination shows the absence of phosphorylase - a constitutive enzyme, able to demote glycogen [11]. The electron microscopy examinations have revealed glycogen granules in the dermal layer [12]. Video-dermatoscopy has been introduced among the modern methods, for the diagnosis of clear cell acanthoma, highlighting homogeneous pinpoint-like vascular lesions, that have a bush-like aspect if is set a higher magnification [13].

Multiple clear cell acanthoma – from two up to four hundred lesions – have been described in the medical literature until the moment date. The first multiple clear cell acanthoma has been first described by Delacretaz in 1964 [14].

Differential diagnoses include vulgar warts, pyogenic granuloma, Kaposi disease, amelanotic melanoma, dermatofibromas, traumatized hemangioma, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, irritated seborrheic keratosis, and psoriasis [15-21].

The treatment consists is complete removal (standard surgical excision, cryotherapy, electrofulguration alone, carbon dioxide laser or shave removal or curettage followed by electrofulguration) [22]. For the cases with multiple lesions, cryotherapy, or topical 5-fluorouracil are preferred [23, 24]. In our case, even if the lesions were multiple, the surgical approach supplemented with cryotherapy was found to be a good choice. Therefore, we opted for standard surgical excision, cheap and painless (because we used local anesthesia with Xiline) for larger tumor formations and the other smaller lesions were treated by cryotherapy, using liquid nitrogen. After two sessions, lesions were completely healed without relapse and with a good aesthetic result. In conclusion, we can say that cryotherapy is still an optimal method for treating forms of multiple eruptive clear cell acanthoma, but if there are lesions with a larger diameter among the tumors, classical surgical excision may also be combined.

CONCLUSIONS

Clear cell acanthoma is a rare benign epithelial tumor that presents typically as a solitary tumor, but there are cases with multiple lesions. The tumor is red/red-brown, dome-shaped papule, or nodule. A peripheral wafer-like scale collarette represents the classical presentation in majority lesions, but this sign may not always be present. The surface may have a crusted appearance or a moist appearance and may bleed with minor trauma. The tumor slowly enlarges over several years.

Dermoscopy reveals a highly characteristic pattern, a sign that can be utilized to aid in diagnosing a clear cell acanthoma - the the "pearl necklace" appearance (glomerular/pinpoint blood vessels present in a curvilinear and reticular pattern), but a skin biopsy is usually performed to confirm the diagnosis. The preferred treatment of clear cell acanthomas is complete removal (standard surgical excision, cryotherapy, electrofulguration alone, carbon dioxide laser or shave removal or curettage followed by electrofulguration). In our case, even if the lesions were multiple, the surgical approach (for larger tumor formations) supplemented with cryotherapy (for the smaller lesions) was found to be a good choice. In conclusion, we can say that cryotherapy is still an optimal method for treating forms of multiple eruptive clear cell acanthoma, but if there are lesions with a larger diameter among the tumors, classical surgical excision may also be used.

Although solitary lesions represent the most common form of presentation, less than thirtieth cases of multiple clear cell acanthoma have been described in the medical literature to date. Therefore, our case with approximate fifteen lesions could be classified as multiple eruptive clear cell acanthoma.

References:

29. Degos R, Delort J, Civatte J, Poiares Baptista A. Epidermal tumor with an unusual appearance: clear cell acanthoma. Ann Dermatol Syphiligr. 1962;89:361–371. [PubMed] [Google Scholar]

30. Wang SH, Chi CC. Clear cell acanthoma occurring on the hallux: the first case report. J Eur Acad Dermatol Venereol. 2006;20:1144–1146. [PubMed] [Google Scholar]

31. Betti R, Bruscagin C, Inselvini E, Palvarini M, Crosti C. Successful cryotherapic treatment and overview of multiple clear cell

acanthomas. Dermatol Surg. 1995;21:342–344. [PubMed] [Google Scholar]

32. Innocenzi D, Barduagni F, Cerio R, Wolter M. Disseminated eruptive clear cell acanthoma - a case report with review of the literature. Clin Exp Dermatol. 1994;19:249–253. [PubMed] [Google Scholar]

33. Fine RM, Chernosky ME. Clinical recognition of clear-cell acanthoma (Degos) Arch Dermatol. 1969;100:559–563. [PubMed] [Google Scholar]

34. Wang SH, Chi CC. Clear cell acanthoma occuring in a splitthinckness skin graft. Plast Reconstr Surg. 2005;116:146–149. [PubMed] [Google Scholar]

35. Finch TM, Tan CY. Clear cell acanthoma developing on a psoriatic plaque: further evidence of an inflammatory aetiology. Br J Dermatol. 2000;142:842–844. [PubMed] [Google Scholar]

36. Bugatti L, Filosa G, Broganelli P, Tomasini C. Psoriasis-like dermoscopic pattern of clear cell acanthoma. JEADV. 2003;17:452–455. [PubMed] [Google Scholar]

37. Ohnishi T, Watanabe S. Immunohistochemical characterization of keratin expression in clear cell acanthoma. Br. J. Dermatol. 1995 Aug;133(2):186-93. [PubMed]

38. Prodea MC, Sandru F, Carpenco E, Gaje PN, Horhat ID, Ceausu AR, Mederle N, Mederle OA. A rare sweat gland tumor-imunohistochemical features. Rev. de Chimie. 2019;70(5):1863-1865.

39. Trau H, Fisher B, Schewach-Millet M. Multiple clear cell acanthomas. Arch Dermatol. 1980;116:433–434. [PubMed] [Google Scholar]

40. Desmons F, Breuillard F, Thomas P, Leonardelli J, Hildebrand HF. Multiple clear-cell acanthoma (Degos): histochemical and ultrastructural study of two cases. Int J Dermatol. 1977;16:203–213. [PubMed] [Google Scholar]

41. Lacarruba F, de Pasquale R, Micali G. Videodermatoscopy improves the clinical diagnostic accuracy of multiple clear cell acanthoma. Eur J Dermatol. 2003;13:596–598. [PubMed] [Google Scholar]

42. Delacretaz J. Acanthomes à cellules claires. Dermatologica. 1964;129:147-153. [PubMed] [Google Scholar]

43. Blum A, Metzler G, Bauer J, Rassner G, Garbe C. The dermatoscopic pattern of clear-cell acanthoma resembles psoriasis vulgaris. Dermatology. 2001;203:50–52. [PubMed] [Google Scholar]

44. Sandru, F, Popa, A, Dumitrascu, M (2019). Skin lesions mimicking melanoma. Medical Image Database,2019, 2(2), 9-10

45. Sandru F, Popa A, Dumitrascu M (2019). Keratinized tumor with aggressive evolution at the orofacial level. Medical Image Database, 2019,2(2), 9-10.

46. Stanescu AMA, Grajdeanu IV, Iancu MA, Pantea Stoian A, Bratu OG, Socea B, Socea LI, Diaconu CC. Correlation of oral vitamin D administration with the severity of psoriasis and the presence of metabolic syndrome, Rev Chim. 69(7), 2018, 1668-1672.

47. Surcel M, Huica RI, Munteanu AN, Isvoranu G, Pirvu IR, Ciotaru D, Constantin C, Bratu O, Caruntu C, Neagu M, Ursaciuc C. Phenotypic changes of lymphocyte populations in psoriasiform dermatitis animal model, Exp ther med. 17(2), 2019,1030-1038.

48. Isvoranu G, Surcel M, Huica RI, Munteanu AN, Pirvu IR, Ciotaru D, Constantin C, Bratu O, Neagu M, Ursaciuc C. Natural killer cell monitoring in cutaneous melanoma - new dynamic biomarker, Oncol Lett. 17(5), 2019, 4197-4206.

49. Cristian Scheau, Ioana Anca Badarau, Gratiela Livia Mihai, Andreea Elena Scheau, Daniel Octavian Costache, Carolina Constantin, Daniela Calina, Constantin Caruntu, Raluca Simona Costache, A Caruntu. Cannabinoids in the Pathophysiology of Skin Inflammation, Molecules, 2020, 25(3), 652; https://doi.org/10.3390/molecules25030652 , ISSN 1420-3049

50. García Almagro D, Bueno C, Corripio F, Lecona M, Jaqueti G. Multiple clear cell acanthoma in a patient with psoriasis. Treatment with 5-fluorouracil. Med Cutan Ibero Lat Am. 1979;7:109–113. [PubMed] [Google Scholar]

51. Altman AR, Basler E, Rosen T. Cryosurgical treatment of clear cell acanthoma. Int J Dermatol. 1989;28:334–335. [PubMed] [Google Scholar]

52. Chi CC, Wang SH, Huang HS. Clear cell acanthoma successfully treated with a carbon dioxide laser. Dermatol Surg. 2005;31:1355–1358. [PubMed] [Google Scholar]

The article was received on February 6, 2020, and accepted for publishing on May 13, 2020.

VARIA

The effect of implementing collaborative care model on diet compliance in hemodialysis patients

Hossein Habibzadeh[1], Sima Pourteimour[1], Rasool Gharaaghaji Asl[2], Sahar Kazemi[1]

Abstract: *Non-compliance to diet and increased fluid intake can lead to unpleasant side effects and premature mortality in hemodialysis patients. Intervention strategies in educational and cognitive-behavioral domains can be used to improve diet compliance and restrict fluid intake in hemodialysis patients. The present study aimed to implement a participatory care model on diet compliance in patients undergoing hemodialysis referred to the Urmia Hemodialysis Center of Urmia in 1397.*

The present study is an experimental-randomized study that was performed on 60 patients undergoing diet without hemodialysis referring to Urmia Hemodialysis Center of Urmia. From 175 patients undergoing hemodialysis based on laboratory parameters of non-compliance patients and 60 patients were selected based on simple randomization and were randomly divided into intervention and control groups. After intervention steps of participatory care, diet compliance of the two groups was compared using the results of the comparable laboratory parameters. Analysis of the results of the present study showed that the collaborative care model significantly improved the results of laboratory parameters related to diet compliance in the intervention group compared to the results of the laboratory parameters before the intervention and the control group ($p < 0.05$). Based on the results of the present study, it seems that participatory care intervention can be useful in improving diet compliance and fluid restriction in hemodialysis patients. The aim is to improve the quality of life of hemodialysis patients.

Keywords: *chronic kidney failure, collaborative care model, diet compliance, hemodialysis*

INTRODUCTION

Chronic renal failure is a progressive and irreversible disorder that causes the formation and increase of urea and other toxins in the blood [1]. In other words, chronic renal failure is defined as the progressive and irreversible loss of renal function, often leading to end-stage renal disease (ESRD) [2]. Hemodialysis is the main end-stage treatment for kidney disease (ESRD). Researchers have not considered the growing number of patients with ESRD as a growing problem in Iran and have estimated it to be a worldwide problem. Unfortunately, in Iran, due to a lack of control over diseases such as diabetes and blood pressure, there has not been significant success in preventing chronic kidney disease [3]. This failure to control the underlying diseases has resulted in an increase of 12% per year in the number of patients requiring hemodialysis nationwide (compared to the 6%

[1] School of Nursing and Midwifery, Urmia University of Medical Sciences, Urmia, Iran
[2] Department of Community Medicine, School of Medicine, Urmia University of Medical Sciences, Urmia, Iran

Corresponding author: Sahar Kazemi
Kazemi.PHD.20018@gmail.com

average increase in hemodialysis patients worldwide) and thus the rate of renal disease growth. It is much higher than the world average [4-6]. During the hemodialysis process, extra fluids and wastes are extracted from the blood of patients and this improves the patient's life and prolongs their life, but without proper diet, fluid restriction, and appropriate drug therapy, hemodialysis is not effective [7]. Nutrition has a major impact on the treatment and fate of patients undergoing hemodialysis, and diet compliance is associated with mortality in this disease, such that compliance to a low-potassium diet leads to muscle weakness, arrhythmia, and stasis. Cardiac and death and elevated serum phosphate levels lead to hyperparathyroidism and coronary artery disease, as well as fluid compliance in these patients leading to weight gain between two dialysis sessions and complications such as muscle cramps, shortness of breath, Vertigo, anxiety, pulmonary edema, heart failure, and severe hypertension and threaten the patient's lifestyle [8, 9]. Low levels of blood albumin decrease as 1–91 g of the amino acid are lost in each hemodialysis session, increasing the need for hemodialysis patients to have more protein than normal. Decreased blood albumin levels are strongly correlated with hospitalization and mortality rates and are a determinant of mortality in these patients [10]. Therefore, due to the effect of renal failure on different parts of the body, proper nutrition, prevention or correction of malnutrition and dietary restriction are essential, so patients need a special diet to continue living. It includes restrictions on the consumption of food and liquids [11]. Patient compliance to diet is influenced by factors such as personal beliefs, cultural and social characteristics. Most studies on hemodialysis patients do not follow the proper diet regimen [12]. Although patient-centered dietary supplementation is complementary to hemodialysis and is recommended for the effective control of signs and symptoms of uremic syndrome along with the prevention of long-term complications, many patients do not follow the nutritional and fluid restriction plan. This will lead patients to dialysis inadequacy; therefore, to improve dialysis adequacy, educate, justify, and modify patients' attitudes about diet and the need to monitor the complexity of human behaviors in health decision-making and health decisions. Moreover, behavioral health promotion patterns the benefits of dialysis and timely referral are important [13]. The collaborative care model is one of the localized teaching methods that has been used in recent years in the Iranian nursing field. The model of participatory care is the use of participation in the care process. The purpose of this model is to establish and maintain an effective, balanced, and continuous relationship between the members and the therapeutic team and the patient, to increase collaboration, motivation, and collaboration, and to take responsibility for the treatment team in the treatment and care process [14]. Work-based on a nursing model helps to evaluate patients' status, establish meaningful useful communication between patients and nurses, set goals of care, improve quality of care, guide, and clarify care [15]. Therefore, the concept of "participation" in the care process can be used to improve and maintain an effective care relationship, which then creates an effective care relationship between the three main pillars of the care process: the patient, the nurse, and the physician. Collaborative care is a spectrum from 100% self-care to 100% professional care in which families or health providers, including health personnel, physicians, nurses, social workers, and pharmacists are partnered [16]. Collaborative care encompasses part of the spectrum of care, can be a large or small component of self-care, and can ultimately lead to improved health. It will be necessary to strengthen the caregiver's abilities as a patient with constant stress and anxiety [17]. Also, the use of new participatory teaching methods increases confidence, understanding, and learning, and improves communication skills among members [18]. The purpose of this study was to investigate the effect of the collaborative care model on diet compliance in patients undergoing hemodialysis referred to Urmia Hemodialysis Center of Urmia in 1397.

METHODS

The present study is an experimental study with code IRCT20180730040641N1 in which diet non-compliance is considered as a risk factor for hemodialysis patients. The statistical population in this study was all patients undergoing hemodialysis referred to Urmia Hemodialysis Center of Urmia who was enrolled in the study according to inclusion criteria. Inclusion criteria included no mental illness, cognitive impairment, known hearing, and visual impairment, no use of drugs and psychotropic substances, at least 6 months history of hemodialysis, and ability to stand on weights to control weight between two sessions. Then, of the 175 patients undergoing hemodialysis at the center based on the mean laboratory, sodium, potassium, phosphorus, and albumin parameters in the past 6 months, 60 patients were randomly selected as the study population (patients who did not adhere to their diet). They started studying. After informing the patients about the process of completing the study and completing the informed consent form in these patients, the collaborative care model was administered to the patients in the intervention group for 7 sessions and routine care was performed for the control group patients. The intervention was performed by implementing a collaborative care model. To achieve the

objectives of the model, the following steps were presented in the form of a systematic structure that was followed by a logical and evolutionary set of interconnected and dynamic sequences, consisting of four steps: 1- Motivation: 2- Preparation; 3- Involvement; 4- Evaluation that was anticipated for each stage of the specific action plans.

Motivation Stage: To motivate patients by communicating with them appropriately, familiarizing them with the ward and facilities available, raising awareness of patients with chronic renal failure, its consequences, and dangerous consequences were summarized.

Educational need assessment was also done by reviewing and identifying patients' problems by taking biographies and interviews, which was a 2-hour session after filling out the demographic questionnaire during the hemodialysis process.

Preparation Stage: Model objectives and timing of participatory training programs and follow-up were identified (one-hour session).

Involvement phase: Training sessions and follow-up sessions were held at a stage (each session for 30 minutes) that included:

1) The first participatory training session

2) Second educational participatory meeting

3) Participatory follow-up meeting first (one-month interval between each session half an hour)

4) Second follow-up collaborative meeting (one-month interval between each session half an hour)

Evaluation Stage: Achievement of the goals was evaluated in the implementation stages of the model. The evaluation was performed in stages at the beginning and end of each training session as a question and answer session. The training steps were simple and lecture-based.

Implementation of the training program in 4 sessions in the patient's bedside with the nephrologist in the Hemodialysis ward of the Urmia Hemodialysis Center in Urmia for 30 minutes individually and individually for patients.

In the first session, the patient was provided with the necessary information about the nature of the disease, diagnostic methods, and treatment, in each training session after completing the training during the last 20 minutes, in the last 10 minutes, summarizing information, and asking patients questions about problems. The answer was raised. The second session provided information and skills on the importance and how to maintain a proper diet concerning the disease, and the third session on the final evaluation of education, with emphasis on follow-up and participation rates.

Educational information was also provided in the form of educational pamphlets and pamphlets.

Laboratory parameters were measured and reported in two stages, once at the end of the intervention and the second time at one month interval and compared with pre-study values. Also, educational content was collected from accredited hemodialysis and nurse nursing textbooks and approved patient education guidelines, physicians, and nursing professors.

Training sessions were also conducted by the researcher and supervised by the project executives. Data were analyzed using a t-test for independent samples and chi-square and repeated measures in SPSS 23 software.

RESULTS

The statistical population of this study consisted of 60 patients undergoing hemodialysis with laboratory parameters indicating diet compliance who were randomly divided into two equal groups of intervention and control.

The mean age of the patients in the intervention and control groups were (53.60 13 13.27) and (48.63 14 14.88) years, respectively, in terms of the mean duration of dialysis in both groups (intervention and control). It was equal to 31.02 20 20.45 and 33.13 18 18.54 months, respectively.

There was no significant difference between the two groups in terms of age and duration of dialysis. The t-test was homogeneous in terms of mean age (p = 0.17), duration of dialysis (p = 0.84) and patient weight (p = 0.16) (Table 1).

Table 1: Comparison of quantitative demographic characteristics of the studied samples in the two intervention and control groups

Variable	Intervention group		Control group		Test statistics Independent t-test	P-value
	Mean	SD	Mean	SD		
Age of patients	53.60	13.27	48.63	14.88	t=1.36 df=58	0.17
Duration of dialysis	31.02	20.45	33.13	18.54	t=-0.19 df=58	0.84
Weight of patients	68.83	11.59	72.98	10.98	t=-1.43 df=58	0.16

SD – standard deviation

Regarding the qualitative demographic characteristics that could influence the outcome of the intervention, based on the results of the Chi-square test in Table 2, no significant difference was observed between the two groups (intervention and control). In other words, two groups were gender (P = 0.43), occupational status (P = 0.46), educational status (P = 0.60), marital status (P = 0.71) and income (P = 0.51) were homogeneous.

Table 2: Comparison of qualitative demographic characteristics of the samples in the intervention and control groups

Variable		Intervention group		Control group		Test result
		Number	Percent	Number	Percent	
gender	female	17	56.7	14	46.7	X^2=0.60 Df=1 P=0.43
	man	13	43.3	16	53.3	
job	retired	11	36.7	14	46.7	X^2=1.55 Df=2 P=0.46
	housewife	9	30	5	16.7	
	does not have	10	33.3	11	36.7	
education status	illiterate	10	33.3	10	37	X^2=1/84 Df=3 p=0/60
	high school	15	50	12	44.4	
	diploma	1	3.3	3	11.1	
	above the diploma	4	13.3	2	7.4	
marital status	married	26	86.7	25	83.3	X^2=0.13 p=0.71
	single	4	13/3	5	16.7	
income	more than spending	4	13.3	3	10	X^2=1.34 Df=2
	spending equal expense	7	23.3	4	13.3	
	less than spending	19	63.3	23	76.7	

Table 3: Comparison of mean scores of laboratory parameters between the intervention and control groups in hemodialysis patients

Variable	Group	Intervention group	Control group	P-value
		Mean ± SD	Mean ± SD	
potassium	Before intervention	5.65±0.68	5.63±0.43	0.86
	After the intervention	5.11±0.52	5.41±0.42	0.017
	After one month of intervention	4.10±0.26	5.25±0.40	<0.001
	P-value	<0.001	<0.054	
Phosphorus	Before intervention	5.42±0.98	5.45±0.55	0.87
	After the intervention	5.19±0.7	5.34±0.54	0.31
	After one month of intervention	4.22±0.59	5.31±0.27	0.001
	P-value	<0.001	0.15	
Sodium	Before intervention	139.74±3.24	138.63±0.77	0.15
	After the intervention	138.07±3.25	137.90±2.33	0.82
	After one month of intervention	136.97±2.64	138.30±2.50	0.050
	P-value	<0.001	0.34	
Albumin (protein)	Before intervention	4.07±0.54	3.93±0.44	0.28
	After the intervention	4.24±0.46	3.78±0.41	<0.001
	After one month of intervention	4.54±0.42	3.59±0.52	<0.001
	P-value	<0.001	0.058	

SD – standard deviation

The results of the t-test of two independent groups concerning Table 3 show that before the intervention, the hypothesis of equality of mean laboratory parameters between the two groups at a 5% error level was not significant (P>0.05). There was no significant difference between the two groups in terms of mean laboratory parameters and after the intervention; there was a significant difference between the intervention and control groups (P<0.05). The results of the repeated measures test showed that in the intervention group there was a significant

difference between before and after the intervention and after one month of intervention (P<0.05). Therefore, it can be said that the intervention was effective but in the control group was significantly higher than 0.05 indicating no significant difference in the control group before and after the intervention and after one month of intervention.

DISCUSSION AND CONCLUSSION

Various studies have shown that changes in the lives of individuals following the onset of chronic kidney disease require serious support and support to improve and tolerate behavior change [19]. Non-compliance to treatment regimens is common in chronic kidney patients and is associated with an increased rate of disease progression and mortality in these patients and is directly related [20]. Compliance with a diet is the result of a range of behaviors that are in line with the recommendations made in compliance with the prescribed dietary regimen, including medication, diet, and so on. Compliance with a diet as part of the treatment regimen can be effective in controlling many diseases [21]. Symptoms and symptoms include fluid and electrolyte imbalances, and accumulation of these substances in the body, hyperkalemia, metabolic acidosis, hyper-phosphatemia, anemia, hyperparathyroidism. Malnutrition, etc. are occurring and intensifying over time [22]. Protein-energy nutrition also occurs in 40% of patients with chronic kidney failure. One of the reasons for all these problems is the lack of diet; one of the needs of the patient at this stage is the need to obtain information about nutrition and nutrition. Nutrition in these patients suggests appropriate approaches to reduce the adverse effects of the disease. Increased mortality and morbidity due to toxins in the cassette may also be caused by the increased awareness of these patients in the diet [23]. Today, trying to adhere to a nutritional diet because of its cheapness compared to other health interventions and fewer side effects is considered an important treatment option in the early treatment of patients, and patient education is a valuable method. Compliance with the diet of the patients is considered. The purpose of this study was to evaluate the effect of the participatory care model on diet compliance in patients undergoing hemodialysis referred to Urmia Hemodialysis Center of Urmia in 1397. In the present study, two intervention and control groups, including hemodialysis patients who did not adhere to the diet, were compared after the intervention. The intervention group underwent an interventional process of collaborative care according to the standard model presented in the study method. The control group continued the normal hemodialysis procedure until the end of the study. At first, both groups were compared in terms of demographic characteristics. The results showed that there was no significant difference between the intervention and control groups in terms of demographic variables such as gender, age, marital status, education, patient occupation, monthly income, which could affect the results of the study. In other words, both groups were homogeneous. After successive steps of intervention, both groups were compared in terms of laboratory parameters related to diet compliance. The results showed that there was a significant relationship between the experimental and control groups in terms of laboratory parameters of phosphorus, potassium, sodium, and albumin. Participatory care reduces the toxicological parameters of patients with chronic kidney disease and reduces the weight difference due to the accumulation of toxic substances in the intervention group. In other words, participatory care has a significant direct relationship with compliance to the diet. Parvinian Nassab et al. 2014 A study "Determining the impact of collaborative care model on the anxiety of adolescents with beta-thalassemia major" by selecting 21 mothers available and randomly sampling in two control and intervention groups at Shahid Hospital Coliseum. Dastgheib Shiraz was designed for 3 months. The results of the study showed that the mean score of worry before intervention in the control and intervention groups was not statistically significant, but there was a significant difference between the mean worry in the intervention group before and after the implementation of the collaborative care model [24].

In 2015, Mamne et al. designed a study to investigate the impact of collaborative care model training on the nutritional behavior of type 2 diabetic patients. In this study, simple random sampling (random numbers) was performed from 411 cases to 42 cases in two experimental (control) and control (21 patients) groups at Tabriz Diabetes Training Center with two samples. The results showed that there was no significant difference in age, sex, educational level, occupation, marital status, and economic status between the two groups. Experimental group after training intervention in the areas of fast food consumption, fruit and vegetable consumption, canned, pastry, solid vegetable oil, sausage and sausage, the usual method of cooking and eating heavy and late dinner better performance than the control group. [25].

A quasi-experimental clinical trial study conducted by Khoshab et al. 2012 aimed to determine the impact of the collaborative care model on depression and anxiety in patients with heart failure in 11 patients with heart failure from CCU, PCCU, and internal heart wards. Afzalipour and Shafa hospitals of Kerman were randomly divided into control and experimental groups. The results of the study showed that the mean scores of anxiety in the intervention

group decreased after implementing the collaborative care model [26].

The Lashkari et al. Study in 2015 aimed to investigate the effect of the collaborative care model on the fatigue of 12 conservative hemodialysis patients by purposeful sampling in two experimental and control groups randomly for 3 months in Golestan and Imam Ahwaz hospitals. According to the results of the study after intervention in the intervention group, the level of fatigue at a mild level increased (from 23.9% to 42.2%) and the level of fatigue at a severe level decreased significantly (from 42.3% to 7%). Severe fatigue in the control group increased from 42.2% before the intervention to 34.2% after the intervention. Results also showed that after the intervention, the mean score of total fatigue severity in the intervention group was reduced and it was statistically significant [27]. Our study was similar in terms of the implementation of the collaborative care model. The results of applying the collaborative care model to the crisis created in these studies were also in line with our study.

Based on the results of this study, it can be concluded that the participatory care model has been successful in explaining dietary compliance behavior. Therefore, it is suggested to implement a participatory care model of patients undergoing hemodialysis in planning to change dietary behaviors. Although the findings of this study provide an accurate description of the relationship between the incubation care model and diet compliance, it also has some limitations, including the ability to accurately and sequentially monitor laboratory parameters by a laboratory apparatus and an expert operator who can be useful to achieve better results. It is also recommended to consider the role of other standardized behavioral models in identifying the effective aspects of behavioral or behavioral changes in treatment planning and to consider effective educational methods to increase compliance with dietary restrictions. To improve both the quality of treatment and to reduce the cost of treatment for the consequences of noncompliance.

CONCLUSION

The findings of this study in general indicate the usefulness and effectiveness of the participatory care model in the process of compliance to diet in patients with hemodialysis. Therefore, participatory care intervention seems to play a key role in improving diet compliance and fluid restriction in hemodialysis patients, requiring comprehensive plans focusing on participatory model steps by health care professionals and hemodialysis patients. The effectiveness of the model as well as its simplicity is one of the strengths and weaknesses of this model compared to other models.

Acknowledgment

This article derives from a research project with a code of ethics IR.UMSU.REC.1397.176. The authors would like to express their gratitude to the Research Deputy of Urmia University of Medical Sciences, the authorities, and nurses of the Hemodialysis Hemodialysis Center of the Urmia Dialysis Center in Urmia, as well as to all patients undergoing hemodialysis who could not have been enrolled without their participation.

Conflicts of Interest

No conflict of interest is declared by the authors.

References:

1. Ghaffari M, Morowatisharifabad MA, Mehrabi Y, Zare S, Askari J, Alizadeh S. What Are the Hemodialysis Patients' Style in Coping with Stress? A Directed Content Analysis. International journal of community based nursing and midwifery. 2019 Oct; 7(4):309.

2. Kara B. Health beliefs related to salt-restricted diet in patients on hemodialysis: Psychometric evaluation of the Turkish version of the Beliefs About Dietary Compliance Scale. Journal of Transcultural Nursing. 2014 Jul;25(3):256-64.

3. Tranter S. Review of Haemodialysis for Nurses and Dialysis Personnel. Renal Soc Australasia J 2016; 12(1):34.

4. Motedayen M, Sarokhani D, Ghiasi B, Khatony A, Hasanpour Dehkordi A. Prevalence of Hypertension in Renal Diseases in Iran: Systematic Review and Meta-Analysis. Int J Prev Med. 2019 Jul 5;10:124..

5. Rezaei Z, Jalali A, Jalali R, Khaledi-Paveh B. Psychological problems as the major cause of fatigue in clients undergoing hemodialysis: A qualitative study. International J Nursing Sciences 2018;5:262-7

6. Ebrahimi H, Sadeghi M. The effect of dietary regimen education on the laboratory variables in hemodialysis patients. J Nurs Educ 2014; 2(4):12– 22. (Persian).

7. Park OL, Kim SR. Integrated self-management program effects on hemodialysis patients: A quasi-experimental study. Japan Journal of Nursing Science. 2019 Jan 22.

8. Kalantar-Zadeh K, Tortorici AR, Chen JLT, Kamgar M, Lau W-L, Moradi H, et al. Dietary restrictions in dialysis patients: is there anything left to eat? Semin Dial 2015;28(2):159–68. (Persian)

9. Montilla CM, Duschek S, del Paso GA. Health-related quality of life in chronic kidney desease: Predictive relevance of mood and somatic symptoms. Nefrología (English Edition). 2016 May 1;36(3):275-82.

10. Royani Z, Rayyani M, Vatanparast M, Mahdavifar M, Goleij J. The relationship between self-care and self-efficacy with empowerment in patients undergoing hemodialysis. Military Caring Sci 2015;1(2):116–22. (Persian).

11. Beerendrakumar N, Ramamoorthy L, Haridasan S. Dietary and Fluid Regime Compliance in Chronic Kidney Disease Patients. J Caring Sci. 2018 Mar 1;7(1):17-20.

12. Rysz J, Franczyk B, Ciałkowska-Rysz A, Gluba-Brzózka A. The

Effect of Diet on the Survival of Patients with Chronic Kidney Disease. Nutrients. 2017;9(5):495. Published 2017 May 13. doi:10.3390/nu9050495.

13. Goraya N., Wessona D.E. Dietary interventions to improve outcomes in chronic kidney disease. Curr. Opin. Nephrol. Hypertens. 2015;24:505–510.

14. Andersen-Hollekim TE, Kvangarsnes M, Landstad BJ, Talseth-Palmer BA, Hole T. Patient participation in the clinical pathway-Nurses' perceptions of adults' involvement in haemodialysis. Nurs Open. 2019 Feb 14;6(2):574-582.

15. Hashemi MS, Irajpour A, Abazari P. Improving Quality of Care in Hemodialysis: a Content Analysis. J Caring Sci. 2018 Sep 1;7(3):149-155.

16. Roumelioti ME, Steel JL, Yabes J, Vowles KE, Vodovotz Y, Beach S, Rollman B, Weisbord SD, Unruh ML, Jhamb M. Rationale and design of technology assisted stepped collaborative care intervention to improve patient-centered outcomes in hemodialysis patients (TĀCcare trial). Contemp Clin Trials. 2018 Oct;73:81-91.

17. Shamsi A, Amiri F, Ebadi A, Ghaderi M. The effect of partnership care model on mental health of patients with thalassemia major. Depression research and treatment. 2017;2017.

18. Snaie Neda, Alahani Fatemeh, Zolfagari MITRA. The Effect of Education with the partnership approach on the self- efficacy and self-esteem of family caregivers of patients undergoing Coronary Artery Bypass Graft (CABG). Journal of Medical-Surgical Nursing.2015;21-28.

19. Carrero J.J., Cozzolino M. Nutritional Therapy, Phosphate Control and Renal Protection. Nephron Clin. Pract. 2014;126:1–7.

20. Donderski R, Miśkowiec-Wiśniewska I, Kretowicz M, Grajewska M, Manitius J, Kamińska A, Junik R, Siódmiak J, Stefańska A, Odrowąż-Sypniewska G, Pluta A. The fructose tolerance test in patients with chronic kidney disease and metabolic syndrome in comparison to healthy controls. BMC nephrology. 2015 Dec;16(1):68.

21. Ricardo AC, Anderson CA, Yang W, Zhang X, Fischer MJ, Dember LM, Fink JC, Frydrych A, Jensvold NG, Lustigova E, Nessel LC. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. American Journal of Kidney Diseases. 2015 Mar 1;65(3):412-24.

22. Aghakhani N, Hoseini SL, Kamali K, Vahabzadeh D. Effects of Appropriate Nutrition Training in Small Groups on Laboratory Parameters in Hemodialysis Patients from Iran. Maedica (Buchar). 2017;12(4):276–280.

23. Karavetian M, Vries N, Rizk R, et al. - Dietary educational interventions for management of hyperphosphatemia in hemodialysis patients: a systematic review and meta-analysis. Nutrition reviews. 2014;7:471–482.

24. Parviniannasab A, rosta S, vejdani M, dehghani A, keshtkar Z, anshorshori N, et al . The Effects of the Group Reminiscence on Cognitive Status of Mild Cognitive Impaired Elders. IJPN. 2014; 1 (4) :25-36.

25. Mamene M, Rahmani A, Behshid M. The effect of teaching based collaborative care model on diet habits in diabetes type II: A clinical trial study. Scientific Journal of Hamadan Nursing & Midwifery Faculty. 2014 May 15;22(1):41-51.

26. Khoshab Hadi, Bagheryan Behnaz, Abbaszadeh Abbas, Mohammadi Eesa, Kohan Simin. The effect of partnership care model on depression and anxiety in the patients with heart failure. Evidence Based Care. 1021;1(1):24.-57.

27. Lashkari F, Brazparandjani S, Latifi S M, Chahkhoei M, Khalili A, Paymard A, et al . The Effect of Collaborative Care model on the Fatigue in Patients Undergoing Maintenance Hemodialysis: A Randomized Clinical Trial. Qom Univ Med Sci J. 2016; 10 (8) :71-79.

The article was received on June 4, 2019, and accepted for publishing on October 23, 2019.

VARIA

Are there only records of success in urology, or are there errors, mistakes, and risks as well?

Viorel Tode

The history of urology dates back to the antiquity, before Christ. The panels decorated in low relief of Saqqara, located at the Institute for the History of Medicine in London, depict the oldest surgical procedure in the world – the circumcision – dating from 2200 BC.

Hippocrates knew about genito-urinary disorders and treated them with medication, leaving bladder stones to be treated by lithotomists.

Cystolithectomy is also known to be dating back to ancient times, having been performed in Egypt, the Middle East, and Ancient Greece.

Urology has always been and still is, an exceptional profession, requiring both intelligence and effort in scheduling and executing the necessary techniques, in assuming risks, and in accomplishing spectacular results.

I will only mention here several of the events that marked the exceptional evolution of urology: defeating pain using anesthesia, progresses of pathological anatomy, the development of the cystoscope by Nitze and the beginnings of endoscopic explorations, the use of Roentgen rays in medicine, Pasteur's contribution to the study of microbes and Lister's in asepsis and antisepsis, the renal transplantation – using which, the urologist gives another lease of life to the patient – the tremendous achievement of Mathias, Jaboulay and Alexis Carrel, percutaneous, laparoscopic and robotic urology as well as other exceptional accomplishments.

The title of this article is addressed as a question: are there only records of success in urology, or are there errors mistakes, and risks to take as well?

However, the word urology can be replaced by any other specialty: surgery, gynecology, ENT, ophthalmology, and why not even internal medicine, neurology, psychiatry, endocrinology, family medicine, and so on.

Hippocrates said: "In medicine, the one who has to be praised is the one who makes the fewer mistakes".

Reflecting upon my professional life, recalling now at senescence, I concluded that I remember less about my many successes in healing patients, but have more vivid memories of some intra or postoperative complications that I have lived intensely.

One can hardly forget, for instance, bleedings that were hard to contain, the slip of a ligature on a vascular pedicle, a vena cava or iliac tear, a large posttraumatic retroperitoneal hematoma, a complex kidney rupture, a pelvic fracture that affects the urethra, urinary bladder or rectum, a postoperative urinary fistula and so on.

In 1971, in medical literature, the second edition of a valuable work by Academy Professor Th. Burghele was published in French – "Erreurs, fautes et risqué en Urologie", from which I will cite only the title of the first chapter – The complexity of urology, factors of error and faults (La complexite de l'urologie, factor d'erreurs et de fautes) and the title of the last chapter – The ontological aspects of faults and errors in urological practice (Les aspects deontologiques des fautes et des erreurs de la practique urologique).

Specialty medical journals are rich in articles presenting, and rightfully so, the successes accomplished by urologists, however, very few publish the occasional failures: errors, mistakes, and risks met or faced during surgery. Professor Th. Burghele once introduced a chapter in the journal "Surgery" – deaths on the surgical table – but after a few case studies, no one published anything related anymore.

It would be difficult for me to believe that in medical practice, one could fully believe one never made a mistake. Medical mistakes in general, and surgical-urological ones in

particular, given the human element on which the work is being done, can sometimes generate severe consequences and are thus not admitted.

Momentous errors punishable by law notwithstanding, some mistakes often look insignificant, that occasionally pass undetected by some and that only a urologist in the know would notice. Those are the kinds of mistakes that sometimes would genuinely shake the morality of the urologist tougher than any legal sanction.

Technical progress, modern means of investigation, and new therapeutic options have made urology more benign, with lesser risks and fewer possibilities for errors. The extension of urology to new areas, some not attempted before, exposed other possibilities for complications and postoperative incidents. However, with all the developments of urology and medicine in general, what we still only partially fathom are the reactions of the organism.

Despite technical or analytical errors, it is sometimes possible for the organism, utilizing its reactions to avert or at least limit important consequences that might follow. Other times, through a lack of response, paradoxical or unanticipated reactions, complications and mistakes might be aggravated, thus requiring re-intervention to ensure positive results.

No one in the world, in any profession, can be above mistake: the urologist has the moral duty to do whatever he can to minimize errors.

All active people, and especially those who try new things in the name of growth made mistakes. Progress in all fields, in medicine and particularly in surgery, meant repeated attempts with a mistake, repetition, effort, and sacrifice, and people often paid dearly for surgical advance. But often, from mistake came more knowledge than from success.

To admit errors and to look for their source is the essential condition for a better tomorrow.

Marshal Foch, the highest commander of allied armed forces, victorious in World War I said: “of course I have made many mistakes, but if I hadn’t made them, I wouldn’t have accomplished everything I did in 1918”.

But to misstep as little as possible is no simple or easy task. For the urologist, few mistakes mean having thorough professional training that never ceases to perfect.

For the urologist, making few mistakes means having the chance to stay young at heart, to have the will to constantly improve, and at the same time to keep an unshaken belief in the promise of a better future. It also means understanding and cherishing this ingrate but unimaginably beautiful profession which is urology. And to assimilate it well, the urologist is bound to forfeit his youth, sacrifice his freedom, and surrender all thoughts.

In my personal opinion, a resident in urology should only train in clinics that alongside highly qualified faculty, have the means of instructing residents in all areas of the specialty: open surgery, low and high endoscopic urology, ESWL, abundant imaging possibilities, laparoscopy, robotic surgery and so on.

Once a specialist, the urologist has to constantly oversee his professional progress and keep up with all modern attainments in our specialty.

To obtain the title of the primary physician, there should be a return to a competitive exam form factor, with a limited number of positions, exams not attestations, held before a commission with valued members of the faculty from the country. The primary physician title is a higher degree within the specialty, one that should be aspired to, and only received by the valuable urologists.

Competitive exams should be set to obtain the position of head of the unit, on a period of no more than 4 or 5 years, same as the presidency of the country. The head of the unit should be the best trained professional, highly competent, and capable of solving the most complex cases, known through his profession and case studies held at conferences, symposiums, or published in specialty publications.

There was once even an institute for specializing and perfecting doctors in Romania, housed within Fundeni Hospital. Bygone…

The urologist, like any other person, can slip, and without a doubt will make errors the more he works and the more intricate, tough problems he attempts. But what portrays a proper urologist is not that he is never mistaken, but the fact that he recognizes the mistake and has the conscience and power to fix it.

Celsius, the great anatomist and surgeon of the middle ages said from the beginnings of surgery:” recognizing mistakes is only fit for the intelligent man”.

Diagnosing and identifying complications that necessitate re-intervention is far from being a simple, easy feat.

The numerous paraclinical investigations available have particular importance in appreciating postoperative evolution and occurrences, with imaging being one of the most important means of investigating in diagnosing and indicating re-intervention.

However, all those, without minimizing their importance, cannot replace the clinical assessment, repeated examinations, careful and continuous observation of the patient, and especially the evaluation of the sometimes subtle signs of aggravation.

The character Sherlock Holmes, by Sir Arthur Conan Doyle, said: ”You know my method. It is founded upon the observation of trifles”.

Joseph Okinczy wrote the famous book that will forever remain in the history of surgery ”The small rules of perfect surgery”.

Due to the rapid progress of the last years in the area of biomedical sciences, and in cellular and molecular biology,

genetics, and medical imaging, in particular, some clinicians developed the tendency to put less of an emphasis on the anamnesis and clinical examination, relying solely on "adequate" paraclinical examinations, which often prove to be inadequate. This leads frequently to not only unnecessary spending but to diagnosing faults which reflect on the patient's well-being.

The problem of re-intervening reflects upon the character of the urologist and his professional condition in the most profound dimensions of the specialty and subtlest forms of knowledge.

Whenever complications occur, the experience, expertise, and professional value, as well as the temper of the urologist are often put to the test.

Urology was not always as we see it currently. To achieve perfection and the shine we see today, every civilization contributed in spirit, every century laid its rocks, every people brought their input. In its constant evolution, it was only natural that the passive attitude towards incidents and complications had to change.

Currently, such accidents can undergo surgery, a large number of patients can be healed. A detailed study has shown how to best avoid those incidents.

Sure enough, several re-interventions have nothing to do with the primary procedure, nor any urological error. But when in doubt and more importantly when errors exist and the following complications require surgical remedy, re-intervention, no matter how severe, is the only act which allows the urologist to fix, often successfully, that which was wrong.

Within our need and tendency to better ourselves, we must not only see the mistakes of others. It would be despicable to comment in bad faith any errors of our colleagues while justifying our own.

The constant growth of urology offers indisputable potential for great success, but also occasions to fail.

As far as I am concerned, whenever I made a mistake, I prayed to the providence that it be the last one.

But I never forgot that the urologist, as long as he is working, cannot say that he has made his final mistake.

The article was received on May 22, 2020, and accepted for publishing on September 9, 2020.

VARIA

Artificial Intelligence in cardiovascular medical imaging

Silviu Stanciu[1], Irina A. Tache[2], Magdalena Gurzun[1], Alexandru Sorici[2], Alexandru Croitoru[3], Dragos Cuzino[3], Diana L. Tudor[3], Sorin Lazar[4]

Abstract: *Artificial Intelligence (AI) has become an important tool for computer-aided diagnosis of medical imaging. This review aims to provide an overview for clinicians, explaining the relevant aspects of artificial intelligence and machine learning (ML) and presenting up-to-date applications of AI and ML techniques to medical imaging methods such as angiography, magnetic resonance, and echocardiography.*

For each imaging method, we present the acquisition process, the types of diagnostic test interpretation, and the challenges related to them, as well as how AI/ML techniques, have improved the process of decision making.

A summary of selected works applying AI/ML techniques to medical imaging is organized into a table, which highlights the scope of the study, the dataset used, the details of each approach as well as the measured results, including objectives and criteria. The overall benefits of AI in medical imaging are extracted based on the diverse applications and high evaluation scores. In the end, cardiologists should have an advanced understanding of using AI to integrate clinical data and making the final decision in diagnosis.

Keywords: *machine learning, cardiology, angiography, echography*

INTRODUCTION

The application of AI algorithms to a data set has the usual initial steps of developing the algorithm's ability to "learn" based on the training data and to apply the knowledge gained in making predictions. The “learning phase” of an algorithm consists of an incremental optimization of the model parameters with which it is configured, so that performance on a given training objective (e.g. classification of the most likely diagnosis, regression of numerical value of a health parameter) increases.

Machine Learning is a methodology used to recognize such patterns; the applicability of this can be extended very well in the context of medical imaging. Usually, this technique starts with the use of an ML-based system that determines those characteristics of the images that are considered to be important in making the prediction or diagnosis. As a result, the system identifies the best combination of these characteristics for the image classification and computes statistical data for the different regions identified.

The last decade demonstrates the huge potential of machine learning techniques in many domains along with the development of the graphical processing units (CPU/GPU),

[1] Carol Davila University Central Emergency Military Hospital Bucharest, Romania
[2] Faculty of Automatic Control and Computers,“Politehnica” University of Bucharest, Romania
[3] “Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania
[4] University of Illinois Chicago, USA

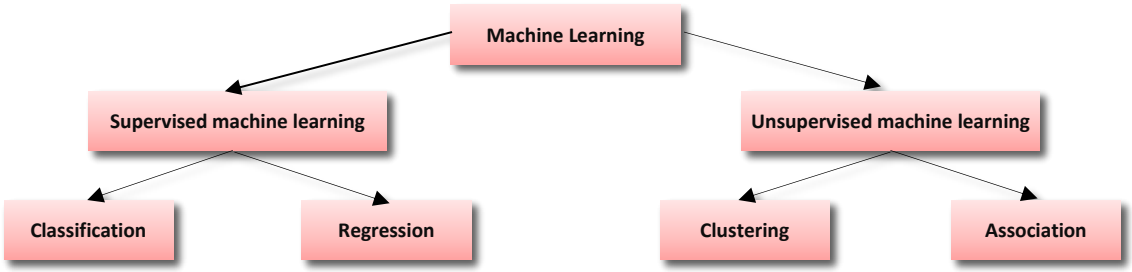
the availability of big data, and the growth of the learning algorithm efficiency [1].

Figure 1 shows the principal categorization of ML algorithms according to their main functionality. One can distinguish between Supervised Machine Learning (i.e. having an expert provide the so-called ground truth - the correct class or value - for each example in a dataset) and Unsupervised Machine Learning, where the objective is to find interesting patterns and frequent associations between examples in a dataset, without any human supervision (e.g. finding an automatic grouping of diseases by the similarity of symptoms).

Medical imaging applications mostly belong to the supervised ML category, because the correct interpretation (e.g. diagnosis, the classification of severity of a disease) of the result is provided by the medical experts who have analyzed it.

In the past decades, there was substantial growth in the healthcare applications one example is the deep learning algorithm that proved to have an outstanding accuracy in diabetic retinopathy identification [2].

Figure 1: Grouping the different types of machine learning algorithms according to the type of learning [3]



Yang et al [4] demonstrated the importance of AI about big data and parallel programming in medicine, especially in the field of cardiac imaging.

These last decades have also demonstrated the importance of medical imaging in the detection, diagnosis, and treatment of various conditions. In clinical applications, medical imaging is largely performed by a group of experts, such as cardiologists, radiologists, endocrinologists, and so on [5]. In this regard, the computer-assisted analysis enables a better interpretation of the medical image database available. Regarding the decoding of the parameters highlighted by the medical images, it is worth noticing the recent advances in deep learning techniques, which represent a considerable leap in the identification, classification, and quantification of medical conditions and/or health parameters based on input from different medical imaging techniques [6].

ARTIFICIAL INTELLIGENCE IN ECHOCARDIOGRAPHY

In the world of multimodal imaging in cardiology, echocardiography remains crucial for the diagnosis and management of patients with cardiovascular disease [7]. The advantages of the ultrasound of the heart compared to other imaging tools are low price, portability, the possibility of being repeated, short examination time, and the fact that the administration of contrast medium is unnecessary. However, errors in echocardiography quantification and conflict in the interpretation of echo images are frequent in everyday clinical practice.

Although it remains the main imagining modality used in cardiology, echocardiography has several shortcomings that can be improved. The echo machines have developed intensively during the last year (leading to accurate 2D and Doppler imaging and new technologies like tissue Doppler, speckle tracking, or 3D echocardiography). However, one of the main limitations of this method is high operator dependence. The learning curve in echocardiography is very steep and the knowledge, the experience, and sometimes even the mood of the echocardiographer are very important for the exam interpretation. For example, left ventricle ejection fraction is a crucial parameter for patient management but has a high inter- and intraobserver variability. Therefore, the result given by one observer can be different compared to another one or, even more, the same observer can give different interpretations when the reading is repeated. The purpose of AI is to overcome these issues.

Another important role of AI in this field is to solve the problem of a mismatch between the high number of echocardiography required in clinical practice and the number of cardiologists/echocardiographers available to interpret the studies. Moreover, a large volume of already acquired data is under-utilized during a routine

echocardiogram and AI offers the possibility to interpret multiple datasets in a very short time [8].

The purpose of artificial intelligence in echocardiography is to detect the disease based on some specific echocardiographic criteria [9, 10]. AI can be used in the image-acquisition process as well and helps people with limited echocardiography training to obtain standard views by anatomic guidance.

Although the implication of AI in echocardiography is still less important compared to other imaging modalities, there are many examples of applications already being used.

Software algorithms are capable of correct identification of the ultrasound modality (2D, pulse wave Doppler or continuous wave Doppler) or the view (four-, two- or three-chamber view) [11]. Moreover, the identification of structures and even the quantification of some related parameters based on border detection are also possible. One of the first applications of AI in echocardiography was the assessment of left ventricular volumes and function initially based on 2D and subsequently on 3D [12]. Based on 3D echocardiography, the correct identification of the heart chamber borders offers results comparable to those measured by cardiac magnetic resonance (left ventricle volumes and function [13], right ventricle volumes, and function [14]. The new software can compute the chamber volumes not only at a maximum or minimum level but also dynamically through the cardiac cycle [15]. Some models for the automated diagnosis of regional wall motion abnormalities and myocardial infarction using deep learning algorithms are still developing [16].

AI is already aiding in valvular heart disease; there is automated software that offers the assessment of mitral [17] or aortic valve.

Some applications can already differentiate, with high sensitivity, between some pathological conditions that need an experienced human examination: left ventricular hypertrophy in athletic population vs. in hypertrophic cardiomyopathy [18], constrictive pericarditis vs. restrictive cardiomyopathy [19].

AI can change the way we read echocardiograms. Normally the interpretation of an echocardiogram is based on consecutive views analysis. For example, in aortic stenosis grading, the observer has to integrate information from multiple non-consecutive views (annulus diameter from the parasternal long axis, continuous wave and pulse wave Doppler data from apical 5 chamber or right parasternal). AI allows the classification of these images and the analysis of the ones related to aortic stenosis grading although they have not been acquired consecutively. Therefore, in the future, the reading of an echocardiogram will be based on the chamber or valve analysis in multiple views and not on the interpretation of consecutively acquired views.

A very important aspect is that using artificial intelligence in echocardiography can modify our understanding regarding the echocardiographic data. Our knowledge of echo interpretation is based on clinical trials that have included a target population. However, this population may not always be representative of the entire population. The large amount of data obtained by including artificial intelligence and machine learning in echocardiography can change our classifications, cut-offs, and interpretation of these data. For example, a recent study based on the NEDA registry (Australian New Zealand Clinical Trials registry) showed that patients with moderate aortic stenosis have similarly high rates of mortality compared to patients with severe aortic stenosis and, likely, we'll need to reevaluate our current data regarding the indications for intervention in aortic stenosis [20].

Therefore, in echocardiography, AI offers the possibility to interpret data from the real world and not from selected patients included in clinical trials and probably a better understanding of the diseases.

Recently, machine learning and deep learning have become the main direction of development in echocardiography, which is proved by the number of publications in PubMed [21]. The possible impact of artificial intelligence on echocardiography is impressive but for now, the human mind is still far too complex compared to AI [22].

Although we all dream of an automated program for echocardiogram interpretation, there is still a long journey ahead. Thus, cardiologists should have advanced knowledge and the capability to use artificial intelligence as extended intelligence.

ARTIFICIAL INTELLIGENCE IN CARDIAC MAGNETIC RESONANCE IMAGING

There is a concern among radiologists and medical students that AI will replace the radiologist. This is not likely to be the natural evolution, but radiologists who use artificial intelligence will replace those who do not or do not think they can use it.

The modern principles of medical imaging are based on the most efficient use of the techniques that bring the maximum amount of information in the shortest time possible, starting from the moment of clinical suspicion. This aspect makes it necessary for the clinician to know the value and the limits

of each type of sectional imaging exploration, to optimize the indications of the examinations. Cardiac MRI has a very wide range of clinical applications and has been included in the guidelines for the assessment of congenital heart disease, heart tumors, pericardial disease, cardiac ventricular dysplasia, or myocardial ischemia - hibernating myocardium [23]. Other indications such as the evaluation of myocardial perfusion, ventricular or valvular function can be accurately evaluated by MRI, but compete with other imaging modalities, such as single-photon emission computed tomography (SPECT) and echocardiography, more commonly used in outpatient settings.

The major advantages of MRI are the absence of ionizing radiation and the very strong contrast and temporal resolutions (as opposed to CT, where the spatial resolution is very high [27]. Cardiac MRI provides a wealth of morphological and functional information about the heart. In some practices, the evaluation of the heart MRI requires a long global time, so the tendency is to standardize and reduce the time required for the exploration, but also for the analysis of the images obtained, by using the FAST MRI type techniques. To optimize these protocols for analyzing the data obtained from the scanning of the heart, AI techniques have been developed and used in clinical practice.

They are based on automatic machine learning techniques to enhance the ability to analyze images and data obtained by MRI scanning. The results are remarkable both in the optimization of scanning techniques and protocols, as well as in the analysis and integration of data and results. In an impressive achievement, the introduction of AI and the optimization through the machine learning algorithm can increase the speed of interpretation of the images obtained by cardiac MRI from an average of 13 minutes to about 4 seconds [24].

Cardiac MRI can establish the most appropriate plan for cardiac surgical planning, implantation of cardiac defibrillators, and assessment of cardiac toxicity in patients with oncological pathology. These decisions are based on the accuracy measurements made by MRI.

Multiple studies performed on significantly large numbers of patients have used the information to develop machine learning protocols [25]. These are based on neural network learning. For the time being, it is still necessary to validate the superiority of the efficient application of these AI-type protocols over the aspect of the presently considered examinations. At this moment, the cardiac MRI examinations intend to use a large database which, after a standardized examination and by using a minimum of subsequent maneuvers, the results will be offered in the form of measurements made automatically by the computer capable of filling an MRI result with multiple preformed fields. Also included in this result with preformed fields, the neural network algorithm also offers the diagnostic suspicions based on which differential diagnoses can be issued. The vision of those who work and create this advanced analysis and diagnostic software is to increase the speed of examination without sacrificing the accuracy and precision of interpretation.

The use of artificial intelligence is used to solve the following problems and challenges - the small number of radiologists, the long time required for each examination, the insufficient use of radiological equipment without corresponding efficiency [26].

Traditionally, CT and ultrasound are the most frequent techniques used for cardiac imaging examinations. However, MRI can occupy a very important place due to the very important contrast of tissue structures without ionizing radiation.

One of the major disadvantages of cardiac MRI is that the examination lasts for about an hour. For example, an existing software solution, called Heat Vista (available in the US), reduces the examination for suspected cardiac ischemia from 90 minutes to 15 minutes, and the solution is applied to existing equipment. The software recommends the protocol for about 10 seconds. All these technological advances also eliminate the need to examine through sequences with blocked breathing. This progress is achieved through sequences that recognize and detect artifacts and alert the technician if the sequence needs to be redone [28].

Another challenge is MRI examinations for patients with cardiac and vascular implants of various types of devices. It is necessary to adapt these protocols to the particular aspects of each patient and this aspect can be efficiently optimized by AI protocols depending on the type of implant and the manufacturer that produced them. Considering all the above, cardiac imaging and especially cardiac MRI will benefit from the integration of various AI solutions.

ARTIFICIAL INTELLIGENCE IN CARDIAC ANGIOGRAPHY

X-ray angiography is a medical imaging technique dedicated to the diagnosis and even treatment of vascular diseases. An angiography is obtained using an X-ray source and a detector located on both ends of a C-arm gantry. The imaging apparatus provides temporal images series for several seconds.

Table 1: Artificial Intelligence in cardiovascular medical imaging

Imaging Technique	Scope	Dataset	Approach Details	Measured Results
Cardiac MRI	Ventricle Segmentation [29]; Estimating Left Ventricle and Right Ventricle functioning	Cardiac MRI datasets, MICCAI 2012 RV segmentation challenge; 48 patients (16 training, 32 test)	Region of Interest (ROI) extraction using 960 cardiac MRI images with manually labeled RV and LV bounding boxes of size 150 x 150 px. Train CNNs for endocardium and epicardium semantic segmentation of RV on extracted bounding boxes.	Objective: contour overlap of segmented RV with ground truth Criteria: DM, HD, R, ME for EDV, ESV, and EF.
	Heart chamber segmentation [30]; Analyzing abnormality of wall motions	Cardiac MRI datasets, MICCAI 2012 RV segmentation challenge	Heart chamber ROI extraction using a deep learning approach for semantic segmentation. The segmentation approach was initialized with input from a prior edge detection algorithm.	Objective: contour overlap of segmented RV with ground truth Criteria: DM, HD, R, ME for EDV, ESV and EF.
Echocardiography	Regression task: left ventricular volume and ejection fraction computation; Decision making in valvular heart disease, heart failure and post-infarct care [31]	255 usable 2-dimensional echocardiography (2DE) studies	Local Ejection Fraction (EF) estimation. Comparative evaluation of automated EF measurements against manual inspection.	Objective: automated EF estimation Criteria: Intraclass correlation coefficients Bland-Altman analyses
	Regression task: left ventricular volume and Ejection Fraction estimation; [32]	218 patients including 165 with abnormal left ventricular (LV) function. 10,000 apical 4- and 2-chamber view images, from patients with cardiomyopathies, wall motion abnormalities, and dyssynchrony. Cardiac MRI for 21 patients	Identification of the Left Ventricle cavity. Manual tracing of the endocardial border. Left Ventricle volume estimation using modified Simpson's rule for Ejection Fraction computation.	Objective: automated EF estimation Criteria: 2-tailed Student t-test Bland-Altman analysis
Myocardial Perfusion Imaging (MPI) + Coronary angiography	Automatically predicting obstructive disease likelihood from myocardial perfusion imaging (MPI) [33]	1,638 patients without known coronary artery disease, undergoing stress 9mTc-sestamibi or tetrofosmin MPI in 9 different sites Coronary angiography performed within 6 months of MPI	Semantic segmentation of myocardium using a neural network method trained on raw and quantitative polar maps. Input for the network obtained using manual annotation of images obtained from nuclear cardiology software tools.	Objectives: obstructive disease prediction Criteria: area under the receiver-operating characteristic curve (AUC), sensitivity (SS)
SPECT+ computed tomography angiography	Estimating the likelihood of abnormality of coronary arteries in patients with ischemia [34]	1001 patients Coronary angiography within 60 days of myocardial perfusion SPECT for 59 patients with stable coronary artery disease	Semantic segmentation of artery zones with perfusion disorders. Use of segmentation to extract features such as shape, extent, location, count, perfusion homogeneity, regional motion, wall thickening, and sex	Objectives: obstructive disease prediction Criteria: SS, specificity, accuracy, AUC

DM – Dice metric, HD – Hausdorff distance, R – correlation coefficient, ME for EDV – mean errors for end-diastole volumes, ESV – end-systole volumes, EF – ejection fraction, MRI – magnetic resonance imaging

There are three types of angiograms: (i) monoplane angiography, which is the most common method and utilizes the single view principle, (ii) biplane angiography, which uses two C-arm systems for simultaneous acquiring of two different projections, and finally, (iii) rotational angiography, which can give the most accurate three-dimensional scenes by making a complete rotation around the patient.

In [33], the angiography and myocardial perfusion imaging are acquired from the same patient and used as training data on an artificial neural network (ANN) for an automatic prediction of obstructive disease. In [34], the coronary angiography is acquired within 60 days of myocardial perfusion SPECT for patients with stable coronary artery disease from a Japanese hospital. The purpose of ANN was to detect the coronary arteries responsible for the patients' cardiac ischemia. The algorithm accuracy to diagnose the culprit artery was similar to that of a medical expert.

Opportunities for AI applications at the peri-intervention stage are presented in [35] where diverse clinical investigations such as angiography, EKG, biomarkers are reunited for diagnosing STEMI patients. Some applications of machine learning techniques in angiography and other cardiac imaging methods can be found in Table 1.

CONCLUSIONS

The next challenge will be moving from focusing on technique and image analysis to tasks dedicated to physicians in the context of automation of other tasks. This may increase the time efficiency of the medical procedures, job satisfaction, better communication between patient-physician, and improvement of healthcare equality. AI-based solutions will contribute to fighting modern days' challenges, such as the decreasing number of skilled radiologists, leak of medical equipment used, and time-consuming diagnoses.

The final decision after integrating clinical data belongs to cardiologists. The role of artificial intelligence is not to replace humans but to make their work more accurate, fast, and efficient.

Acknowledgments

The work has been funded by the Operational Programme Human Capital of the Ministry of European Funds through the Financial Agreement 51675/09.07.2019, SMIS code 125125**.**

References:

1. Spector L., "Evolution of artificial intelligence," Artificial Intelligence, vol. 170, no. 18, pp. 1251–1253, Dec. 2006.

2. Shen D., Wu G., Suk H., 2017. Deep Learning in Medical Image Analysis

3. Garbade M.J. 2018. Regression Versus Classification Machine Learning: What's the Difference?

4. Yang A., Troup M. 2017. Scalability and validation of big data bioinformatics software

5. Brody H. 2013. Medical imaging. Nature

6. Erickson B. J., Korfiatis P., Akkus Z., Kline T. L. 2017. Machine Learning for Medical Imaging

7. Alsharqi M., Woodward W.J., Mumith J.A., Markham D.C., Upton R., Leeson P. Artificial intelligence and echocardiography. Echo Res Pract. 2018 ;5(4): R115–R125.

8. Sengupta P.P., Huang Y.M., Bansal M., Ashrafi A., Fisher M., Shameer K., Gall W., Dudley J.T. Cognitive machine-learning algorithm for cardiac imaging: a pilot study for differentiating constrictive pericarditis from restrictive cardiomyopathy. Circulation: Cardiovascular Imaging. 2016; Jun;9(6). pii: e004330.

9. Kenya Kusunose, Akihiro Haga, Takashi Abe, Masataka Sata. Utilization of Artificial Intelligence in Echocardiography, Circulation Journal, 2019, Volume 83, Issue 8, Pages 1623-1629.

10. Zhang J., Gajjala S., Agrawal P. et al. Fully Automated Echocardiogram Interpretation in Clinical Practice. Circulation 2018; 138:1623-35.

11. Khamis H., Zurakhov G., Azar V., Raz A., Friedman Z., Adam D. Automatic apical view classification of echocardiograms using a discriminative learning dictionary. Medical Image Analysis 2017:36:15–21.

12. Cannesson M., Tanabe M., Suffoletto MS, McNamara D.M., Madan S., Lacomis J.M., Gorcsan. A novel two-dimensional echocardiographic image analysis system using artificial intelligence-learned pattern recognition for rapid automated ejection fraction. Journal of the American College of Cardiology 2007;49: 217–226.

13. Levy F., Dan Schouver E., Iacuzio L., Civaia F., Rusek S., Dommerc C., Marechaux S., Dor V, Tribouilloy C., Dreyfus G. Performance of new automated transthoracic three-dimensional echocardiographic software for left ventricular volumes and function assessment in routine clinical practice: Comparison with 3 Tesla cardiac magnetic resonance. Archives of Cardiovascular Diseases 2017:110:580–589.

14. Stebbing R.V., Namburete A.I., Upton R., Leeson P., Noble J.A. Data-driven shape parameterization for segmentation of the right ventricle from 3D echocardiography. Medical Image Analysis 2015;21: 29–39.

15. Tsang W., Salgo I.S., Medvedofsky D. et al. Transthoracic 3D Echocardiographic Left Heart Chamber Quantification Using an Automated Adaptive Analytics Algorithm. JACC Cardiovasc Imaging 2016; 9:769-82.

16. Kusunose K., Haga A., Abe T., Sata M. Utilization of Artificial Intelligence in Echocardiography. Circulation Journal 2019;83: 1623-1629.

17. Cobey F.C. Intelligent algorithms in perioperative echocardiography: a new era. Journal of the American Society of Echocardiography 2017;30: A26–A27

18. Narula S., Shameer K., Salem Omar A.M., Dudley J.T., Sengupta P.P. Machine-Learning Algorithms to Automate Morphological and Functional Assessments in 2D Echocardiography. J Am Coll Cardiol.

2016 Nov 29; 68(21):2287-2295.

19. Mahmoud A., Bansal M., Sengupta P.P. New Cardiac Imaging Algorithms to Diagnose Constrictive Pericarditis Versus Restrictive Cardiomyopathy. Curr Cardiol Rep. 2017 May; 19(5):43.

20. Strange G., Stewart S., Celermajer D. et al. Poor long-term survival in patients with moderate aortic stenosis. JACC imaging 2019, in press.

21. Sengupta P., Adjerh D. Will artificial Inteligence Replace the Human Echocardiographer? Circulation. 2018;138: 1639–1642.

22. Narang A., Lang R. Artificial intelligence and Echocardiography. Expert Analysis in ACC, 2019, 18 june.

23. Siegersma K.R., Leiner T., Chew D. P., Appelman Y., Hofstra L. & Verjans J. W. Artificial intelligence in cardiovascular imaging: state of the art and implications for the imaging cardiologist (2019)

24. Dey D., Slomka P.J., Leeson P., Comaniciu D., Shrestha S., Sengupta P.P., Marwick T.H. Artificial Intelligence in Cardiovascular Imaging: JACC State-of-the-Art Review Am Coll Cardiol. 2019.

25. Petersen, Abdulkareem M., Leiner T. Artificial Intelligence Will Transform Cardiac Imaging-Opportunities and Challenges. Front Cardiovasc Med. 2019 Sep 10;6: 133. doi:10.3389/fcvm.2019.00133. eCollection 2019

26. Thrall J.H., Li X., Li Q., Cruz C., Do S., Dreyer K., Brink J.J. Artificial Intelligence and Machine Learning in Radiology: Opportunities, Challenges, Pitfalls, and Criteria for Success. Am Coll Radiol 2018 Mar;15(3 Pt B):504-508.2017.12.026. Epub 2018 Feb 4.

27. Arsanjani R., Dey D., Khachatryan T. et al. Prediction of revascularization after myocardial perfusion SPECT by machine learning in a large population. J Nucl Cardiol. 2015; 22:877–884.

28. Avendi M.R., Kheradvar A., Jafarkhani H. A combined deep-learning and deformable-model approach to fully automatic segmentation of the left ventricle in cardiac MRI. Med Image Anal. 2016;30: 108–119.

29. G. Luo, R. An, K. Wang, S. Dong and H. Zhang, "A Deep Learning Network for Right Ventricle Segmentation in Short Axis MRI," 2016 Computing in Cardiology Conference (Cin C), Sep. 2016.

30. M. Avendi, A. Kheradvar and H. Jafarkhani, "Fully automatic segmentation of heart chambers in cardiac MRI using deep learning," Journal of Cardiovascular Magnetic Resonance, vol. 18, no. S1, Jan. 2016.

31. N. Furiasse and J. D. Thomas, "Automated Algorithmic Software in Echocardiography," Journal of the American College of Cardiology, vol. 66, no. 13, pp. 1467–1469, Sep. 2015.

32. M. Cannesson, M. Tanabe, M. S. Suffoletto, D. M. McNamara, S. Madan, J. M. Lacomis and J. Gorcsan. "A Novel Two-Dimensional Echocardiographic Image Analysis System Using Artificial Intelligence-Learned Pattern Recognition for Rapid Automated Ejection Fraction," Journal of the American College of Cardiology, vol. 49, no. 2, pp. 217–226, Jan. 2007.

33. J. Betancur, F. Commandeur, M. Motlagh, T. Sharir, A. J. Einstein, S. Bokhari, M. B. Fish, T. D. Ruddy, P. Kaufmann, A. J. Sinusas, E. J. Miller, T. M. Bateman, S. Dorbala, M. Di Carli, G. Germano, Y. Otaki, B. K. Tamarappoo, D. Dey, D. S. Berman, and P. J. Slomka, "Deep Learning for Prediction of Obstructive Disease From Fast Myocardial Perfusion SPECT," JACC: Cardiovascular Imaging, vol. 11, no. 11, pp. 1654–1663, Nov. 2018.

34. H. Yoneyama, K. Nakajima, J. Taki, H. Wakabayashi, S. Matsuo, T. Konishi, K. Okuda, T. Shibutani, M. Onoguchi, and S. Kinuya, "Ability of artificial intelligence to diagnose coronary artery stenosis using hybrid images of coronary computed tomography angiography and myocardial perfusion SPECT," European Journal of Hybrid Imaging, vol. 3, no. 1, Mar. 2019.

R.R. Bond, K. Rjoob, D. Finlay, V. Mc Gilligan S. J. Leslie, C. Knoery, A. Iftikhar, A. McShane, I.A. Tache, P. Biglarbeigi, M. Manktelow, A. Peace. Near future artificial intelligence in interventional cardiology: new opportunities and challenges to improve the care of STEMI patients. Digital Health Virtual Journal, 31 Mar 2020

The article was received on February 27, 2020, and accepted for publishing on July 9, 2020.

VARIA

The role of career anchors in human resource strategy (Case study: Students of Management Faculty of Yadegar-e-Imam Khomeini (RAH) Shahre Rey Branch, Islamic Azad University)

Mir M. Peidaie, Mohammad Belal

Abstract: *Maintenance of efficient, highly specialized, and valuable forces in the present age is one of the most important concerns of organizations, especially organizations with advanced technologies. The importance of human resources planning and management in these organizations has greatly increased, and in the various areas of human resource management, the approach to occupational anchor planning has been very much considered. The purpose of this study was to investigate the role of the job path anchors in human resource strategy among the target community. Participants were selected randomly from among 3500 students at the Faculty of Management of Yadegar-e-Imam Khomeini (RAH) Shahre Rey Branch, Islamic Azad University in Tehran Province, Iran. The sample size was 346 by the Cochran method and the questionnaire was collected by electronic means. At the time of the study, 346 questionnaires were completed and the analysis was performed based on 346 questionnaires. To collect data, standard job anchor questionnaires, and Human Resources Strategic HR Questionnaire was used. The study population included 346 people, of whom 203 were male and 143 were female. The age of the people below the age of 20 was 38, from 20 to 25 years old, 94, between the ages of 26 and 30, 60, people aged 31 to 35, and 76 people over the age of 35 years. The reliability of the work anchors was 91% and the human resources strategy questionnaire was 80%. Investigations have shown that, on the anchors of the career path, the factors of creativity - entrepreneurship, autonomy-independence, pure challenges and public management with a committed strategy and public management, creativity-entrepreneurship, security-stability in the strategy of contracting businesses and creativity - entrepreneurship, Pure challenges, security with secondary jobs, and creativity-entrepreneurship, public management, pure challenges in parenting jobs. According to the results of this study, it seems that the emphasis on reducing organizational structures, empowerment, and participatory decision making can determine the necessary grounds for determining the type of human resources strategy in an organization.*

Keywords: *job path anchors, HR strategies, management, human resources, strategy*

INTRODUCTION

In today's world, the power, economic power, and prosperity of any country depend on the optimal use of its facilities, industries, and especially its human resources. Qualified and skilled human resources are the endless value and capital contributions to the growth and development of

Corresponding author: Mohammad Belal
mhd.belal5@gmail.com

Faculty of Accounting and Management, Yadegar-e-Imam Khomeini (RAH) Shahre Rey Branch, Islamic Azad University, Tehran, Iran

organizations and countries, and the greatest asset of a country is its growth factor. If labor, capital, and land were the main factors of production in the past, today technological change, manpower, and increased productivity is considered to be the drivers of growth [1]. In today's world, organizations are in constant competition. The intensity of competition increases every year and all organizations are constantly in need of improved organizational performance for their survival and growth. Therefore, through an efficient and effective human resources management system, individuals can be considered as strategic assets [2]. The term human resource strategy as a process is a specific set of human resource requirements developed by an organization to achieve its goals. Price, in defining a definition of the human resources strategy, stated that the human resources strategy encompasses all activities related to managing people in the organization in the form of coherent plans to achieve the strategic goals of the organization. Some writers have stated in the concept of strategy as a consequence that "human resource strategy is a model of decisions related to human resource system policies and actions" [3]. Creating a job in a world with diminished job security, changing technology, and increased personal responsibility for the training of certain skills, employment, and lifelong learning are key to meeting the challenges of today's world. Researchers have found that the complexity of the burgeoning context today has a significant impact on people's work attitudes and experiences in their working lives [4]. The concept of a career path, as a link between the organizations and the individuals they work for, is explored from both an internal and an external point of view. Slow and defined as organizational indicators of a career path, while the internal career path is the tendency for employees to move to or from the job anchor. It consists of three main categories: 1. Talents and abilities Self-perception; 2. Core values; 3. Evolved feelings about the motivations and needs that drive the career path [5].

Edgar Shine Model Career Anchors, with 8 Anchors:

1. Technical-Functional Competence: In this anchor, one is primarily motivated by automated content and tends to be employed in technical and specialized positions and jobs.

2. Managing Competency: This personal anchor is motivated by the opportunity to study complex conceptual issues under uncertain circumstances and incomplete information and tend to managerial positions and jobs in large organizations.

3. Security - Stability: In this personal anchor, it is promoted to a reputable organization through job security and long-term attachment.

4. Creativity - Entrepreneurship: In this anchor, one is motivated by the need to build or create projects that belong to him/her.

5. Autonomy - Independence: In this anchor, a person is essentially seeking job opportunities that enjoy maximum freedom in terms of organizational boundaries and are thus stimulated.

6. Serving and Sacrifice and Sacrifice: In this anchor, one is motivated to serve and pursue a sacred cause and to meet the needs of others.

7. Pure Challenges: In this anchor, the individual is challenged to overcome major obstacles, solve difficult problems, or win over competitors.

8. Lifestyle: People with this anchor tend to balance their career paths with their families [6].

Human Resources Strategy

In the early years of 1980, strategic human resource management was the focus of a large number of influential management consultants and researchers in practicing management practices. These authors found that effective human resource management can guarantee quality and be effective in terms of competitive advantage. Not surprisingly, in the mid-1980s, many HR researchers favored the view that more HR units should play a greater role. The first models of human resource strategy formulation were introduced in the middle of this decade. These models, with a strong emphasis on human resource strategy adherence to organizational strategy, presented a rational and logical approach to unifying strategic issues for managing the overall human resources of organizations [7]. But the first models that could offer different strategies for different organizational conditions were single-dimensional models based on the labor market type or control type factor in 1987. These models did not necessarily coincide with the strategy of the organization, thus preventing the possible errors in the process of formulating the organization's strategy into a strategy of human resources. Combined, by introducing the "one-piece model", they proposed the use of strategic reference points (SRPs) to formulate HR strategies (8). The importance of this model is that, in addition to the logic of attraction, for the reason that it is compatible with the fundamentals of management philosophy, it can be formulated and implemented without the need for organization strategy, while maintaining its alignment with the organization's strategy. On the other hand, the HR strategy formulation using this model does not rely on the examination and modeling of the status quo. Using two main

dimensions of control (efficiency or process control) and labor market (concerning internal or external market), they have formulated four HR strategies [9].

Secondary strategy

This strategy is suitable for simple, duplicate, and standardized jobs that have a sufficient supply of labor outside the company and there is no need to nurture and retain them. In other words, they can be easily disconnected if they are not needed or unsatisfied with each other and can hire serious employees with the least training and cost if needed.

Paternal strategy

This strategy is also applicable to simple, repetitive, and standardized jobs, with the exception that corporate management tends to retain and enhance existing employees and align them with corporate culture. Therefore, vacancies can be filled by upgrading existing staff.

Contracting Strategy

This strategy is suitable for those complex and specialized jobs that require constant and formal hiring of relevant experts for the company, as the company needs these jobs in short and temporary terms. Therefore, these experts are usually highly compensated, solely for consulting or part of an invitation plan, and then return to the job market after the project is completed to provide similar services. Of course, some organizations (especially virtual organizations) also eliminate the constant need for their expert staff by using these experts' temporary or unnecessary services because the management of these organizations has been able to take full control of the organization's specific knowledge. Also, apply evaluation and promotion tools [10].

Committed strategy

This strategy is also applied to complex and specialized jobs, except that the experts in these jobs are constantly in need of the company and because they in many cases master the complex production network and specific knowledge required by the company. They are not easy to replace. Therefore, it is necessary to have an effective approach to the labor market within the organization, that is, to develop and train company experts and to strengthen their commitment and loyalty to the organization in such a way that these experts are exposed to higher market rights and benefits in the face of a secure and dynamic career future. Ignore work outside the organization. In the strategic reference point's theory, a three-dimensional matrix is used to determine the reference points that includes the internal conditions of the organization, the external conditions of the organization, and time [11].

METHOD

The purpose of this study is cross-sectional applied in terms of purpose and type of research method and the research population is comprised of management students of Islamic Azad University, Yadegar Imam Branch - Shahre Ray. To ensure that the sample selected represents the real community, the sample was selected using correct sampling methods. Random sampling was also used to select the sample members. Morgan table was used to determine sample size in the present study. Since the target population in this study was 4 people, the sample size in this study was 9 people. Data were collected using the standard Anchor Job Inventory and HR strategy questionnaire as measured in previous studies. Surveying is one of the most common methods in quantitative social science research. Since quantitative research is not possible to study the behavior of all individuals in the community, the study is conducted through sampling. In this regard, a sample is selected and the result is generalized to the whole community [12]. After completing the questionnaire and collecting and removing the defective questionnaires, the data were analyzed with SPSS 23 software.

DISCUSSION

This section presents all the analyzes based on the assumptions of the present study. The analysis of the results will greatly help the scientific and purposeful discussion of the research topic.

The demographic variables of this study are as follows: The total number of participants was 346 persons, 203 men, and 143 women. The age group of people under the age of 20 is 38, 20 to 25, 94, between 26 and 30 are 60, people between 31 and 35 are 76, and people over 35 are 76. In terms of marital status, 192 were married and 154 were single; 118 were married, 36 were married, and 85 were single and 107 were single. The level of education in the associates is 50, 142 bachelors, and 154 masters. In terms of job status, 84 students were self-employed, 106 were employed in private companies, 109 were employed in public offices and 47 were employed in semi-public offices. Of these, 53 were freelance male, 78 were male, 78 were male, and 25 were semi-public, with a total population of 203.

Hypothesis 1: What are the career path anchors in committed business executives and what are their priorities?

To respond to this hypothesis, the relationship between the two factors of job anchors and commitment factors of the

HR strategy questionnaire was measured. Regression analysis can be used to determine the correlation between occupational anchor factors and the occupational commitment factor. Regression is a method for estimating and modeling the relationship of several independent variables to one dependent variable.

According to Table 1 and statistical significance at the level of 0.8, the regression model is significant. On the other hand, model estimation data show that independent variables account for approximately 5% of the total variance of the response variable. In other words, the 5 factor of job anchors is the ability to predict the factor of the committed jobs. Based on this, it is possible to determine appropriate modeling to determine the simultaneous relationship between occupational anchor factors and the occupational factor.

Table 1: Regression model and model evaluation indices

Estimation error		**The adjusted coefficient of determination**		**The coefficient of determination**		**Model evaluation**
5.103		0.268		0.285		
P	F statistics	The average sum of square	Degrees of freedom	The sum of the regression squares		
0.000	16.822	438.076	8	3504.610	regression	Significance of the model
		26.041	337	8775.834	Error	
			345	12280.474	Total	

According to the results of Table 2, variables A1, A4, A6, and A8 are not significant. In other words, in assessing the simultaneous relevance of job anchor factors, only the five key factors of public management, autonomy-autonomy, creativity-entrepreneurship, and sheer challenges are effective on the commitment factor. In other words, measuring and scoring these 5 factors can determine the type of person's job.

Table 2: Model coefficients and their significance

Model coefficients	Coefficients	Regression coefficient	Governor error	Standardized coefficient	T statistics	P
	Constant coefficient	9.224	1.921	-	4.801	0.000
	Technical-Applied Orientation (A1)	-0.087	0.112	-0.052	-0.773	0.440
	Public Management Tendency (A2)	0.452	0.092	0.299	4.892	0.000
	Autonomy - Independence (A3)	0.358	0.125	0.215	2.863	0.004
	Security-stability orientation (A4)	-0.001	0.083	-0.001	-0.013	0.989
	Creativity-Entrepreneurship (A5)	-0.258	0.085	-0.175	-3.012	0.003
	Serving and Sacrifice and Sacrifice (A6)	0.041	0.125	0.024	0.328	0.743
	Pure Challenges (A7)	0.451	0.097	0.300	4.636	0.000
	Lifestyle (A8)	-0.198	0.122	-0.117	-1.617	0.107

So the mathematical model would be as follows:

Committed Jobs = *A7 0.451+ *A5 0.258 - *A3 0.358 + *A2 0.452 + 9.224

This mathematical model implies that for each unit score increase in the A2, A3, A5, and A7 factors the commitment factor score will increase by 10.227 points.

Hypothesis 2: What are the career anchors of contractors and what are their priorities?

To answer this hypothesis, as in the first hypothesis, one can determine the relationship between job anchor factors and contractor job factors using a statistical regression method.

According to Table 3 and statistical significance at the level of 0.9, the regression model is significant. On the other hand, model estimation data show that independent variables account for approximately 5% of the total variance of the response variable. In other words, the 5 factor of job anchors is the ability to predict the factor of contracting jobs. Based on this, it is possible to determine appropriate modeling to determine the concurrent relationship between occupational anchor factors and contractor occupation factors.

Table 3: Regression model and model evaluation indices

Estimation error		The adjusted coefficient of determination		The coefficient of determination		Model evaluation
3.732		0.127		0.147		
P	F statistics	The average sum of square	Degrees of freedom	The sum of the regression squares		
0.000	7.271	101.275	8	810.203	regression	Significance of the model
		13.928	337	4393.799	Error	
			345	5504.003	Total	

According to the results of Table 4, variables A1, A3, A6, A7, and A8 are not significant. In other words, in evaluating the simultaneous relevance of job anchor factors, only the five key factors of public management, security-stability, and creativity-entrepreneurship are effective contractors. In other words, measuring and scoring these 5 factors can determine the type of person's job.

Table 4: Model coefficients and their significance

Model coefficients	Coefficients	Regression coefficient	Governor error	Standardized coefficient	T statistics	P
	Constant coefficient	5.508	1.405	-	3.920	0.000
	Technical-Applied Orientation (A1)	0.145	0.082	0.130	1.767	0.078
	Public Management Tendency (A2)	0.161	0.068	0.159	2.377	0.018
	Autonomy - Independence (A3)	-0.170	0.092	-0.152	-1.855	0.064
	Security-stability orientation (A4)	0.183	0.061	0.183	3.010	0.003
	Creativity-Entrepreneurship (A5)	0.175	0.063	0.178	2.804	0.005
	Serving and Sacrifice and Sacrifice (A6)	0.024	0.091	0.021	0.259	0.796
	Pure Challenges (A7)	-0.028	0.071	-0.028	-0.391	0.696
	Lifestyle (A8)	0.019	0.090	0.017	0.212	0.832

So the mathematical model would be as follows:

Contracting Jobs = *A5 0.175 +*A4 0.183+*A2 0.161 +5.508

The concept of this mathematical model is that for each unit score increase in the A2, A4, and A5 factors the contractor job factor score will increase by 6.0۲۷.

Hypothesis 3: What are the job anchors in secondary jobholders and what are their priorities?

To answer this hypothesis, as with the previous hypotheses,

one can determine the relationship between job anchor factors and secondary job factors by the statistical regression method.

According to Table 5 and statistical significance at the level of 0.05, the regression model is significant. On the other hand, model estimation data show that independent variables account for approximately 23% of the total variance of the response variable. In other words, the 5 job anchor factors can predict the secondary job factor. Accordingly, it is possible to determine the appropriate modeling to determine the correlation between the job anchor factors and the secondary job factor.

Table 5: Regression model and model evaluation indices

Estimation error		The adjusted coefficient of determination		The coefficient of determination		Model evaluation
4.576		0.226		0.244		
P	F statistics	The average sum of square	Degrees of freedom	The sum of the regression squares		
0.000	13.565	284.084	8	2272.671	regression	Significance of the model
		20.943	337	7057.760	Error	
			345	9330.431	Total	

According to the results of Table 5 the variables A1, A2, A3, A6, and A8 are not significant. In other words, in assessing the concurrent relevance of job anchor factors, only the three key factors of security-stability, creativity-entrepreneurship, and sheer challenges to effective secondary jobs are effective. In other words, measuring and scoring these 3 factors can determine the type of person's job.

So the mathematical model would be as follows:

Secondary occupations = *A7 0.336- *A5 0.237 + *A4 0.384 + 6.340

The concept of this mathematical model is that for each unit score increase in A4, A5, and A7 the secondary job factor score will increase by 6.625 points.

Hypothesis 4: What are career path anchors in parenting and what are their priorities?

To answer this hypothesis, as with the previous hypotheses, one can determine the relationship between job anchor factors and secondary job factors by the statistical regression method.

According to Table 6 and statistical significance at the level of 0.05, the regression model is significant. On the other hand, model estimation data show that independent variables account for approximately 23% of the total variance of the response variable.

In other words, the 8 job anchor factors can predict the parent job factor. Based on this, appropriate modeling can be determined to determine the correlation between the job anchor factors and the parent job factor.

According to the results of the table below, variables A1, A3, A4, A6, and A8 are not significant. In other words, in evaluating the simultaneous relevance of job anchor factors, only the five key factors of public management, creativity-entrepreneurship, and sheer challenges are effective on the factor of hospitable jobs.

In other words, measuring and scoring these 3 factors can determine the type of person's job.

Table 6: Regression model and model evaluation indices

Estimation error		The adjusted coefficient of determination		The coefficient of determination		Model evaluation
5.734		0.227		0.245		
P	F statistics	The average sum of square	Degrees of freedom	The sum of the regression squares		
0.000	13.680	449.745	8	3597.964	regression	Significance of the model
		32.875	337	11071.929	Error	
			345	14676.893	Total	

So the mathematical model would be as follows:

Paternal Occupation = *A7 0.807+ *A5 0.261-A2 0.281+ 7.154

The concept of this mathematical model is that for each unit score increase in the A2, A5, and A7 factors, the secondary job factor score will increase by 7.981 points.

Table 7: Model coefficients and their significance

Model coefficients	Coefficients	Regression coefficient	Governor error	Standardized coefficient	T statistics	P
	Constant coefficient	7.154	2.159	-	3.314	0.001
	Technical-Applied Orientation (A1)	-0.169	0.126	-0.093	-1.342	0.181
	Public Management Tendency (A2)	0.281	0.104	0.17	2.704	0.007
	Autonomy - Independence (A3)	0.155	0.141	0.085	1.104	0.27
	Security-stability orientation (A4)	-0.024	0.093	-0.014	-0.254	0.800
	Creativity-Entrepreneurship (A5)	-0.261	0.096	-0.163	-2.718	0.007
	Serving and Sacrifice and Sacrifice (A6)	-0.135	0.14	-0.073	-0.965	0.335
	Pure Challenges (A7)	0.807	0.109	0.492	7.395	0.001
	Lifestyle (A8)	0.02	0.138	0.011	0.142	0.887

Explain the first hypothesis: Anchors of managerial competence, sheer challenges, and autonomy – independence and creativity – entrepreneurship are effective in committed jobs. Given that these jobs are complex and specialized and require specific knowledge, replacing them in these jobs is simply not possible and the specific characteristics of this group, which is autonomy and independence, the manager of the organization should have sufficient authority to act. It created these people. At the same time, people need to have adequate training in problem-solving to make the organization more effective. Management can use these people in managerial positions to advance organizational goals.

Explain the second hypothesis: In this hypothesis, job anchors include security – stability, creativity – entrepreneurship, and managerial competence. These contractors are highly specialized in the organization and have a high cost to the corporations, so hired individuals must possess the qualities of managerial competence, creativity, and entrepreneurship. In the meantime, they tend to do things that are more stable and secure. Besides, given the creativity of the staff, the organization can create the potential for individuals to emerge [13].

Hypothesis 3: Job Anchors are the most effective - security, stability, sheer challenges, and creativity - entrepreneurship. Given that, people in the workforce are simple, repeatable, and standardized, and there are enough people in the job market, so people are looking for job stability that they need to be creative and entrepreneurial to solve the challenge. Establish their sustainability organization [14].

Hypothesis 4: Job Anchors include pure challenges, managerial competence, and creativity-entrepreneurship. These jobs are very simple, repetitive, and standard. In these jobs, people have longer-term contracts, and the organization tends to stay in the organization and benefit from it when needed. In the strategy of committed and contracted jobs, due to the specialization of these jobs and jobs in this strategy, anchors of managerial competence and creativity - entrepreneurship are common and the subject of sheer challenges in commitment and security - stability in the contractor is different. The results show that managerial competence and creativity-entrepreneurship are an important issue in these two strategies. The results show that there are three factors of managerial competence, creativity-entrepreneurship, and pure challenges between committed and paternal strategies. The distinction between these strategies in autonomy is that they are required for extraordinarily specialized work (committed strategy) [15].

The results of the present study show that there is a significant and positive relationship between the

components of public management competency, creativity-entrepreneurship, and pure challenges with HR strategies.

In the study of Amirtash et al. (2011), the comparison of job anchors and organizational commitment between physical education and non-physical education faculty members of Islamic Azad University of Iran was used by Edgar Shine Job Anchor Questionnaire. We have used [16].

Khayef Elahi et al. (2015).on the impact of anchor dimensions concerning job factors on organizational outcomes, in line with the results of the research that considers job path anchors as effective [17] is in line with the results of this study [17].

Gholamzadeh et al. (2012) used a bumper questionnaire in a study on the impact of HR strategy based on the theory of strategic bumper reference points and on the performance of managers and staff, which we also used [18].

CONCLUSION

The present study is the anchor of autonomy and independence as a common component in all four strategies, which emphasizes the importance of reducing organizational structures and participatory decision-making. It also emphasizes that it empowers employees and provides the necessary framework for staff decision-making. There is also a plan to help employees, such as solving personal problems of employees that impede their effective performance path. Where employees have the knowledge and skills and therefore the issue of managerial competencies is important. In management and specialist careers, the choice must be very careful. Managers are advised to pay attention to the provision and promotion of workforce development and support, as well as training and development of staff, and staff promotion based on their career path and merit. In the four strategies available, anchors of technical and functional competence, self-sacrifice, and sacrifice, as well as lifestyle, are missing. These anchors focus on the topics and personal lives of individuals and draw the attention of executives to motivate their employees to create a path that leads the individual forward with idealism and self-control. This raises the challenge that managers by integrating individual and organizational goals can play a special role in promoting the individual and the organization and enhancing the organization and the individual.

Acknowledgments: This article is excerpted from a master's thesis by Mohammad Bilal. The authors are extremely grateful to all those who contributed to this study.

Conflicts of interest: The authors declare that they have no conflict of interest.

References:

1. Aryee S, Leong C. C. Career orientations and work outcomes among industrial R&D professionals. Group & Organization Studies. 1991; 16(2): 193-205.

2. Bamberger P, Phillips B. Organizational environment and business strategy: Parallel versus conflicting influences on human resource strategy in the pharmaceutical industry. Human Resource Management. 1991; 30(2): 153-182.

3. Bernhut S. An interview with Jim Collins. Ivey Business Journal Online. 2009; 73(4):10-15.

4. Buono A. F. Managing Human Resources: Productivity, Quality of Work Life, Profits. Personnel Psychology. 1998; 51(4): 1041.

5. Coetzee M, Schreuder D. A. Career anchors as a meta-capacity in organizational career development. In Psycho-social career meta-capacities. Springer International Publishing. 2014; 139-154.

6. Danziger N, Rachman-Moore D, Valency R. The construct validity of Schein's career anchors orientation inventory. Career Development International. 2008; 13(1): 7-19.

7. Garratt B. Developing strategic thought: Rediscovering the art of direction-giving. McGraw-Hill.1995.

8. Jiang J.J, Klein G. Supervisor support and career anchor impact on the career satisfaction of the entry-level information systems professional. Journal of management information systems. 1999; 16(3): 219-240.

9. Lumley E.J. Exploring the relationship between career anchors, job satisfaction and organisational committment(Doctoral dissertation). 2008.

10. McNamara C. Strategic Planning (in nonprofit or for-profit organizations). Free Management Library. 2001.

11. Meier H, Roy R, Seliger G. Industrial product-service systems—IPS2. CIRP Annals-Manufacturing Technology. 2010; 59(2): 607-627.

12. Meiliani M. Career anchors and job satisfaction: the role of psychological empowerment in the Indonesian public university context. 2014.

13. Mingers J, White L. A review of the recent contribution of systems thinking to operational research and management science. European journal of operational research. 2010; 207(3): 1147-1161.

14. Chapman R.L, Brown L.B. An empirical study of the career anchors that govern career decisions. Personnel Review. 2014; 43(5):717-740.

15. Vui-Yee K. The impact of strategic human resource management on employee outcomes in private and public limited companies in Malaysia. Journal of Human Values. 2015; 21(2):75-86.

16. Amirtash A, Mozafari S, Mehri K, Janani H. Comparison of Career Anchors and Organizational Commitment amongst Physical & Non-Physical Education Faculties of Islamic Azad Universities in Iran. 2011; 5: 111-130.

17. Elahi Kh, The Effects of Career Aspects on Organizational Outcomes through Consideration of Job Factors. Journal of Research in Human Resources Management. 2015; 6(4): 157-182.

18. Golamzadeh D, jalali S. Human Resources Strategy Formulation by Strategic Reference Points Theory (Case Study: RPK Company). Journal of Public Administration.2012; 4(10): 137-152.

The article was received on April 28, 2020, and accepted for publishing on July 9, 2020.

VARIA

Overview of telemedicine use aspects in natural and technical disaster and combat situation

Hamid R. Rasouli[1], Karim S. Kondor[2], Fathollah Ahmadpour[1], Mohammad Nobakht[2], Ali A. Esfahani[2], Mohsen A. Farajzadeh[2]

Abstract: *Background: Preparation and hospital development estimated an essential part of the policies and strategic purposes of healthcare in each government. Today, applications of management to reduce the burden of natural and technical disasters appear are very necessary.*

Objectives: The study aimed to review the major relevant articles in the case of the application of telemedicine for trauma injuries in disaster and military situations.

Methods: Original clinical trials investigating the effects of telemedicine on trauma injuries published before April 2018 were aggregated, and used in this study. We search the scientific sources such as PubMed, MEDLINE, Wiley, EMBASE, ISI, and Scopus. The keywords that applied to identify these articles combined: Telemedicine, Mobile Health, Health, Mobile, mHealth, Telehealth, eHealth, Trauma, War, military, medicine, Wounds and Injuries, injuries.

Results: The text of the articles and abstracts were examined from various aspects, the 21 articles were evaluated for quality, and then 10 papers entered in a systematic review. We found that the use of telemedicine in trauma injury, rural and the military is very helpful for high-quality trauma care; also the telemedicine and telephone consultations can be were demonstrated reducing the risk of physician-related medicine mistakes. The economic evaluation of telemedicine was demonstrated cost-saving and cost-effective of telemedicine consultations. We also realized the importance and practicable of telemedicine for improving rural trauma care.

Conclusions: Ultimately, the telemedicine can help patients and health government organizations economically, the telemedicine consultations due to cost-saving and cost-effective. Further studies to evaluate the running of telemedicine need to abating the practical and high-efficiency method, that can be done everywhere and it's free from mistakes and defects.

Keywords: *telemedicine, trauma, disaster*

BACKGROUND

Preparation and hospital development estimated an essential part of the policies and strategic purposes of healthcare in each government. Today, applications of management to reduce the burden of natural and technical

Corresponding author: Mohsen Abbasi Farajzadeh
mohsen10_fam@yahoo.com

[1] Trauma Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Marine Medicine Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

disasters appear are very necessary. [1, 2]. Telemedical technology is increasingly moving into the medical system. Teleconsultation between crisis positions with a lack of specialists' physician and a trauma center in surgical and trauma patients could save interventions [3-5]. In recent years, Telemedicine is growing more prevalent in intensive care medicine, but its impacts and the excellent organizational pattern is also ambiguous [6-8]. Particularly in situations that there is a shortage of extremely educated healthcare workers on-scene such as rural EMS, disaster, and military conditions, conditions teleconsultation could improvements in patient care via consultation of a specialist [3-7].

Telemedicine is a valuable method of implementing remote diagnoses such as ophthalmology, dermatology, and radiology [8]. Telemedicine represents the use of medical knowledge transferred from one position to another by electronic connections to enhance patients' health situation and care [2-5]. Crisis management in natural and technical disasters should decrease the harmful impacts of trauma events, mortality, and morbidity applying a designed program of development and mobilization. Notwithstanding, there are a lot of experiences in crisis management, it has limited application of telemedicine in disaster and military situations [2-6].

Application of the telemedicine in disaster and military situations management is the principal subject to maintain the health of accident patients [7]. Regarding the destruction created in the health services infrastructure, infrastructure has become a significant issue, the existence, and utilization of telemedicine technology and according to continuous development in electronic technology, communication to deliver health services in remote regions [6-8].

We try to review the major relevant articles in case of application of telemedicine for trauma injuries in disaster and military situations to help clinicians and patients to have a better understanding of these technologies and choosing the better therapeutic option. A highly standardized evidence-based review can be one of the best references for clinicians to decide about their treatment plan.

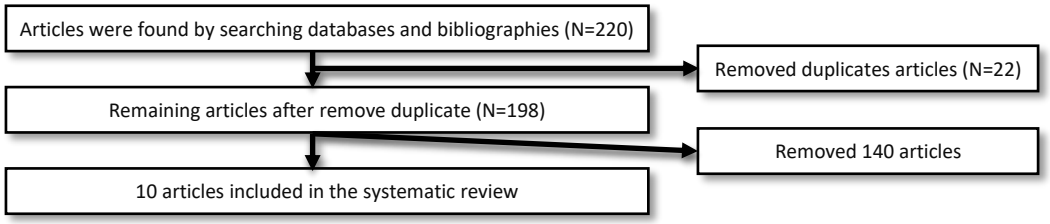
MATERIALS AND METHODS

Original clinical trials investigating the effects of telemedicine on trauma injuries published before April 2018 were aggregated, and used in this study. We search the scientific sources such as PubMed, MEDLINE, Wiley, EMBASE, ISI Web of Knowledge, and Scopus.

The keywords that applied to identify these articles combined: Telemedicine, Mobile Health, Health, Mobile, mHealth, Telehealth, eHealth, Trauma, War, military, medicine, Wounds and Injuries, injuries. Two authors have independently assessed the titles and abstracts of all papers obtained by the searching method outlined above.

The studies with the following criteria were excluded: did not evaluate the performance of Telemedicine; were not English-language study, and were review studies and letters to editors or conference abstracts. The two reviewers who carried out the literature search also individually made decisions and selected studies considering inclusion criteria. The following details were extracted from included studies independently by two reviewers, study location, year of publication, the first author's surname, study design, and outcomes.

Figure 1: Flow chart the inclusion studies



RESULTS

Ten studies matched the criteria for analysis and discussion.

Daniel et al. (2013) in a randomized trial study examined emergency care between two groups. Doctor-staffed EMS teams compare to paramedic teams that were established telemedical by an EMS doctor. Overall 16 teams that each team contained one EMS physician and two paramedics randomly divided into the control and telemedicine group. Telemedical functionalities included 2 methods of audio communication, transportation of vital information, and video streaming from the situation place to the remotely placed EMS doctor. There were no significant differences in the case-specific items and, no potentially hazardous mistreatments were reported. They showed telemedical supported paramedic care as possible and at least not poor

respect to conventional EMS teams with a doctor on-scene in these situations [9].

Table 1: Author's name, type of study and summaries of outcomes in the studies

Author's name	Type of study	Outcomes
Daniel et al. (2013) [9]	Randomized trial study	They showed telemedical supported paramedic care as possible and at least not poor respect to conventional EMS teams with a doctor on-scene in these situations
Brennan et al. (1998) [10]	Randomized trial study	They concluded that telemedicine was observed to be a satisfying system for pre-chosen emergency department patients and was observed by the doctors as an admissible way of complementary application.
Bowman et al. 2003 [11]	Cross-Sectional	Their results showed Telemedicine was a precise, reliable, and effective way of diagnosing and controlling these patients, particularly if slit-lamp images were applied.
Yang et al. 2015 [12]	Cross-Sectional	They concluded that a healthcare payer aspect, telemedicine to health care workers of severely sick and pediatric patients performing to rural EDs are cost-saving or cost-effective regarding the telephone.
Mohr et al. 2016 [13]	Observational cohort study	The telemedicine consultation was requested for severely injured rural traumatic patients (burns, penetrating trauma, and those with abnormal vital signs) in the Emergency Department, but Telemedicine consultation was not decreased interhospital transfer.
Oeveren et al. 2017 [14]	Cross-Sectional	They demonstrated a success rate of 96% of telemedicine during emergency intubation. Telemedicine-assisted intubation can be performed in rural hospitals practically.
Gilmore et al. 2014 [15]	Cross-Sectional	HBT can provide mental health services in a preferable procedure of location in military sexual trauma with PTSD patients and help to them for reducing mental pains and increasing readiness.
Dayal et al. 2016 [16]	Retrospective cohort study	The performance of a telemedicine program is designed to assist in the seriously ill children at admission to the PICU. They provided evidence for improving clinical outcomes in pediatric critical care with telemedicine programs.
Shah et al. 2016 [17]	Prospective cohort study	High-intensity telemedicine can be alternative to traditional severe disease care and it must be included in population health programs.
Dharmar et al. 2018 [18]	Retrospective chart reviews	They were demonstrated reducing the risk of physician-related medicine mistakes among critically sick and traumatic children of 8 rural EDs from academic children's hospital.

Brennan et al. (1998) conducted a randomized clinical study in the emergency department. Overall 104 patients were included. Fifty-four participated in the telemedicine group and 50 to the control group. There are no differences between the groups for an incident of 72 hours emergency department return visits; the requirement for further care; doctor communication; nurse communication; satisfaction. The mean patient throughput period for the telemedicine group was 106 minutes; the mean for the control group was 117 minutes. They concluded that telemedicine was observed to be a satisfying system for pre-chosen emergency department patients and was observed by the doctors as an admissible way of complementary application [10].

Bowman et al. (2003) assessed the precision and effectiveness of telemedicine in diagnosing and treating eye injuries. The methods were a clinical trial with a face-to-face group (40 patients) and a telemedicine group (40 patients). In the face-to-face group, consultations were in person; in the telemedicine group, researcher one handled video conferencing technology at 384 kbit/s, and observer two observed the patient face to face. In this study, 80 patients were included in the department. Principal result measures were agreement levels between the two observers for every phase, time of consultation, and several unnecessary recalls. There were more important conflicts applying telemedicine, in per sample the telemedicine diagnosis and management failed on the side of safety; consequently, no patient would have experienced via the improper administration because of the consultation using telemedicine. Their results showed Telemedicine was a precise, reliable, and effective way of diagnosing and controlling these patients, particularly if slit-lamp images were applied [11].

Yang et al. (2015) carried a financial assessment to

determine the price, effect, and return on investment of telemedicine consultations presented to health care workers of severely sick and pediatric patients in rural EDs confronted with phone consultations from a healthcare payer prospect. The cost-effectiveness investigation was according to program effectiveness, obtained from change choices after telemedicine and telephone consultations. They concluded that a healthcare payer aspect, telemedicine to health care workers of severely sick and pediatric patients performing to rural EDs are cost-saving or cost-effective regarding telephone [12].

Nicholas M. Mohr et al. evaluated factors associated with telemedicine and interhospital transfer as a cohort study of all adult treated traumatic patients between 2008 and 2014 in North Dakota critical-access hospital (CAH). They demonstrated telemedicine consultation was requested for severely injured rural traumatic patients (burns, penetrating trauma, and those with abnormal vital signs) in the Emergency Department, but Telemedicine consultation was not decreased interhospital transfer [13].

Lucas Van Oeveren et al. evaluated intubations which done by telemedicine in rural EDs with ED telemedicine network. They were collected probable data of all patients with video telemedicine-assisted intubation from May 1, 2014, to April 30, 2015, and telemedicine involvement/intervention was evaluated using statistical analysis. Lucas Van Oeveren et al have involved 206 intubations with respiratory failure as most common. They demonstrated a success rate of 96% of telemedicine during emergency intubation. Telemedicine-assisted intubation can be performed in rural hospitals practically. This telemedicine-assisted intubation was done at first in emergency tracheal intubations via a live telemedicine link [14].

Amanda K. Gilmore et al. was described a randomized controlled trial comparing Prolonged Exposure (PE) delivered face-to-face and delivered via Home-based telemedicine (HBT) in female veterans, they focused on female veterans with military sexual trauma with PTSD. Their hypothesize was more be effective in improving the quality of life in PE delivered via HBT than SD at the post, 3-, and 6-month follow-up. Ultimately, Amanda K. Gilmore et al concluded HBT can provide mental health services in a preferable procedure of location in military sexual trauma with PTSD patients and help to them for reducing mental pains and increasing readiness. Generally, Home-based telemedicine can reduce systemic barriers for treatment [15].

Parul Dayal et al have compared the effects of access to a telemedicine program (pediatric critical care) on the intensity of disease and results for referral children to children's hospital PICU in the cohort study. The 582 patients with telemedicine that were younger and less sick than 524 patients from without telemedicine were compared during the study period. Parul Dayal et al was indicated the performance of a telemedicine plan for the care of seriously ill children. The performance of a telemedicine program is designed to assist in the seriously ill children at admission to the PICU. They provided evidence for improving clinical outcomes in pediatric critical care with telemedicine programs [16].

Manish N. Shah et al have evaluated the effect High-intensity telemedicine programs on emergency department use for the care of Six senior living community (SLC) residents in a cohort study over 3.5 years. They were indicated reducing emergency department use in High-intensity telemedicine care of SLC residents. Manish N. Shah et al was presented High-intensity telemedicine can be alternative to traditional severe disease care and it must be included in population health programs [17].

Madan Dharmar et al was evaluated the rate of physician-related medicine mistake on seriously 234 patients receiving 85 telephone consultations, 73 telemedicine consultation, and 76 no consultations in rural emergency departments, then outcomes of the study were compared. They were performed retrospective reviews critically sick and traumatic children of 8 rural EDs from academic children's hospital. Ultimately, Madan Dharmar et al was demonstrated reducing the risk of physician-related medicine mistakes among critically sick and traumatic children of 8 rural EDs from academic children's hospitals [18].

DISCUSSION

Traumatic injury is a common cause of death for those under the age of 44 years. On the other hand, accessing sufficient and adequate high-quality trauma care is a secondary problem after the trauma, and one of the main mechanisms associated with bad results in trauma patients. Generally, the improvement of trauma results is under the influence of triage of seriously traumatic patients. Telemedicine is a strategy to improve trauma care, with the aim of given tertiary level services locally. Using telemedicine is particularly increasing and improving the care of trauma patients, it can be valuable when the time-sensitivity is palpable in trauma interventions [19-30].

This study reviews several strengths aspects of telemedicine such as generally, treatment in a high-risk (population, condition, and location) and removal of barriers to care of traumatic patients.

In this systematic review, the literature searched in important databases for telemedicine in various fields such as trauma injury, war, rural, and military. The text of the articles and abstracts were examined from various aspects, the 21 articles were evaluated for quality, and then 10 papers entered in a systematic review. This manuscript is in the first study in various fields of telemedicine.

We found that the use of telemedicine in trauma injury, rural and the military is very helpful for high-quality trauma care; also the telemedicine and telephone consultations can be were demonstrated reducing the risk of physician-related medicine mistakes. Also, telemedicine can useful, practical, and preferable procedure of location for care military sexual trauma patients with PTSD and help to them for reducing mental pains and increasing readiness. The economic evaluation of telemedicine was demonstrated cost-saving and cost-effective of telemedicine consultations. We also realized the importance and practicable of telemedicine for improving rural trauma care.

Duchesne et al. [31] were reported that the performance of a telemedicine plan decreases trauma transfers to 89%. Many rural EDs have not board-certified physicians in emergency medicine [32] despite, the increasing of traumatic injury and trauma-related mortality in rural populations.

In a study that uses tele-emergency services, they were indicated to improve 95% quality of care by using tele-emergency services [33]. The clinical care is improved by using of telemedicine because access to specialized physicians [33]. in the other study, they found the utilization of expert physicians via telemedicine helped stabilize trauma patients during early care [34]. This study demonstrated a limit of 8% of patients have received care that may survive through using telemedicine consultation [34]. On the other hand, the levels of task-based communication of care services can be increased through telemedicine care [35]. Lucas Van Oeveren et al results were illustrated telemedicine improves care and enhances accessibility to treatment.

MST-related PTSD as one of the subjects for telemedicine was investigated by Gilmore et al. in particular; HBT increases treatment access women and even men with their MST histories which suffering from other physical or mental difficulties.

Although quality of care is fairly suitable in most EDs to children, it may behave rates of poor events, such as medication errors in non-children's hospitals for seriously ill children [36–38], nevertheless, the telemedicine can provide access to pediatric expertise for a decrease of physician mistakes [39].

The telemedicine programs significantly increase the quality of care and reduce mortality in traumatic injuries, also the telemedicine is the importance and practicable for improving rural trauma care. This producer can be a suitable alternative to traditional care, in other words, this method causes access to skilled and experienced physicians in far-off areas, subsequently; telemedicine can decrease the risk of physician-related ED medication errors particularly in a pediatric case. Besides, telemedicine can useful and practical producer for PTSD patients; and home-based telemedicine access for these patients in their home.

CONCLUSIONS

Ultimately, the telemedicine can help patients and health government organizations economically, the telemedicine consultations due to cost-saving and cost-effective. Further studies to evaluate the running of telemedicine need to abating the practical and high-efficiency method, that can be done everywhere and it's free from mistakes and defects.

References:

1. Hirshberg A, Holcomb JB, Mattox KL. Hospital trauma care in multiple-casualty incidents: A critical view. Ann Emerg Med. 2001;37:647–52.

2. Demaerschalk BM, Bobrow BJ, Raman R, et al. Stroke team remote evaluation using a digital observation camera in Arizona: the initial mayo clinic experience trial. Stroke 2010;41:1251–8.

3. Meyer BC, Raman R, Hemmen T, et al. Efficacy of site-independent telemedicine in the STRokE DOC trial: a randomised, blinded, prospective study. Lancet Neurol 2008;7:787–95.

4. Audebert HJ, Schenkel J, Heuschmann PU, Bogdahn U, Haberl RL. Effects of the implementation of a telemedical stroke network: the Telemedic Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria, Germany. Lancet Neurol 2006;5:742–8.

5. Pervez MA, Silva G, Masrur S, et al. Remote supervision of IV-tPA for acute ischemic stroke by telemedicine or telephone before transfer to a regional stroke center is feasible and safe. Stroke 2010;41:e18–24.

6. Latifi R, Hadeed GJ, Rhee P, et al. Initial experiences and outcomes of telepresence in the management of trauma and emergency surgical patients. Am J Surg 2009;198:905–10.

7. Boots RJ, Singh S, Terblanche M, Widdicombe N, Lipman J. Remote care by telemedicine in the ICU: many models of care can be effective. Curr Opin Crit Care 2011;17:634–40.

8. Loane M, Bloomer S, Corbett R, Eedy D, Evans C, Hicks N, et al. Randomized controlled trial of assessing the health economics of real time teledermatology compared with conventional care. J Telemed Telecare 2001; 7: 108–118.

9. Rörtgen D, Bergrath S, Rossaint R, Beckers SK, Fischermann H, Na

IS, Peters D, Fitzner C, Skorning M. Comparison of physician staffed emergency teams with paramedic teams assisted by telemedicine–a randomized, controlled simulation study. Resuscitation. 2013 Jan 1;84(1):85-92.

10. Brennan JA, Kealy JA, Gerardi LH, Shih R, Allegra J, Sannipoli L, Lutz D. Telemedicine in the emergency department: a randomized controlled trial. Journal of Telemedicine and Telecare. 1999 Mar 1;5(1):18-22.

11. Bowman RJ, Kennedy C, Kirwan JF, Sze P, Murdoch IE. Reliability of telemedicine for diagnosing and managing eye problems in accident and emergency departments. Eye. 2003 Aug 20;17(6):743.

12. Yang NH, Dharmar M, Yoo BK, Leigh JP, Kuppermann N, Romano PS, Nesbitt TS, Marcin JP. Economic evaluation of pediatric telemedicine consultations to rural emergency departments. Medical Decision Making. 2015 Aug;35(6):773-83.

13. Mohr NM, Harland KK, Chrischilles EA, Bell A, Shane DM, Ward MM. Emergency department telemedicine is used for more severely injured rural trauma patients, but does not decrease transfer: A cohort study. Academic emergency medicine. 2017 Feb 1;24(2):177-85.

14. Van Oeveren L, Donner J, Fantegrossi A, Mohr NM, Brown III CA. Telemedicine-assisted intubation in rural emergency departments: A National Emergency Airway Registry Study. Telemedicine and e-Health. 2017 Apr 1;23(4):290-7.

15. Gilmore AK, Davis MT, Grubaugh A, Resnick H, Birks A, Denier C, Muzzy W, Tuerk P, Acierno R. "Do you expect me to receive PTSD care in a setting where most of the other patients remind me of the perpetrator?": Home-based telemedicine to address barriers to care unique to military sexual trauma and veterans affairs hospitals. Contemporary clinical trials. 2016 May 1;48:59-64.

16. Dayal P, Hojman NM, Kissee JL, Evans J, Natale JE, Huang Y, Litman RL, Nesbitt TS, Marcin JP. Impact of telemedicine on severity of illness and outcomes among children transferred from referring emergency departments to a children's hospital PICU. Pediatric Critical Care Medicine. 2016 Jun 1;17(6):516-21.

17. Shah MN, Wasserman EB, Wang H, Gillespie SM, Noyes K, Wood NE, Nelson D, Dozier A, McConnochie KM. High-intensity telemedicine decreases emergency department use by senior living community residents. Telemedicine and e-Health. 2016 Mar 1;22(3):251-8.

18. Dharmar M, Kuppermann N, Romano PS, Yang NH, Nesbitt TS, Phan J, Nguyen C, Parsapour K, Marcin JP. Telemedicine consultations and medication errors in rural emergency departments. Pediatrics. 2013 Dec 1;132(6):1090-7.

19. Peek-Asa C, Zwerling C, Stallones L. Acute traumatic injuries in rural populations. Am J Public Health 2004;94:1689–93.

20. Carr BG, Branas CC, Metlay JP, Sullivan AF, Camargo CA Jr. Access to emergency care in the United States. Ann Emerg Med 2009;54:261–9.

21. Trauma System: Agenda for the Future. Falls Church, VA: American Trauma Society, 2004.

22. Garwe T, Cowan LD, Neas B, Cathey T, Danford BC, Greenawalt P. Survival benefit of transfer to tertiary trauma centers for major trauma patients initially presenting to nontertiary trauma centers. Acad Emerg Med 2010;17:1223–32.

23. Vogel LD, Vongsachang H, Pirrotta E, et al. Variations in pediatric trauma transfer patterns in Northern California pediatric trauma centers (2001-2009). Acad Emerg Med 2014;21:1023–30.

24. Sorensen MJ, von Recklinghausen FM, Fulton G, Burchard KW. Secondary overtriage: the burden of unnecessary interfacility transfers in a rural trauma system. JAMA Surg 2013;148:763–8.

25. Newgard CD, Staudenmayer K, Hsia RY, et al. The cost of overtriage: more than one-third of low-risk injured patients were taken to major trauma centers. Health Aff (Millwood) 2013;32:1591–9.

26. Ward MM, Jaana M, Natafgi N. Systematic review of telemedicine applications in emergency rooms. Int J Med Inform 2015;84:601–16.

27. Mueller KJ, Potter AJ, MacKinney AC, Ward MM. Lessons from tele-emergency: improving care quality and health outcomes by expanding support for rural care systems. Health Aff (Millwood) 2014;33:228–34.

28. Mohr NM, Harland KK, Chrischilles E, et al. Telemedicine Penetration and Consultation among Rural Trauma Patients in Critical Access Hospital Emergency Departments in North Dakota, Iowa City, IA: Rural Telehealth Research Center, 2016. pp. 1–4.

29. Ward MM, Ullrich F, Potter AJ, MacKinney AC, Kappel S, Mueller KJ. Factors affecting staff perceptions of tele ICU service in rural hospitals. Telemed J E Health 2015;21:459–66.

30. Sterling SA, Seals SR, Jones AE, et al. The impact of the TelEmergency program on rural emergency care: an implementation study. J Telemed Telecare 2016.

31. Duchesne JC, Kyle A, Simmons J, et al. Impact of telemedicine upon rural trauma care. J Trauma 2008;64:92–7; discussion 97–8.

32. Groth H, House H, Overton R, Deroo E. Board-certified emergency physicians comprise a minority of the emergency department workforce in Iowa. West J Emerg Med 2013;14:186–90.

33. Mueller KJ, Potter AJ, MacKinney AC, Ward MM. Lessons from tele-emergency: Improving care quality and health outcomes by expanding support for rural care systems. Health Aff (Millwood) 2014;33:228–234.

34. Rogers FB, Ricci M, Caputo M, et al. The use of telemedicine for real-time video consultation between trauma center and community hospital in a rural setting improves early trauma care: Preliminary results. J Trauma 2001;51:1037–1041.

35. Lazzara EH, Benishek LE, Patzer B, et al. Utilizing telemedicine in the trauma intensive care unit: Does it impact teamwork? Telemed J E Health 2015;21:670–676.

36. Kanter RK: Regional variation in child mortality at hospitals lacking a pediatric intensive care unit. Crit Care Med 2002; 30:94–99

37. Marcin JP, Dharmar M, Cho M, et al: Medication errors among acutely ill and injured children treated in rural emergency departments. Ann Emerg Med 2007; 50:361–367, 367.e1–e2

38. Odetola FO, Miller WC, Davis MM, et al: The relationship between the location of pediatric intensive care unit facilities and child death from trauma: A county-level ecologic study. J Pediatr 2005; 147:74–77

39. Ray KN, Demirci JR, Bogen DL, et al: Optimizing telehealth strategies for subspecialty care: Recommendations from rural pediatricians. Telemed J E Health 2015; 21:622–629

The article was received on April 15, 2020, and accepted for publishing on August 9, 2020.

VARIA

Effect of pharmacist's patient education on patient compliance in the southeast of Iran: A quasi-experimental study

Fatemeh Izadpanah[1], Dariush Rigi[2], Mahdi Afshari[3], Mandana Moradi[4]

Abstract: *Background: As an essential part of the treatment chain and also the link between physicians and patients, pharmacists play a major role in optimizing drug administration. Compliance with a therapeutic regimen is necessary for therapeutic success, while non-adherence can lead to disease progression and eventually treatment failure. This study aimed to evaluate the impact of pharmacist's patient education on different parameters of patient compliance.*

Results: The results showed the patients receiving the intervention compared to the control group, were significantly more adherence to the correct drug use dose (p = 0.016), time of use (p = 0.018), treatment duration (p =0.001), and frequency (p = 0.049).

Conclusions: This study indicates that detailed patient counseling at pharmacies can positively influence different parameters of patients' adherence.

Keywords: *pharmacists; monitoring drug therapy; disease management*

BACKGROUND

Medication adherence knowledge plays a crucial role in treatment success. Pharmacists' scientific skills to teach required information about drug administration, interactions, side effects storage is crucial to improve patient adherence and so treatment success [1, 2]. Patient education by pharmacists can decrease drug therapy problems arising from inappropriate drug administration or prescriptions and decrease overall health care costs [3-5]. Over the past 30 years, the scope of medication therapy management, as well as pharmaceutical care, focused on more specialized and patient-centered care through a more effective pharmacist-patient relationship [4]. Pharmacists also are one of the most important parts of rational drug use based on the World Health Organization (WHO) definition [6] and decreasing its burden [5, 7, 8]. On the other hand, inappropriate administration of antimicrobials may lead to drug resistance and treatment failure that is one of the most challenging problems today [7, 8]. Studies show that one of the main causes of irrational drug use is considering pharmacists only as drug distributors and ignoring their potential role as consultants and educators [9, 10]. In 2003,

Corresponding author: Moradi Mandana
mmandana310@gmail.com

[1] Laboratory Research Center of Food & Drug Control, IRFDA, MOHME, Tehran, Iran
[2] Student research committee Zabol University of Medical Sciences, Zabol, Iran
[3] Department of Community Medicine, School of Medicine, Zabol University of Medical Sciences, Zabol, Iran
[4] Clinical Pharmacy Department, Faculty of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran

the WHO identified poor patient adherence to achieve all therapeutic goals as a major cause of treatment failure [4]. Although the impact of medication counseling by pharmacists on patient treatment outcome, has not been investigated truly, it has been shown that community pharmacists have a great impact on improving patient adherence especially in patients suffering from chronic diseases as well as improving overall community health [1, 11, 12]. Thus, growing an effective patient-pharmacist relationship is a key factor to optimize medication use and it seems necessary to focus on pharmacists consulting skills and supportive laws [13]. In the present study, considering the undeniable role of pharmacists in patient education and improving their compliance with therapeutic regimen, we evaluated the impact of medication consultation on the appropriate use of medication by patients referring to community pharmacies in Zabol city, southeast of Iran at 2019.

METHODS

Design and participants

This quasi-experimental study was conducted on 56 newly diagnosed patients in one governmental hospital (xxxx) affiliated to XXXX University of Medical Science in the southeast of XXXX from March 10, 2019, to August 30, 2019. Participants were selected using a simple random method and distributed to intervention and control groups. Patients were defined new to therapy if they had no evidence of filling prescriptions with their current medications during the past 6 months. Considering the mean scores for treatment belief for two control (5.04 ± 3.4) and intervention (2.52 ± 2.64) groups in pilot research, the type I error of 0.05, the test power of 0.80 as well as 20% sample loss, the required sample size was estimated as of 23 people in each group.

Intervention

The intervention group received their medications with written instructions on drug packages as well as face-to-face education by pharmacists mainly about dosage, regimen, and length of treatment of each drug in their prescriptions. In the control group received their medications only with routine written instructions on each drug package. Each patient in the control group who had a question that needs further education was excluded from the study.

Instruments

The patient's demographic information was included in data collection forms. Two separate questionnaires designed based on literature review and pilot tested. Patients or family caregiver received the first questionnaire, before collecting their prescriptions and the second one 14 days after. The first questionnaire consisted of four questions about their risk of non – adherence [14] as well as eight questions about their belief about prescribed medicines [15]. The second one consisted of five questions about the patient's practice (correct dose, time, frequency, and therapeutic course) about each of their prescribed medications. The investigator who reviewed patient medications after 14 days and filled out the second questionnaire did not know whether patients are in sample or control groups. The face and content validity of the questionnaire was determined by collecting the six experts' opinions. The questionnaires were then distributed to 20 people in a pilot form. The final questionnaires were designed after identifying the bugs and fixing them. To assess the reliability of the questionnaire. Belief about prescribed medication score and total performance score was obtained from the sum of scores of the relative questionnaires.

Statistical analysis

Statistical analysis of the present data was carried out using an independent t-test and chi-square test using SPSS software (version 21). P-value < 0.05 was considered as significant.

Ethical consideration

The study protocol was approved by the XXXX University of Medical Sciences Ethics Committee (code: XXXXXX) and patients provided written informed consent before participating in the study.

RESULTS

After considering the exclusion criteria, 56 patients were eligible to enroll in this study, 28 patients in both the intervention and control group. Our participants consisted of 45 (80.4%) male and 11 (19.6%) female 7.1% of whom were uneducated. Their ages ranged between 15 - 75 years with the mean age of 33.46 (14.20) years. The mean scores of the patient's primary risk of non-adherence and belief about prescribed medicines were 5.27 (0.92) and 23.89 (3.08) respectively.

There was no statistically significant difference between intervention and control groups in terms of age (p = 0.640), gender (p = 0.313), level of education l (p = 0.968), belief about prescribed medicines (p=0.180) and risk of non-adherence (p = 0.679) (Table 1).

Table 1: Demographic characteristics of sample and control groups

		Control	Sample	P-value
Age		30.03 (18.09)	24.43 (15.75)	0.640
Sex	Male	21 (75%)	24 (85.7%)	0.313
	Female	7 (25%)	4 (14.3)	
Level of education	Uneducated	2 (7.1%)	2 (7.1%)	0.968
	Under high school diploma	9 (32.2%)	7 (25%)	
	High school diploma	13 (46.4%)	14 (50%)	
	College degree	1 (3.6%)	3 (10.7%)	
	Bachelor degree	3 (10.7%)	2 (7.1%)	
Belief about prescribed medicines		24.11 (2.92)	23.68 (3.27)	0.679
Risk of non-adherence		5.11 (0.91)	5.43 (0.92)	0.180

Our results showed that patients receiving face-to-face education were significantly more adherent to the correct dose (p = 0.016), exact time (p=0.018), frequency of drug administration (0.049), and completing the therapeutic course (p <0.001), compared to the control group (Table 2).

Table 2: Comparison of patient's adherence to correct dose, time, frequency and completing the therapeutic course in control and sample groups

	Control No (%)	Sample No (%)	P-value
Correct dose	16 (57.1%)	25 (89.3%)	0.016
Correct Time	7 (25%)	17 (60.7%)	0.018
Correct frequency	14 (50%)	22 (78.6%)	0.049
Completing therapeutic course	3 (10.7%)	19 (67.9%)	<0.001

Finally, 100 % of the patients in the intervention group and 17.9% of the control group were satisfied with the pharmacist's services (p < 0.001) (Table 3).

Table 3: Comparison of participants' satisfaction in control and sample groups.

Satisfaction		Control	Sample	P-value
Agree	No (%)	5 (17.9)	28 (100)	<0.001
No Idea	No (%)	7 (25)	0 (0)	
Disagree	No (%)	16 (57.1)	0 (0)	
Total	No (%)	28 (100)	28 (100)	

DISCUSSION

Pharmacists as an essential part of the treatment chain and also the link between physicians and the patients play major roles in health care systems [16]. Studies have shown that pharmacists can improve patient adherence and the rate of treatment success. Noncompliance can lead to irrational drug use, expansion of drug therapy costs, the prolongation of therapeutic courses, and adverse drug reactions. In this study, we evaluated the impact of patient education by pharmacists in different aspects of patient compliance and concluded its positive impacts. Our study population is divided into two intervention and control groups. The intervention group received medication counseling especially about dose, time, and frequency of drug administration and duration of therapy besides routine written instructions on drug packages that were consistent in both groups. We observed that although sample intervention groups were not significantly different in terms of demographic data, risk of non-adherence, and belief about their prescribed medication but their final behavior about their prescribed medications were completely different. Adherence to the correct dosage, timing, frequency, and therapeutic course was significantly higher in patients receiving drug education by pharmacists. They were also more satisfied with the pharmacist's services. These results were in agreement with the previous results of previous studies [17-21].

They proved positive impacts of patient counseling at the pharmacies on accomplishing therapeutic goals, reducing adverse drug reactions, and administration drug errors in their researches. Our findings showed that a relatively high number of patients who did not receive counseling did not

properly follow their treatment course, which can lead to therapeutic failure and its related complications. Especially, when patients are on antibiotics, non-adherence can lead to drug resistance and finally affect both patients and society. The small sample size was one of our limitations in this study, besides if we could monitor a patient's performance more often, we would be able to provide more accurate results and lower possible bias. One of the strengths of this study was that patients with a history of the same disease were excluded from the study so that their previous experiences did not affect the final results.

CONCLUSIONS

It can be concluded that detailed patient counseling by pharmacists, can positively influence patients' adherence. In this regard, it seems necessary to focus on communicating and counseling skills of pharmacists and even motivational tools as counseling fees.

References:

1. Al-Arifi MN. Patients' perception, views and satisfaction with pharmacists' role as health care provider in community pharmacy setting at Riyadh, Saudi Arabia. Saudi Pharmaceutical Journal. 2012;20(4):323-30.

2. Psihogios AM, Gutiérrez-Colina AM, Iskander JM, Wasserman RM, Ramsey RR. Adherence knowledge and education needs among pediatric psychology trainees: A needs assessment and recommendations. Clinical Practice in Pediatric Psychology. 2019.

3. Azhar S, Hassali MA, Ibrahim MIM, Ahmad M, Masood I, Shafie AA. The role of pharmacists in developing countries: the current scenario in Pakistan. Human Resources for Health. 2009;7(1):54.

4. Worley MM, Schommer JC, Brown LM, Hadsall RS, Ranelli PL, Stratton TP, et al. Pharmacists' and patients' roles in the pharmacist-patient relationship: are pharmacists and patients reading from the same relationship script? Research in Social and Administrative Pharmacy. 2007;3(1):47-69.

5. Al-Hilfy TKY. Toward quality and accreditation in health profession education in Iraq-accreditation in health professions education. The Middle East Journal of Family Medicine. 2007;5(4):3-7.

6. System WCGotRotPitHC. The Role of the Pharmacist in the Health Care System: Report of a WHO Consultative Group: New Delhi, 13-16 December 1988; Report of a WHO Meeting: Tokyo, Japan, 31 August-3 September 1993: World Health Organization; 1994.

7. Iversen L, Mollison J, MacLeod TNN. Attitudes of the general public to the expanding role of community pharmacists: a pilot study. Family Practice. 2001;18(5):534-6.

8. Eades CE, Ferguson JS, O'Carroll RE. Public health in community pharmacy: a systematic review of pharmacist and consumer views. BMC public health. 2011;11(1):582.

9. Brown NW. Psychoeducational groups: Process and practice: Routledge; 2018.

10. Popper K, Eccles J. The Self and its Brain, Berlin and New York. Springer International; 1977.

11. Al-Wazaify M, Matowe L, Albsoul-Younes A, Al-Omran OA. Pharmacy education in jordan, saudi arabia, and kuwait. American journal of pharmaceutical education. 2006;70(1).

12. Lussier ME, Evans HJ, Wright EA, Gionfriddo MR. The impact of community pharmacist involvement on transitions of care: A systematic review and meta-analysis. Journal of the American Pharmacists Association. 2019.

13. Pierpont TM, Limper CB, Richards KL. Past, present, and future of rituximab—the world's first oncology monoclonal antibody therapy. Frontiers in oncology. 2018;8:163.

14. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Medical care. 1986:67-74.

15. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and health. 1999;14(1):1-24.

16. Law AV, Sakharkar P, Zargarzadeh A, Tai BWB, Hess K, Hata M, et al. Taking stock of medication wastage: unused medications in US households. Research in Social and Administrative Pharmacy. 2015;11(4):571-8.

17. Helal R, Abou-ElWafa H. Self-medication in university students from the city of Mansoura, Egypt. Journal of environmental and public health. 2017;2017.

18. Esan DT, Fasoro AA, Odesanya OE, Esan TO, Ojo EF, Faeji CO. Assessment of Self-Medication Practices and Its Associated Factors among Undergraduates of a Private University in Nigeria. Journal of environmental and public health. 2018;2018.

19. Ghadimi H, Esmaily HM, Wahlstrom R. General practitioners' prescribing patterns for the elderly in a province of Iran. Pharmacoepidemiology and drug safety. 2011;20(5):482-7.

20. Jafari F, Khatony A, Rahmani E. Prevalence of self-medication among the elderly in Kermanshah-Iran. Global journal of health science. 2015;7(2):360.

21. Gidman W, Ward P, McGregor L. Understanding public trust in services provided by community pharmacists relative to those provided by general practitioners: a qualitative study. BMJ open. 2012;2(3):e000939

The article was received on August 12, 2020, and accepted for publishing on October 2, 2020.

VARIA

Clinical and therapeutic particularities of acute gallstones disease during COVID-19 pandemic

Simona Balasescu[1], Andra Maria Trotea[1,2], Dragos Margaritescu[3], Alexandru Sabau[4]

Abstract: *Gallstones disease (GD) is a common pathology, with an incidence of approx. 20% in developed countries, a third of these cases being symptomatic. The paper aims to identify the diagnostic and therapeutic features of acute manifestations of gallstones during the COVID-19 pandemic.*

Materials and method: A retrospective, comparative study was performed of the cases presented to the emergency room (ER) and hospitalized for acute manifestations of gallstones in April-June 2020 vs similar period of 2019. The data regarding clinical form, associated pathology, therapeutic management were analyzed from the ER presentation register, hospitalization sheets and surgical protocols.

Results: During the COVID-19 pandemic, the number of hospitalized cases for acute cholecystitis and other acute manifestations of GD was significantly lower than in the same period last year (21 vs 49 patients). In both study groups the main form of presentation was acute catarrhal cholecystitis (52.4% vs 63.2%). During the SARS-Cov-2 pandemic, we report an increased incidence of complicated forms, mainly hydrops (23.8% vs. 4.1%, p <0.05) and angiocholitis (19% vs. 4.1%, p <0.05). Conservative treatment was chosen more frequently during the pandemic (48% vs. 29%). For operated patients, laparoscopic cholecystectomy was the main option, performed in 85.7% in both groups.

Conclusions: We maintain that laparoscopic cholecystectomy remains the gold standard for acute cholecystitis, even in the COVID-19 pandemic, as it guarantees the best outcomes for the patients. Conservative management may be an option for mild cases, but it carries the risk of recurrence of symptoms and increased incidence of severe complications.

Keywords: *laparoscopic cholecystectomy, gallstones disease, COVID-19 pandemic, acute cholecystitis*

INTRODUCTION

Gallstones disease (GD) is a common pathology, with an incidence of approx. 20% in developed countries, a third of these cases being symptomatic [1].

Laparoscopic cholecystectomy is the gold standard of treatment for this condition. Acute forms are of clinically variable severity, from possible regressive under conservative treatment to life-threatening, namely: biliary colic, acute cholecystitis, cholecysto-pancreatitis and acute angiocholitis. Early surgical treatment was recommended as

Corresponding author: Simona Balasescu
sim_deea90@yahoo.com

[1] University Emergency Hospital Bucharest, IVth Surgery Department, Bucharest, Romania
[2] "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[3] University of Medicine and Pharmacy Craiova, Romania
[4] "Lucian Blaga" University, Faculty of Medicine, Sibiu, Romania

standard in acute cholecystitis to prevent subsequent recurrent episodes, as well as migratory and infectious complications related to the displacement of stones in the main bile duct [2, 3].

The global spread of SARS-CoV-2 pandemic, with the declaration of a state of emergency in our country on the 16th of March 2020, for 60 days, followed by the state of alert since 15th of May, still in force today, had a profound impact on the surgical practice. The initial recommendations of the International and National Surgical Societies were to delay elective surgery, and to attempt first-hand a conservative management of mild and moderate forms presented to the emergency room. Another aspect was that of the aerosolization potential in laparoscopic interventions associated with the induction and dessuflation of the pneumoperitoneum, trocar leakage and laparoscopic smoke. Since the time of SARS-CoV, in 2003, there has been convincing evidence that aerosol-generating procedures (AGP) could potentially result in a wider human-to-human coronavirus transmission radius [4]. Bioaerosols range in size from 0.3 to 100 µm, and particles up to 5 µm remain airborne and can travel distances of more than 100 m, which may be a transmission path for SARS-CoV-2 [5]. Safety guidelines have been developed in laparoscopic surgery to prevent infection of medical personnel in patients suspected or infected with SARS-Cov2, which focuses on preoperative testing of patients, wearing appropriate PPE, consisting of FFP2 masks, goggles or faceshields, ultrafiltration of pneumoperitoneum and preventing accidental leakage of CO2 and plume during laparoscopic surgery [6-13]. Also, the addressability of the population and the desire for surgical treatment was lower for this pathology, partly explained by the fear of a possible contamination in the emergency room or hospital.

Aim

The paper aims to identify the diagnostic and therapeutic features of acute manifestations of gallstones during the COVID-19 pandemic.

MATERIALS AND METHODS

A retrospective, comparative study was performed of the cases presented to the guard room and hospitalized in emergency for acute manifestations of gallstones in April-June 2020 vs similar period of 2019. The data from the presentation register at the guard, hospitalization sheets and surgical protocols, on the particularities related to the clinical form at hospitalization, associated pathology, therapeutic management of patients with acute gallbladder disease, in the absence and during the SARS-CoV-2 pandemic. Changes in the surgical practice of patients with acute manifestations of gallstone disease imposed by international and national guidelines were also analyzed, as well as organizational changes in institutional circuits to prevent the spread of SARS-CoV-2 infection.

RESULTS

Establishing separate circuits within the department for the prevention of SARS-CoV-2 infection

During the pandemic COVID-19, our hospital, an emergency university center with many specializations, made sustained efforts to remain COVID-free, to be able to ensure the safe treatment of patients, and to prevent nosocomial contamination with SARS-Cov2.

In this regard, a strict protocol was implemented which involves testing by RT-PCR at the time of admission of all patients in the emergency room, their isolation respecting separate circuits until the result is obtained, simultaneously with the beginning of the appropriate treatment. If surgery is required immediately, it was performed by treating the patient as SARS-CoV-2 suspect, with all the precautions required by this: proper equipment of PPE in the operating room, avoidance as much as possible of aerosol-generating methods, including laparoscopic surgery, according to the recommendations of the national endoscopic surgery company ARCE in force during the analyzed period. When it was possible to delay the intervention for 24 hours until the result was obtained, in case of negative, the patient was operated laparoscopically, with standard PPE. If the test confirms the infection, the patient was transferred to one of the hospitals designated as a COVID-support hospital and further treated according to the guidelines in force.

Study group analysis

During April-June 2020, during the COVID-19 pandemic, the number of hospitalized cases for acute cholecystitis and other acute manifestations of GD was significantly lower than in the same period last year (21 vs 49 patients). Of the total presentations at the emergency room during the COVID-19 pandemic, only a percentage of 27.6.% agreed with the hospitalization (vs 48.5% in 2019), the rest expressing their request for conservative treatment.

The sex ratio was similar in the 2 groups (F: M = 2: 1), but the incidence of patients treated with rural origin was lower, this could be correlated with the travel difficulties imposed by the legislation during the state of expedite. The average age was higher in 2020, but statistically insignificant (64 vs 56 years).

Regarding the clinical forms, in both study groups the main

form of presentation was acute catarrhal cholecystitis (52.4% vs 63.2%). We note, during the SARS-Cov-2 pandemic, the absence of mild forms of biliary colic, with increasing incidence of complicated forms, mainly hydrops (23.8% vs. 4.1%, p <0.05) and angiocholitis (19% vs. 4.1%, p <0.05).

From the analysis of associated comorbidities, we notice the increase of the share of cardiovascular diseases and diabetes in patients hospitalized during the pandemic, these diseases increasing the potential for aggravation of the general condition in patients with acute cholecystitis, making them unsuitable for conservative management.

Table 1: Comparative analysis of patients with acute manifestations of GD during the COVID-19 pandemic compared to the same period last year: demographic data, clinical forms at hospitalization, comorbidities

	April-June 2020	**April-June 2019**
Number	21	49
Male	33.3%	36.7%
Female	66.7%	63.3%
Urban/Rural	6:1	4:1
Age	64+/-3.2 years	56+/-2.7 years
Clinical form		
Biliary colic	0	8 (16.3%)
Acute cholecystitis		
- Cataral	11 (52.4%)	31 (63.2%)
- Phlegmonous	1 (4.7%)	2 (4.1%)
- Gangrenous	0	1 (2%)
Hydrops	5 (23.8%)	2 (4.1%)
Pio-cholecystitis	0	1 (2%)
Cholecistopancreatitis	1 (4.7%)	2 (4.1%)
Angiocholitis	4 (19%)	2 (4.1%)
Associated pathology:		
Obesity	6 (28.5%)	10 (20.4%)
Adherential Syndrome	5 (23.8%)	16 (32.6%)
Cardiac pathology	6 (28.5%)	6 (12.2%)
High Blood pressure	6 (28.5%)	16 (32.6%)
Diabetes	5 (23.8%)	3 (6.1%)
Gastritis/ Dyspeptic syndrome/Ulcer	3 (14.3%)	5 (10.2%)
Bronchopulmonary chronic obstructive disease	2 (9.5%)	0
Recent cerebrovascular accident	1 (4.7%)	0
Hepato-splenomegaly. Port vein thrombosis	1 (4.7%)	0
Hiatal hernia	0	1 (2%)
Neuropsychiatric disorders (epilepsy, drug addiction)	0	2 (4%)

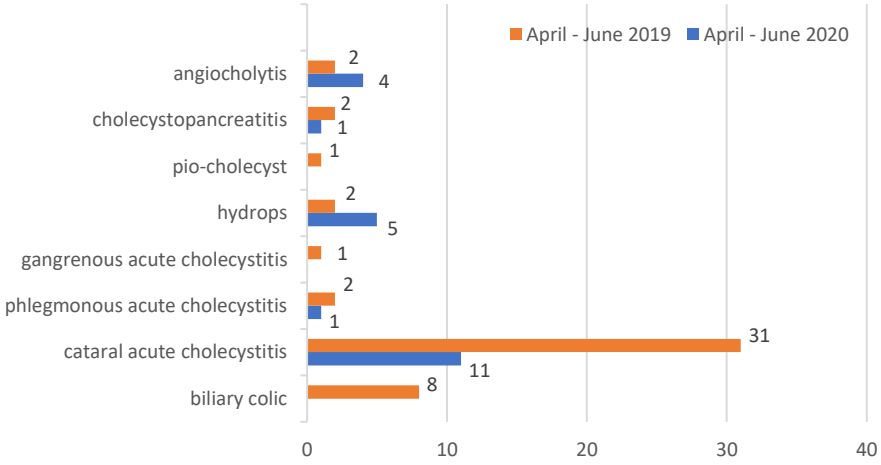


Figure 1: Comparative data for clinical forms during Covid-19 pandemic vs non-COVID period

After admission, all patients in the pandemic group were tested for Sars-CoV-2 infection and were hospitalized in a COVID-19 suspect area, with separate circuits from the rest of the department. Medical therapy was initiated,

depending on the clinical form, with spasmolytics, analgesics, antibiotics and hydro-electrolytic rebalancing. In 20 of 21 cases, surgery could be delayed for up to 24 hours until the absence of COVID infection was documented. In one case, a piocholecyst with imminent of perforation was operated on in an immediate emergency, by open approach, and a cholecystectomy and subhepatic drainage were performed, with a slowly favorable evolution. In a case diagnosed with angiocholitis, SARS-CoV-2 positive, the patient was transferred for ERCP to a surgery department at a COVID-19 support hospital, evolving favorably under minimally invasive treatment.

Table 2: Therapeutic management and postoperative outcome in the COVID-19 pandemic group vs control group.

	April-June 2020	**April-June 2019**
% surgery	11 cases (52%)	35 cases (71%)
Type of surgery:		
LC	18 (85.7%)	30 (85.7%)
Conversion	0	2 (5.7%)
OC	1 (4.7%)	0
ERCP	1 (4.7%)	3 (8.6%)
ERCP+LC	1 (4.7%)	0
Hospital days	6.62	5.6
Postoperative complications:		
Deaths	2 (comorbidities)	0
Bleeding	1 (conservatory)	1
Infection of the wound	0	0

LC: laparoscopic cholecystectomy; OC: open cholecystectomy; ERCP: Endoscopic retrograde cholangiopancreatography

Regarding therapeutic management, there is an increase in cases that benefited from conservative treatment during the pandemic (48% vs. 29%). For operated patients, laparoscopic cholecystectomy was the main option, performed in 85.7% in both groups, except that during the pandemic, the intervention was delayed 24-48 hours to obtain confirmation of the absence of SARS-CoV-2 infection. There were no conversions for the pandemic group, a possible explanation being the better documentation of cases and the favorable effect of early medical therapy in cases with an increased risk of conversion due to local inflammatory anatomical changes.

The average hospital stay was slightly increased, but statistically insignificant, a possible explanation being the timing related to RT-PCR, but also the higher incidence of comorbidities and more severe forms of treated patients. The latter aspect also explains the higher rate of postoperative deaths (9.5% vs 0%), being related to cardiovascular and metabolic decompensation through the associated countries, in elderly patients.

DISCUSSION

The COVID-19 pandemic had a major impact on the management of acute gallstones. During this period, the proportion of cases treated conservatively increased, either outpatient, in the case of patients who refused hospitalization, or in hospitalized patients. This is communicated by similar studies conducted in Spain. Italy, UK or USA, also countries with a significant number of SARS-CoV-2 infections nationwide [1, 14-19].

One of the causes is the reluctance of patients to go to the emergency room or to consent to hospitalization for fear of infection. Harnett et al. estimates in this regard a decrease of up to 50% in the presentation of patients in the emergency room in the US during the pandemic [20]. On the other hand, given the increased pressure on health systems, but also of studies that show a bad outcome in surgeries performed on COVID + patients during the incubation period, international practice guidelines recommend conservative management and avoidance of surgery, if safe for the patient [6, 7, 12, 22-25].

Another important aspect is the reluctance to laparoscopic surgery, due to the possibility of aerosolization of surgical plume and CO2 at pneumoperitoneum desufflation [4]. Preoperative testing of patients is encouraged, as far as resources allow, however studies show a 30% chance of false-negative results, which can have unfavorable consequences for both the patient and the medical staff [26]. Considering possible presence of the infectious agent in blood, feces and intestinal wall and to avoid leakage near the trocar orifices, the use of low pneumoperitoneum pressure and low energy levels during electrocautery.

Regarding gallstone disease, laparoscopic cholecystectomy has established itself worldwide as a gold-standard, due to its indisputable advantages related to the reduction of operative complications, early recovery and reduced hospitalization time. Even during the COVID-19 pandemic, when the open approach was encouraged due to avoiding aerosolization, laparoscopic cholecystectomy remained the preferred technique in surgical practice in our department, being practiced in 87.5% of cases. Similar results are reported by Manzia, Narvaez and Kabir [1, 17, 27]. Moreover, Flemming and Kabir show that SARS-CoV-2 is not present in bile, gallbladder samples and peritoneal fluid [27, 28]. These preliminary findings suggest that the potential infectious risk for operating theater staff and surgeons during open and laparoscopic operations in SARS-CoV -2 patients is lower than initially expected.

Another observation found in the present study is the increase in the severity of cases hospitalized and operated

during the SARS-Cov-2 pandemic compared to the same period last year. Gallstones disease, even if not an emergency, should receive surgical treatment when symptomatic. Neglecting this extremely common pathology can increase the incidence of severe, life-threatening complications such as cholangiopancreatitis or angiocolitis [28-33].

Additionally, a more advanced disease at the time of surgery may result in increasingly morbid operations, which are associated with prolonged hospital stay and higher costs. Since the global healthcare community has never faced a dramatic scenario such as the COVID-19 pandemic, it is difficult to forecast the effects of untreated GD and the development of its related complications during and after COVID-19 [1].

CONCLUSIONS

In light of recent findings, but changes to the surgical protocol are required to increased safety for medical personnel.

We maintain that laparoscopic cholecystectomy remains the gold standard for acute cholecystitis, even in the COVID-19 pandemic, as it guarantees the best outcomes for the patients.

Conservative management may be an option for mild cases, but it carries the risk of recurrence of symptoms and an increased incidence of severe complications.

References:

1. Manzia T M, Angelico R, Parente A, Muiesan P, Tisone G, & MEGAVID (ManagEment of GAllstone disease during coVID-19 pandemic) Clinical Investigator Group (2020). Global management of a common, underrated surgical task during the COVID-19 pandemic: Gallstone disease - An international survery. Annals of medicine and surgery,2020(57): 95–102. https://doi.org/10.1016/j.amsu.2020.07.021

2. Ansaloni, L., Pisano, M., Coccolini, F et al. WSES guidelines on acute calculous cholecystitis. World J Emerg Surg. 2016;2016(11):25.

3. Wakabayashi G., Iwashita Y., Hibi T. Tokyo Guidelines 2018: surgical management of acute cholecystitis: safe steps in laparoscopic cholecystectomy for acute cholecystitis (with videos) J Hepatobiliary Pancreat Sci. 2018;25(1):73–86. doi: 10.1002/jhbp.517.

4. Dascalu, AM, Tudosie, MS ; Smarandache, GC; Serban, D : Impact of the covid-19 pandemic upon the ophthalmological clinical practice; Rom J Legal Med, 2020, 28(1),pg. 96-100, DOI: 10.4323/rjlm.2020.96

5. Serban, D.; Smarandache, C.G.; Tudor, C.; Duta, L.N.; Dascalu, A.M.; Aliuș, C. Laparoscopic Surgery in COVID-19 Era—Safety and Ethical Issues. Diagnostics 2020, 10, 673.

6. Săftoiu A, Tomulescu V, Tanţău M, et al. SRED-ARCE Recommendations for Minimally Invasive Interventions During the COVID-19 Pandemic in Romania. Chirurgia (Bucur). 2020;115(3):289-306. doi:10.21614/chirurgia.115.3.289

7. COVID Surg Collaborative. Global Guidance for surgical care during the COVID-19 pandemic. Br J Surg 2020; 107: 1097–1103.

8. The Royal College of Surgeons of England. Intercollegiate General Surgery Guidance on COVID-19. https://www.rcseng.ac.uk/coronavirus/joint-guidance-for-surgeons-v2/

9. ACS . COVID-19 Guidelines for Triage of Emergency General Surgery Patients [American College of Surgeons: COVID-19 and Surgery web site], 2020. Accessed May 14, 2020. https://www.facs.org/covid-19/clinical-guidance/elective-case/emergency-surgery

10. De Simone, B., Chouillard, E., Di Saverio, S et al. Emergency surgery during the COVID-19 pandemic: what you need to know for practice. Ann R Coll Surg Engl. 2020;102(5):323-332.doi:10.1308/rcsann.2020.0097

11. Savlovschi C, Brănescu C, Serban D, et al. Hernia Amyand--caz clinic [Amyand's hernia--a clinical case]. Chirurgia (Bucur). 2010;105(3):409-414.

12. Society of American Gastrointestinal and Endoscopic Surgeons SAGES and EAES, recommendations regarding surgical response to COVID-19 cases. 2020. https://www.sages.org/recommendations-surgical-response-covid-19/ Accessed March 30.

13. Shabbir A., Menon R.K., Somani J. ELSA recommendations for minimally invasive surgery during a community spread pandemic: a centered approach in Asia from widespread to recovery phases [published online ahead of print, 2020 May 11] Surg. Endosc. 2020:1–6. doi: 10.1007/s00464-020-07618-0

14. Oseran, Andrew S., et al. "Changes in Hospital Admissions for Urgent Conditions During COVID-19 Pandemic." Am J Manag Care 26 (2020): 8.

15. Cano-Valderrama O, Morales X, Ferrigni CJ, et al. Reduction in emergency surgery activity during COVID-19 pandemic in three Spanish hospitals. Br J Surg. 2020;107(8):e239. doi:10.1002/bjs.11667

16. Savlovschi C, Serban D, Andreescu C, Dascalu A, Pantu H. Economic analysis of medical management applied for left colostomy. Chirurgia (Bucur). 2013;108(5):666-669.

17. F. Narvaez, J. R., Cooper, C., Brewer, J. J., Schwaitzberg, S. D., & Guo, W. A. (2020). Do We “Do No Harm” in the Management of Acute Cholecystitis in COVID-19 Patients? The American Surgeon. https://doi.org/10.1177/0003134820939881

18. Dumitrescu D, Savlovschi C, Borcan R, et al. Caz clinic--hernie diafragmatică voluminoasă--abdomen acut chirurgical: dificultăţi diagnostice şi terapeutice [Clinical case--voluminous diaphragmatic hernia--surgically acute abdomen: diagnostic and therapeutical challenges]. Chirurgia (Bucur). 2011;106(5):657-660.

19. Kabir T, Kam JH, Chew MH. Cholecystectomy during the COVID-19 pandemic: Current evidence and an understanding of the 'new' critical view of safety: Correspondence. Int J Surg. 2020;79:307-308. doi:10.1016/j.ijsu.2020.06.012

20. Hartnett KP, Kite-Powell A, DeVies J, et al. Impact of the COVID-19 Pandemic on Emergency Department Visits — United States, January1, 2019–May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69:699–704. DOI: http://dx.doi.org/10.15585/

mmwr.mm6923e1external icon

21. Oseran, Andrew S., et al. "Changes in Hospital Admissions for Urgent Conditions During COVID-19 Pandemic." Am J Manag Care 26 (2020): 8.

22. Campanile FC, Podda M, Arezzo A, et al. Acute cholecystitis during COVID-19 pandemic: a multisocietary position statement. World J Emerg Surg. 2020;15(1):38. Published 2020 Jun 8. doi:10.1186/s13017-020-00317-0

23. Savlovschi C, Serban D, Trotea T, Borcan R, Dumitrescu D. Post-surgery morbidity and mortality in colorectal cancer in elderly subjects. Chirurgia (Bucur). 2013;108(2):177-179.

24. Nahshon C., Bitterman A., Haddad R., Hazzan D., Lavie O. Hazardous postoperative outcomes of unexpected COVID-19 infected patients: a call for global consideration of sampling all asymptomatic patients before surgical treatment [published online ahead of print, 2020 may 16] World J. Surg. 2020:1–5. doi: 10.1007/s00268-020-05575-2.

25. Cano-Valderrama O, Morales X, Ferrigni CJ, et al. Reduction in emergency surgery activity during COVID-19 pandemic in three Spanish hospitals. Br J Surg. 2020;107(8):e239. doi:10.1002/bjs.11667

26. Giulio M., Achilli P., Dario M. An underestimated "false negative COVID cholecystitis" in Northern Italy and the contagion of a surgical ward: it can happen everywhere [published online ahead of print, 2020 May 13] Surgery. 2020;1-2 doi: 10.1007/s13304-020-00781-y.

27. Flemming S., Hankir M., Hering I. Abdominal fluid samples (negative for SARS-CoV-2) from a critically unwell patient with respiratory COVID-19 [published online ahead of print, 2020 May 26] Br. J. Surg. 2020 doi: 10.1002/bjs.11713. 10.1002/bjs.11713.

28. Kabir T, Ngaserin SH, Koh FH, Ong BC, Chew MH. The Covid Conundrum: SARS-CoV-2 is not present in bile. Accepted for publication in Br J Surg.

29. Gupta N, Agrawal H. COVID 19 and laparoscopic surgeons, the Indian scenario - Perspective. Int J Surg. 2020;79:165-167. doi:10.1016/j.ijsu.2020.05.076

30. Şavlovschi C, Comandaşu M, Şerban D. Specifics of diagnosis and treatment in synchronous colorectal cancers (SCC). Chirurgia (Bucur). 2013;108(1):43-45.

31. S.J. Fu, E.L. George, P.M. Maggio, et al., The consequences of delaying elective surgery: surgical perspective, Ann. Surg. (2020), https://doi.org/10.1097/SLA. T.M. Manzia, et al. Annals of Medicine and Surgery 57 (2020) 95–102 101 0000000000003998 [Epub ahead of print]. Accessed on June 20, 2020.

32. Serban D, Smarandache AM, Cristian D, Tudor C, Duta L, Dascalu AM: Medical errors and patient safety culture - shifting the healthcare paradigm in Romanian hospitals, Rom J Leg Med, 2020;2; Rom J Leg Med, 2020; 28(2)195-201

33. Fometescu SG, Costache M, Coveney A, Oprescu SM, Serban D, Savlovschi C. Peritoneal fibrinolytic activity and adhesiogenesis. Chirurgia (Bucur). 2013;108(3):331-340.

The article was received on January 18, 2020, and accepted for publishing on July 19, 2020.

VARIA

Osteoporosis and the fracture risk in systemic lupus erythematosus

Mihai L. Ciobîcă[1], Oana P. Ionescu[1], Bianca A. Săndulescu[1]

Abstract: *Osteoporosis is a systemic skeletal condition, characterized by a microarchitectural degradation of bone density and quality, giving low resistance and an increased risk of fracture. Osteoporosis is an important public health problem, with considerable medical, social and economic impact. Data accumulated in recent years demonstrate a significant incidence of osteoporosis in the group of patients with major collagen diseases; of these, Systemic Lupus Erythematosus (SLE) is the prototype of autoimmune disease in which osteoporosis and associated complications have a significant clinical impact.*

Although additional studies are needed to deepen the relationship between SLE - osteoporosis - associated fractures, we believe that these patients should be managed from the early stages of the disease.

Keywords: *systemic lupus erythematosus, osteoporosis, risk factors, fragility fracture, therapeutic principles*

INTRODUCTION

Osteoporosis is a systemic skeletal condition, characterized by a microarchitectural degradation of bone density and quality, conferring low resistance and an increased risk of fracture [1, 4]. Osteoporosis is a significant public health problem, with considerable medical, social and economic impact, through the associated costs. The prevalence of osteoporosis in Romania in the population over 50 years of age is 20.5% in women and 6.2% in men [1].

Osteoporosis is an asymptomatic disease. The main clinical manifestation and at the same time complication of osteoporosis is the fragility fracture. Worldwide, it causes over 9 million fractures annually, approximately one osteoporotic fracture every three seconds [2].

Classification of osteoporosis [1, 3, 4]:

- Primary osteoporosis: type I (postclimax) and type II (elderly).
- Secondary osteoporosis: occurs in association with other conditions or with the use of certain drugs.

Causes of secondary osteoporosis [3]:

- Endocrinological: thyrotoxicosis, hyperparathyroidism, hypogonadism, Cushing's syndrome, insulin-requiring diabetes, Addison's disease, sarcoidosis.
- Gastrointestinal: severe liver damage, primary biliary cirrhosis, gastrectomy, malabsorption syndromes.
- Metabolic and nutritional: hypophosphatemia, hypercalciuria, hemochromatosis, amyloidosis, parenteral

Corresponding author: Bianca-Andreea Săndulescu
bianca_a_sandulescu@yahoo.com

[1] Department of Internal Medicine and Rheumatology "Dr. Carol Davila" University Central Emergency Military Hospital, Bucharest, Romania

nutrition.

- Hematological disorders and neoplasms: hemophilia, thalassemia, myelomatosis, lymphoma and leukemia, tumors secreting PTH-like peptides.
- Inflammatory diseases: rheumatoid arthritis, systemic lupus erythematosus (SLE), etc.
- Others: chronic kidney disease, cardiovascular, neurological diseases, etc. [4].
- Medications: glucocorticoids (over 5 mg/day prednisone or equivalent, more than three months), anticonvulsants, proton pump inhibitors, heparin, antidepressants, etc.

This classification in primary and secondary is not delimited. Sometimes the causes of secondary osteoporosis can coexist with post-menopausal status or with aging.

Classical risk factors for osteoporosis

Modifiable risk factors:

- Nutritional deficiencies: Diet influences bone mass and risk of fracture. Nutrients with an important role in bone metabolism are calcium, vitamin D and, last but not least, proteins. Low protein intake is an essential determinant of bone mass. Malnutrition can increase the risk of falling both by affecting coordination and reducing the muscle strength [5-9].
- Physical inactivity: A significant cause of bone loss. It has been observed that forced immobilization in healthy volunteers or in patients with neurological disorders such as paraplegia, leads to decreased bone mineral mass. The negative effect of immobilization is much greater than the potential benefit of exercise on an already outpatient subject [10].
- Weight: A low body mass index correlates with a low bone mineral density (BMD), probably due to decreased peripheral estrogen production by adipose tissue and a lower mechanical load on the skeleton that metabolically influences bone composition [3].
- Smoking: After menopause, bone mineral density in women who smoke decreases by two percent/decade compared to non-smokers [12]. A much more significant loss of bone mass was observed in smoking men, especially in the femoral head. The risk decreases with smoking cessation but becomes significant only after ten years of withdrawal [13].
- Excessive alcohol consumption: Indirectly, influences the bone metabolism by decreasing protein and calcium intake, impaired gonadal function, mobility (increases the risk of fracture by falling), and directly, through the toxic effect on the osteoblast [3].

Non-modifiable risk factors:

- History of falls: Falls are the most common cause of osteoporotic fractures. The annual risk of falling increases by about 20% in women between 35 and 49 years and is over 30% in eldery men [14]. The risk of falling is directly correlated with the number of comorbidities (e.g., neurological disorders, cardiovascular diseases, urinary incontinence, depression, etc.). Also, medications such as hypnotics, sedatives, or antidepressants increase the risk of falling [14-17].
- Age over 65 or under 65 who associate several risk factors.
- Women: a higher risk of osteoporosis. Bone loss is 0.86-1.21% and increases after menopause, unlike men, where the loss is about 0.04-0.90% [18]. Despite this, secondary osteoporosis appears to be more common in men [19, 20].
- Fragility fractures in personal history: the presence of an osteoporotic fracture increases the risk of subsequent fractures. Thus, in both men and women who have suffered a distal fracture of the forearm, the risk of subsequent fractures of other skeletal regions is approximately doubled [21-24].
- Genetic predisposition: about half of the total bone mass, as well as bone architecture and geometry (elements relevant for bone strength), can be genetically determined [25, 26].

Preliminary data studied reveal a significant incidence of osteoporosis in patients diagnosed with collagen diseases. Of these, SLE is the prototype of autoimmune disease that predominantly (but not exclusively) affects young women, but also men. For this group of patients, osteoporosis is a frequent long-term complication.

With the progress of therapeutic strategies and the introduction of new effective treatments in SLE, organ complications are much better controlled, which has led to a significant increase in life expectancy. In this context, osteoporosis and associated complications have a greater clinical impact and the therapeutic attitude must focus on this aspect, from the early stages of the disease.

Regarding the method of objectification and osteoporosis diagnosis, there are several techniques for measuring bone mineral density, but the most common is using dual X-ray absorption (DXA). Bone densitometry provides two results: the T score, which provides the result by comparing the patient's bone density to a person with maximum bone density – a healthy 30-year-old, and the Z score, which compares the patient's bone density with that of a person of the same age to assess the degree of bone loss.

PARTICULARITIES OF OSTEOPOROSIS IN SLE

Osteopenia, defined as a T score between 1.0 and −2.5 in the spine and femoral head, has been reported in 25–74% of patients with SLE, while osteoporosis, defined as a T score less than −2.5, in 1.4–68% of patients with SLE in cohort studies [27].

Despite the large variability of epidemiological data, a significantly increased prevalence of low bone mineral density is recognized in SLE patients versus the general population.

Particular risk factors and mechanisms of occurrence

The etiology of bone density reduction and fractures is multifactorial, involving classical, disease-independent risk factors and particular risk factors. Among them, we mention:

• Inflammatory factors: Systemic inflammation contributes to bone loss by influencing the balance between bone resorption and osteosynthesis, causing an increase of osteoclasts activity. In addition, in the active forms of the disease, an increased level of tumor necrosis factor (TNF) and oxidized low-density lipoprotein (LDL) was observed, the latter interfering with the maturation of osteoblasts and activating T lymphocytes [27, 57, 58]. T lymphocytes involved in the synthesis of TNF and nuclear factor kappa B ligand receptor activator (RANKL) stimulate osteoclast differentiation [58]. A low complement C4 level (an indicator of disease activity) was considered a predictor of decreased bone density in the lumbar spine (Hopkins Lupus Cohort) [28]. A 5-year study showed a correlation between the frequency of disease outbreaks and the impact on bone density, confirming the hypothesis that systemic inflammation contributes to bone loss in SLE. In addition, more than half of diagnosed patients develop inflammatory nephritis during the disease, which can progress to renal failure [30]. In severe forms of renal impairment, the appearance of secondary hyperparathyroidism causes an increase in osteoclastic activity and bone resorption [29, 30]. Another mechanism may be a low level of 1.25 dihydroxy vitamin D by decreasing alpha1 hydroxylase activity in the kidney [59].

• Serological factors: Although autoantibodies role in influencing bone metabolism is unclear, anti-Ro may increase the osteoporosis risk [27, 31]. Up to date, no correlation between the presence of anti-dsDNA antibodies and bone mass has been demonstrated. The anti-Sm could have a protective role [31].

• Metabolic factors: Vitamin D deficiency in SLE can be determined by several factors such as photosensitivity, involving avoidance of sun exposure and use of SPF protection screen, kidney failure, disease activity, prolonged glucocorticoid therapy, the presence of anti-vitamin D antibodies (approx. 4 % of patients) [59].

• Hormonal factors: Unlike the general population at risk for osteoporosis, which has an estrogen deficiency (especially women over 50 years), in SLE, there is a predilection for females in the 15-45 age group, with high levels of estrogen. In those patients, low levels of androgen hormones appear to have a stronger influence on bone metabolism than relatively high levels of estrogen [32].

• Genetic factors: The density of bone structures could be influenced by the genetic polymorphisms of the vitamin D receptor - FOK I (FF, Ff, ff). However, a prospective study conducted during 5.3 years did not show a significant difference between the three genotypic groups [33].

The impact of medication on osteoporosis in SLE

Corticosteroid therapy influences in a dual way the bone mineral density in patients with SLE. On the one hand, its risk of inducing osteoporosis is well known, but it may also play a beneficial role by reducing systemic inflammation's effects on the bone. Two extensive prospective studies [29, 34] have shown that bone loss in SLE occurs predominantly in patients treated with at least 7.5 mg prednisone per day.

Hydroxychloroquine. The contribution of this treatment in osteoporosis prevention is not yet well defined. Despite this, the control of systemic inflammation with immunosuppressive drugs is important both by reducing inflammatory outbreaks and also by reducing the dose and duration of corticosteroid therapy. In women with SLE, HCQ use was associated with higher BMD in the lumbar spine [31, 61, 62] and hip [62]. However, more extensive studies are needed in patients with SLE and other rheumatic diseases in which hydroxychloroquine is used.

The risk of fracture in SLE

Fractures can be an important complication in the course of patients with SLE. The data accumulated in recent years demonstrates an increase of 1.2 - 4.7 times the risk of symptomatic fractures than the general population (Echblorn 2013). In the case of vertebral fractures, which can frequently be clinically inapparent, morphometric analysis is important. Morphometric identification of vertebral deformities is also significant for the attending physician because it is associated with significant impairment of quality of life and an increased risk of symptomatic fractures (e.g., hip) [35]. Current studies showed the presence of at least one vertebral fracture in 3.7-50% of patients with SLE [35, 36, 37-42].

The etiology of fractures is multifactorial in patients with SLE, including bone-dependent factors and factors associated with the risk of falling [36].

The main factors associated with the increased risk of symptomatic fractures in SLE are:

- Age;
- Menopause;
- Smoking, alcohol consumption;
- Duration of the disease;
- Kidney damage;
- Decreased BMD;
- Duration of treatment and cumulative dose of glucocorticoids.

In addition, patients with SLE have an increased risk of falling and associated conditions: physical asthenia, joint damage, neurological complications, impaired visual acuity or decreased muscle strength (which may be associated with both inactivity and corticosteroids or vitamin D deficiency) [8, 17].

A particular aspect of SLE patients is the relationship between bone mineral density and fracture risk. The idea of reduced BMD in patients with SLE is generally accepted, but not all studies showed a clear correlation with an increased risk of fracture. In addition, about 1/3 of patients with SLE and vertebral fractures have normal BMD [43, 44]. These data demonstrate the limited value of BMD in estimating fracture risk and the multifactorial etiology of SLE fractures.

PREVENTION AND TREATMENT OF OSTEOPOROSIS ASSOCIATED WITH SLE

SLE is a chronic condition that predominantly affects young women. Therapeutic regimens used to control the disease generally involve extensive and long-term use of glucocorticoids. Thus, decreased bone mineral density and increased fracture risk appear as natural problems in managing this condition. Lifestyle measures and control of risk factors are general principles in the management of osteoporosis and fracture risk. The current recommendations are based mainly on adopting a healthy lifestyle and preventing falls (as a central risk factor in fragility fractures).

Important aspects are: avoiding smoking, alcohol consumption, maintaining an optimal weight and regular physical activity. From a nutritional point of view, the measures are based on optimizing the intake of calcium, proteins and vitamin D, essential for bone mineralization and maintaining an adequate neuromuscular function. Data from the literature recommend a daily calcium intake of at least 1000 mg (1200-1500 mg in patients with corticosteroids), the dosage of serum level and supplementation with 800-1000 IU vitamin D per day and a protein intake of 1 g/kg per day [45].

Pharmacological therapy in SLE is addressed primarily to osteoporosis patients with a history of fragility fracture and glucocorticoid treatment.

The 2010 American College of Rheumatology (ACR) recommendations for preventing and treatment of glucocorticoid-induced osteoporosis include bisphosphonates as the first-line medication for postmenopausal women and corticosteroid patients [45]. This therapeutic class presents consistent evidence of efficacy in increasing BMD and reducing the risk of fracture. The antiresorptive agents inhibit bone resorption by attaching to the active remodeling sites causing apoptosis of osteoclast cells. The main representatives of the class currently used are the second generation drugs (e.g., alendronate, ibandronate, pamidronate) as well as those of the third generation, with much higher potency (e.g., risedronate and zoledronic acid). They are recommended for patients with normal renal function [45] to prevent and treat glucocorticoid-induced osteoporosis. Limited data on the teratogenic effects of bisphosphonates require their administration only to postmenopausal women [46]. In addition, patients should be informed of the risk of complications such as osteonecrosis of the jaw or atypical femoral shaft fractures, especially in patients on corticosteroid therapy [47-49].

Studies have identified new therapeutic targets in osteoporosis, such as cathepsin K, sclerostin, or the RANKL system. Of these, denosumab, an anti-RANKL monoclonal antibody, has entered and prevailed in clinical practice being an option for premenopausal women with glucocorticoid-induced osteoporosis, as well as for patients with SLE and renal impairment [27].

The risk of osteonecrosis of the jaw and atypical fractures remains in this category of therapeutic agents. Potential complications are the rebound fractures phenomenon and the greater tendency towards hypocalcemia [60].

Estrogen replacement therapy to prevent osteoporosis in patients with SLE is not recommended, as it is associated with an increased rate of inflammatory flares and thromboembolic events [50]. Raloxifene, a selective modulator of estrogen receptors, is an option for postmenopausal women with inactive lupus and without a history of thrombotic events or antiphospholipid antibodies [51].

Another treatment, the recombinant human PTH analogs (e.g., teriparatide), may be an option for men and postmenopausal women who have not responded to bisphosphonate therapy and are at increased risk of fracture [53]. The experience in the young adult population, including premenopausal women, is limited, so this treatment should be initiated only when the benefits outweigh the risks. Premenopausal women with glucocorticoid-induced osteoporosis should be considered at high risk of fracture if they have a pre-existing fracture or a combination of risk factors such as low bone mineral density, intensive treatment with glucocorticoids in high doses (≥7.5 mg/day) for at least six months or background disease in acute onset [52]. In patients with glucocorticoid-induced osteoporosis, this drug was associated with an increased BMD and a significant reduction of vertebral and non-vertebral fractures, but not of hip fractures, compared to the group treated with bisphosphonates [53, 52]. The administration must be made with caution in patients with moderate renal impairment [54].

SCREENING AND MONITORING OF TREATMENT

Patients should be monitored during the therapy by periodic reassessments, both biologically (alkaline phosphatase, blood calcium levels, phosphatemia, urine calcium levels, etc.) and imaging (bone densitometry, skeletal radiographs to document fractures). The inadequate response, low adherence, or adverse reactions to treatment, call into question the decision to discontinue or change it [55, 56].

Regarding the direct assessment of fracture risk, we mention that there is no current algorithm accepted and adapted to patients with SLE. The most widely used in practice is the Fracture Risk Assessment (FRAX), proposed by the World Health Organization [55]. FRAX has important limitations in SLE: it was developed for the postmenopausal period (and thus does not cover a significant subgroup of patients), does not take into account the cumulative dose of glucocorticoids (but only their use or not), and does not include fall risk assessment and the presence of vertebral deformities [27].

CONCLUSIONS

The last decades have made significant progress in the evaluation and treatment of patients with SLE, allowing current therapeutic strategies to control and stabilize affected organs. In this context, associated osteoporosis and fracture risk have become important in the medium and long term management of the disease.

At the moment, the practitioner has consistent data on the epidemiology, pathogenic mechanisms, and clinical impact of osteoporosis and fractures in patients with SLE. Current recommendations include: optimizing calcium and vitamin D intake, lifestyle adjustments and drug treatment. Special attention is directed to the group of women at fertile age, for whom treatment options are still limited.

Additional data on screening methodology and algorithms, morphometric assessment and fall risk are expected. In spite of this, there are currently several arguments for rheumatologists in order to turn their attention to the management of these complications from the early stages of the disease.

References:

1. Grigorie D. Clinical Endocrinology 3rd edition, Carol Davila University, 2015.

2. https://www.iofbonehealth.org/facts-statistics

3. Prevention and management of osteoporosis: report of a WHO scientific group. (WHO technical report series; 921)

4. Kanis JA. Osteoporosis. Oxford, Blackwell Science, 1997.

5. B Vellas 1, R N Baumgartner, S J Wayne, J Conceicao, C Lafont, J L Albarede, P J Garry. Relationship between malnutrition and falls in the elderly. Nutrition, 1992, 8:105–108.

6. Bonjour JP, Schürch MA, Rizzoli R. Nutritional aspects of hip fractures. Bone, 1996; 18(suppl):S139–S144.

7. Cumming, R., Nevitt, M., & Cummings, S. Epidemiology of hip fractures. In: Christiansen C, Johansen JS, Riis BJ, eds. Osteoporosis. Viborg, Norhaven A/S, 1987:40–43.

8. J A Grisso 1, J L Kelsey, B L Strom, G Y Chiu, G Maislin, L A O'Brien, S Hoffman, F Kaplan. Risk factors for falls as a cause of hip fracture in women: the Northeast Hip Fracture Study Group. New England Journal of Medicine,1991, 324:1326–1331.

9. Heaney RP. Nutrition and risk for osteoporosis. In: Marcus R, Feldman D, Kelsey J, eds. Osteoporosis. San Diego, CA, Academic Press, 1996:483–509.

10. Marcus R. Mechanisms of exercise effects on bone. In: Bilezikian JP, Raisz LG, Rodan GA, eds. Principles of bone biology. San Diego, CA Academic Press, 1996:1135–1146.).

11. P Ravn, G Cizza, N H Bjarnason, D Thompson, M Daley, R D Wasnich, M McClung, D Hosking, A J Yates, C Christiansen. Low body mass index is an important risk factor for low bone mass and increase bone loss in early postmenopausal women. Early Postmenopausal Interventi on Cohort (EPIC) study group. J Bone Miner Res 1999;

12. Law M.R., Hackshaw A.K. A meta-analysis of cigarett e smoking, bone mineral density and risk of hip fracture: recogniti on of a major eff ect. BMJ 1997; 315: 841-6.

13. Compston J., Cooper C., Kanis J. Bone densitometry in clinical practice. BMJ 1995; 310:1507-10. (Switzerland)

14. Winner SJ, Morgan CA, Evans JG. Perimenopausal risk of falling and incidence of distal forearm fracture. British Medical Journal,

1989, 298:1486–1488.

15. Tinetti ME, Speechley M. Prevention of falls among the elderly. New England Journal of Medicine, 1989, 320:1055–1059.

16. Grisso JA, Capezuti E, Schwartz A. Falls as risk factors for fractures. In: Marcus R, Feldman D, Kelsey J eds. Osteoporosis. San Diego, CA, Academic Press, 1996:599–611.

17. S L Greenspan, E R Myers, L A Maitland, N M Resnick, W C Hayes. Fall severity and bone mineral density as risk factors for hip fracture in ambulatory elderly. Journal of the American Medical Association, 1994, 271:128–133.

18. M T Hannan 1, D T Felson, B Dawson-Hughes, K L Tucker, L A Cupples, P W Wilson, D P Kiel. Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res 2000; 15:710-20.

19. Baillie S., Davison C., Johnson F., Francis R. Pathogenesis of vertebral crush fractures in men. Age Ageing 1992; 21(2):139-41.

20. Francis R., Peacock M., Marshall D., Horsman A, Aaron JE. Spinal osteoporosis in men. Bone Miner 1989; 5(3):347-57. 5. Melton L.J., Bryant S.

21. Gay JD. Radial fracture as an indicator of osteoporosis: a 10-year follow-up study. Canadian Medical Association Journal, 1974, 111:156–157.

22. Mallmin H., Ljunghall S., Persson I., Naessén T., Ulla-Brith Krusemo & Reinhold Bergström. Fracture of the distal forearm as a forecaster of subsequent hip fracture: a population based cohort study with 24 years of follow-up. Calcified Tissue International, 1993, 52:269–272.

23. J. B. Lauritzen MD, P. Schwarz, P. McNair, B. Lund & I. Transbøl. Radial and humeral fractures as predictors of subsequent hip, radial or humeral fractures in women, and their seasonal variation. Osteoporosis International, 1993, 3:133–137.

24. M T Cuddihy 1, S E Gabriel, C S Crowson, W M O'Fallon, L J Melton 3rd. Forearm fractures as predictors of subsequent osteoporotic fractures. Osteoporosis International, 1999, 9:469–475.

25. Johnston CC, Slemenda CW. Pathogenesis of postmenopausal osteoporotic fractures. In: Stevenson JC, Lindsay R, eds. Osteoporosis. London, Chapman & Hall, 1998:53–64.

26. Cooper GS. Genetic studies of osteoporosis: what have we learned. Journal of Bone and Mineral Research, 1999, 14:1646–1648.

27. Bultink IE. Osteoporosis and fractures in systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2012;64:2-8.

28. Petri M. Musculoskeletal complications of systemic lupus erythematosus in the Hopkins Lupus Cohort: an update. Arthritis Care Res. 1995;8(3):137–145. doi: 10.1002/art.1790080305

29. Zhu TY, Griffith JF, Au SK, Tang XL, Kwok AW, Leung PC, Li EK, Tam LS. Bone mineral density change in systemic lupus erythematosus: a 5-year followup study. J Rheumatol. 2014;41(10):1990–1997. doi: 10.3899/jrheum.131190.

30. Cameron JS. Lupus nephritis. J Am Soc Nephrol. 1999;10(2):413–424.

31. Mok CC, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. Lupus. 2005;14(2):106–112. doi: 10.1191/0961203305lu2039oa.

32. Formiga F, Moga I, Nolla JM, Navarro MA, Bonnin R, Roig-Escofet D. The association of dehydroepiandrosterone sulphate levels with bone mineral density in systemic lupus erythematosus. Clin Exp Rheumatol. 1997;15(4):387–392.

33. Jacobs J, Voskuyl AE, Korswagen LA, Theunissen R, Cohen Tervaert JW, Bultink IEM. The association between FOK-I vitamin D receptor gene polymorphisms and bone mineral density in patients with systemic lupus erythematosus. Clin Exp Rheumatol. 2015;33(5):765.

34. Jacobs J, Korswagen LA, Schilder AM, van Tuyl LH, Dijkmans BA, Lems WF, Voskuyl AE, Bultink IE. Six year follow-up study of bone mineral density in patients with systemic lupus erythematosus. Osteoporos Int. 2013;24(6):1827–1833. doi: 10.1007/s00198-012-2157-9.

35. Rentero ML, Amigo E, Chozas N, Ferna´ndez Prada M, SilvaFerna´ndez L, Abad Hernandez MA, Rodriguez Barrera JM, del Pino-Montes J; GHDP study group (2015) Prevalence of fractures in women with rheumatoid arthritis and/or systemic lupus erythematosus on chronic glucocorticoid therapy. BMC Musculoskelet Disord.

36. Bultink IEM, Lems WF, Kostense PJ, Dijkmans BAC, Voskuyl AE (2005) Prevalence of and risk factors for low bone mineral density and vertebral fractures in patients with systemic lupus erythematosus. Arthritis Rheum 54(7):2044–2050.

37. Borba VZ, Matos PG, da Silva Viana PR, Fernandes A, Sato EI, Lazaretti-Castro M (2005) High prevalence of vertebral deformity in premenopausal systemic lupus erythematosus patients. Lupus 14(7):529–533.

38. Mendoza-Pinto C, Garcı´a-Carrasco M, Sandoval-Cruz H, Mun˜ozGuarneros M, Esca´rcega RO, Jime´nez-Herna´ndez M, Munguı´aRealpozo P, Sandoval-Cruz M, Deleze´-Hinojosa M, Lo´pez Colombo A, Cervera R (2009) Risk factors of vertebral fractures in women with systemic lupus erythematosus. Clin Rheumatol 28(5):579–585.

39. Li EK, Tam LS, Griffith JF, Zhu TY, Li TK, Li M, Wong KC, Chan M, Lam CW, Chu FS, Wong KK, Leung PC, Kwok (2009) High pevalence of asymptomatic vertebral fractures in Chinese women with systemic lupus erythematosus. J Rheumatol 36(8):1646–1652

40. Almehed K, Hete´nyi S, Ohlsson C, Carlsten H, Forsblad-d'Elia H (2010) Prevalence and risk factors of vertebral compression fractures in female SLE patients. Arthritis Res Ther 12(4):R153.

41. Garcia-Carrasco M, Mendoza-Pinto C, Riebeling C, SandovalCruz M, Nava A, Etchegaray-Morales I, Jime´nez-Herna´ndez M, Montiel-Jarquı´n A, Lo´pez-Colombo A, Cervera R (2011) Influence of prevalent vertebral fractures on the quality of life in patients with systemic lupus erythematosus. Isr Med Assoc J 13(6):333–337

42. Furukawa M, Kiyohara C, Horiuchi T, Tsukamoto H, Mitoma H, Kimoto Y, Uchino A, Nakagawa M, Oryoji K, Shimoda T, Harada M, Akashi K (2013) Prevalence and risk factors of vertebral fracture in female Japanese patients with systemic lupus erythematosus. Mod Rheumatol 23(4):765–773.

43. D. Jardinet, C. Lefèbvre, G. Depresseux, M. Lambert, J.-P. Devogelaer, F. A. Houssiau. Longitudinal analysis of bone mineral density in pre-menopausal female systemic lupus erythematosus patients: deleterious role of glucocorticoid therapy at the lumbar spine. Rheumatology (Oxford) 2000;39:389–92.

44. Jacobs J, Voskuyl AE, Korswagen LA, Theunissen R, Tervaert JWC, Bultink IE. The association between FOK-I vitamin D receptor gene polymorphisms and bone mineral density in patients with systemic lupus erythematosus [abstract]. Ann Rheum Dis 2014;73:533–4

45. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L,Chen W, Jeffrey R Curtis, Daniel E Furst, Maureen McMahon, Nivedita M Patkar, Elizabeth Volkmann, Kenneth G Saag. American College of Rheumatology 2010 recommendations for the prevention and

treatment of glucocor-ticoid-induced osteoporosis. Arthritis Care Res (Hoboken)2010;62:1515–26.

46. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletalossification and mineralization in rats.Teratology 1999;60:68–73.

47. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. Bisphosphonate-associated osteonecrosis of thejaw: report of a task force of the American Society for Boneand Mineral Research. J Bone Miner Res 2007;22:1479 –91.

48. O'Ryan FS, Khoury S, Liao W, Han MM, Hui RL, Baer D, Martin D, Liberty D, Joan C Lo. Intravenous bisphosphonate-related osteonecrosis of the jaw:bone scintigraphy as an early indicator. J Oral Maxillofac Surg2009;67:1363–72.

49. Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, BrownTD, et al. Atypical subtrochanteric and diaphyseal femoralfractures: report of a task force of the American Society forBone and Mineral Research. J Bone Miner Res 2010;25:2267–94.

50. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, HahnBH, et al. The effect of combined estrogen and progesteronehormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med2005;142:953 –62.

51. Mok CC, To CH, Mak A, Ma KM. Raloxifene for postmenopausal women with systemic lupus erythematosus: a pilotrandomized controlled study. Arthritis Rheum 2005;52:3997–4002.

52. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodsman AB, Eriksen EF, Ish-Shalom S, Genant HK, Wang O, Mitlak BH (2001). Effect of parathyroid hormone (1–34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 344(19):1434–1441.

53. Atsushi Nishikawa, Takehiro Ishida, Masanori Taketsuna, Fumito Yoshiki, Hiroyuki Enomoto. Safety and effectiveness of daily teriparatide in a prospective observational study in patients with osteoporosis at high risk of fracture in Japan: final report. 2016; 11: 913–925.

54. Summary of Product Characteristics "Forsteo" (2013).

55. Kanis,J.A., McCloskey,E.V., Johansson,H., Cooper,C., Rizzoli,R., & Reginster,J.Y. (2013) European guidance for the diagnosis and management of osteoporosis in postmenopausal women.

56. Yazdany J, Panopalis P, Gillis JZ, Schmajuk G, MacLean CH, Wofsy D, et al. A quality indicator set for systemic lupus erythematosus. Arthritis Rheum 2009;61:370 –7

57. Frostegard J, Svenungsson E, Wu R, Gunnarsson I, Lundberg IE, Klareskog L, Ho¨rkko¨ S, Witztum JL (2005) Lipid peroxidation is enhanced in patients with systemic lupus erythematosus and is associated with arterial and renal disease manifestations. Arthritis Rheum 52(1):192–200.

58. Svenungsson E, Fei GZ, Jensen-Urstad K, de Faire U, Hamsten A, Frostegard J (2003) TNF-a: a link between hypertriglyceridaemia and inflammation in SLE patients with cardiovascular disease. Lupus 12(6):454–461.

59. Toloza SM, Cole DE, Gladman DD, Iban˜ez D, Urowitz M (2010) Vitamin D insufficiency in a large female SLE cohort. Lupus 19(1):13–19.

60. Miller PD. A review of the efficacy and safety of denosumab in postmenopausal women with osteoporosis Ther Adv Musculoskel Dis (2011) 3(6) 271–282.

61. G Iftimie, A Pantea Stoian, B Socea, I Motofei, D Marcu, RS Costache, C Diaconu; Complications of systemic lupus erythematosus: A review; Rom J Mil Med, vol. CXXI, No. 3/2018, 9-15

62. Lakshminarayanan S, Walsh S, Mohanraj M, Rothfield N. Factors associated with low bone mineral density in female patients with systemic lupus erythematosus. J Rheumatol 2001; 28: 102– 8.

The article was received on March 31, 2020, and accepted for publishing on August 23, 2020.

VARIA

Serum vaspin and chemerin changes in response to combat physical fitness test in military forces

Hossein Shirvani[1], Alireza Delpasand[1], Behzad Bazgir[1]

Abstract: *The study aimed to investigate serum vaspin and chemerin changes in response to combat physical fitness tests in military forces. In a semi-experimental design with pretest and posttest, twenty volunteers were engaged to participate in the study. Combat Physical Fitness Test consisted: (1) 25-yard(yd) sprint to J-hook, to 25-yd crawl, and 25-yd run through cones to 75-yd line; split (2) 75-yd casualty drag; split (3) ammo can run to grenade toss (75-yd); (4) ammo can run to end (75-yd); and (5) 650-yard endurance run. Pre-test and the post-test blood sample was gained. The data were analyzed by SPSS version 24. Serum chemerin did not change significantly compared to the pre-test whereas Serum vaspin was significantly higher after the test (p = 0.018). Afterward, a direct correlation was observed between serum chemerin and serum vaspin (p = 0.034, r=0.335). It is suggested that serum vaspin is responsive to short-term maximal power output activity required in the combat fitness test and positively correlates with chemerin. However, it appears that 3 to 4 minutes of high-intensity exercise induce comparatively moderate post-exercise serum vaspin increment, which appears to be inadequate to stimulate chemerin secretion.*

Keywords: *combat readiness test, vaspin, chemerin, military, adipokines*

INTRODUCTION

Adipokines are new bioactive adipose tissue secreted factors that induce a variety of local and systemic titled role in the body as systemic metabolic regulators, immunity, and endocrine function. Several adipokines including chemerin, vaspin, omentin-1, and apelin affect the whole-body homeostasis by influencing numerous biological, physiological, and pathophysiological processes [1, 2].

Chemerin is a16 kDa chemoattractant protein, an agonist of the orphan G-protein coupled receptor chemokine-like receptor 1 (CMKLR1, ChemR23) adipokine that play role in innate and adaptive immunity that is expressed highly by innate immune system cells [3, 4], liver, and white adipose tissue (WAT), and expressed moderately in lungs and brown adipose tissue, and weakly expressed in the heart, ovaries, and kidneys and as an adipokine exerts effects on many biological processes, including adipogenesis, angiogenesis, inflammation, immune responses, and food intake [4, 5]. Pathologically, several effector cells of the innate immune system are influenced by chemerin, including dendrite cells, monocytes, macrophages, and NK cells, and might influence the crosstalk between different cell types responsible for controlling the initiation and progression of inflammation [6]. Recent studies suggested either a proinflammatory or

[1] Exercise Physiology Research Center, Life Style Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran

Corresponding author: Behzad Bazgir
bazgirbehzad@yahoo.com

anti-inflammatory role for chemerin and emphasized it's as treatment strategies for obesity [7]. On the other hand, Vaspin(visceral adipose tissue-derived serine protease inhibitor) is a recently discovered 45 kDa adipocytokine predominantly secreted from visceral adipose tissue [1, 8]. Vaspin mRNA was reported to be expressed in subcutaneous and visceral adipose tissue which might play a role in inflammation expansion [9]. Multiple lines of evidence suggest that vaspin protects cells from inflammation and apoptosis. It has been demonstrated that vaspin inhibition of TNF-α induces the expression of adhesion molecules and subsequently decreased lymphocyte adhesion by a reducing ROS generation [10].

Several kinds of research studied the response of adipokines such as chemerin and vaspin to high-intensity exercise and reported contradicted results such as elevation [11, 12], no change [13, 14] or reduction [15, 16]. The most prior studies were focused on obese or metabolically patient subjects while to our knowledge there is no research to investigate acute chemerin and vaspin responses after MANUF. Also, the notable issue is that in previously performed protocols, the movement pattern/type was limited to one of the aerobic/resistance/power modality of exercise such as cycling or running [17-19].

Combat physical fitness is a key factor in armed forces [20]. The maneuver under attack fire (MANUF) is a relevant, high-intensity, and integrated test that its stages are executed by maximal power output and included combat physical items similar to war conditions [21]. Previously it was reported that high-intensity exercise stimulated free radical production in the skeletal muscle and myocardium. Also, high-intensity exercise (HIE) causes cell damage due to mechanical tension imposed on muscle cells that may stimulate the immune system and expand inflammation. In this regard, chemerin and vaspin may play the opposite role in response to high-intensity exercise. However, MANUF is a complete combination of war simulated tasks such as sprint, crawling, tossing a grenade, carrying casualties, or ammo boxes [21]. Hence, it's unclear whether utilizing different movement patterns or muscle groups throughout MANUF makes any difference in serum chemerin and vaspin responses or not. Therefore due to a lack of sufficient information about the metabolic response of the MANUF test, our first aim is to measure and compare serum chemerin and vaspin in pre and post-test. It is reported that serum chemerin and vaspin concentration are elevated after high-intensity exercise. A high-intensity exercise (severe muscle contraction) causes cell damage due to mechanical tension imposed on muscle cells that may stimulate the immune system and expand inflammation. Chemerin regulates activation of dendritic cells and macrophages by some intracellular factors such as the G protein-coupled receptors CMKLR1 (ChemR23), GPR1, and CCRL2. Based on Japanese cohort studies its reported a close association between serum vaspin levels and physical fitness in men also physical activity in women independent of the subject's body composition [22]. So secondly we postulate there is a proposed relationship between serum chemerin and vaspin.

MATERIALS AND METHOD

Statistical sample

In a quasi-experiment study design, fifties cadets volunteers were recruited. At the first visit to familiarize seasons information regards research procedures, its benefits, and potential risks were provided to participants. Written informed consent forms, and the health and physical fitness questionnaire were completed. Height and weight measurements and familiarization with the test were performed the day before the test. In the end, 20 subjects with an average age of 26.95 years, and, the weight of 73.3±7.34 kg were selected as the study sample. Inclusion criteria were healthy male military personnel or personnel with more than one year of fields' military history. The participant exclusion factors were the history of fracture, cardiovascular disease, smoking, and consuming drugs.

The maneuver under attack fire (MANUF) test

The MANUF contains combat-related tasks. The MANUF that aims to assess the combat-related tasks consisted of movement types of actions that are made potentially in combat.

The sort of the items into a single timed event is both a combination of energy systems demonstration, strength/ anaerobic plus aerobic, and a measurement of military combat capability and physical fitness. The test included 300-yard field MANUF tasks such as performing sprint (25 yards), J-hook turn, low and high crawl (25 yards), casualty drag (75 yards); ammo can sweep (30 lb each, 1 in each hand) carries shuttle run (two 75 yards), a grenade toss and at the end, 650 yards running [21]. In the casualty drag item, there is a 10-yard drag, followed by a 65-yard fireman carry. Subjects encourage doing their maximal effort to achieving peak performance from start-up to course end.

Dietary and physical activity control

Subjects were requested to avoid intensive physical activity, supplement consumption such as caffeine and have their habitual diet in the preceding 24 hours of the test. Additionally, participants completed a 24-hour dietary recall before the combat test.

Enzyme-linked immunosorbent assays

Blood samples were collected into K3 EDTA tubes and were isolated by centrifugation (3,000 x G for 10 min). The obtained serum was aliquoted and stored at -80°C until analysis.

Serum chemerin was assessed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Biovendor-Laboratorni medicina a. s., Karasek, Czech Republic). Serum vaspin levels were assayed using a sandwich ELISA kit Vaspin (AdipoGen, Seoul, Korea) according to the manufacturer's instructions.

Statistical analysis

Statistical data analyses were done with descriptive statistic mean and standard deviation. A paired sample student t-test was used to analyze within groups comparison. The possible correlations between chemerin and vaspin serum levels were tested with Bivariate Pearson correlation coefficients. Statistically significant differences were set at $P<0.05$.

The SPSS (IBM Version 24, 2016) was used for data statistical analysis. Written consent form was completed by participants before taking part in the study.

All study protocol was performed according to the criteria set by the declaration of the Helsinki 1975, as revised in 2008, and were approved by Baqiyatallah University of Medical Sciences ethical committee (IR.BMSU.REC.1397.303).

RESULTS

Demographics

Twenty participants were engaged to participate; and completed all trials and are covered in the analysis. Participants' characteristics are shown in Table 1. All individuals had at least one combat deployment before the research with an average history of 43.1 ± 18 months of active duty service recruited.

Table 1: Subjects demographic and physiological characteristics

Variable	Mean± SD
Age (year)	26.95 ± 3.80
Weight (kg)	73.3±7.34
Height (cm)	176.65 ± 6.36
BMI (kg/m^2)	22.13 ±2.78
Rest Heart rate	78.63±12.5

BMI: body mass index, SD: standard deviation

The results of the pretest-posttest comparisons are represented in Table 2. The result of a paired sample t-test demonstrated that chemerin serum levels did not change significantly compared to pretest, While Serum vaspin levels increased significantly after the combat fitness test ($p = 0.018$, Table 2). Additionally, Pearson correlation analysis revealed a positive correlation between chemerin and vaspin serum levels changes in response to combat physical fitness test ($p=0.34$, Figure 1).

Table 2: A within group's comparisons of serum chemerin and vaspin levels

	Pre-test (Mean±SD)	Post-test (Mean±SD)	t	P-value
Serum chemerin (pg/ml)	82.89 ± 19.56	87.38 ± 24.20	-0.68	0.34
Serum vaspin (pg/ml)	0.67 ±0.34	0.90 ±0.41	-2.58	0.02*

** Significant differences at p≤ 0.05*

DISCUSSIONS

The main finding of the present study was that vaspin significantly increased after combat fitness tests and there is a positive correlation between vaspin and chemerin increment although there was no dramatic change in chemerin levels comparing to pre-test level.

To the best of our knowledge, this is the first research that examines the effect of maneuver under attack on circulating serum chemerin and vaspin. Absence of dramatic change may be due to the low volume (frequency/duration) of applied exercise activity and following previous results of Zarei et al. 2018 and conflict with findings of Saremi et al.2010, Chakaroun et al.2012, Aghapour et al. 2013, Venojarvi et al. 2013, Malin et al. 2014, Kim et al 2014, Faramarzi et al. 2016 [23-29]. The present research failed to distinguish any dramatic alteration in serum chemerin levels after MANUF that is predominantly a high-intensity exercise in nature. Lack of such a change in our data series may be due to differences in the intensity, type, duration, and frequency of training compared to the noted studies.

Faramarzi et al. 2016 demonstrated a significant reduction in serum chemerin and vaspin levels in forty healthy women following 12 weeks of combined rhythmic aerobic and core stability exercise training [29]. Lioyd et al. 2016 reported that acute bouts of one hour of moderate-intensity walking (60-

65%Vo2peak) drop chemerin levels in 11 non-insulin resistant obese adults at one and two hours follow up time courses [30]. Liu et al. (2018) studied the effects of four weeks of low to moderate intensity of aerobic exercise in fifty obese adolescent female (14 years old) on chemerin serum levels and showed that whereas slice dieting did not have health benefits, 4 weeks of exercise plus dieting induces a significant decrease in chemerin and body fat [31]. Similar to our results Zarei et al. (2018) indicated nonsignificant changes in chemerin levels after 8 weeks of high-intensity interval training in comparison with control groups [13]. Based on these results, its proposed intensity-dependent changes in chemerin serum levels, in the form of its reduction in response to moderate exercise and non-changes or elevation following high-intensity exercise.

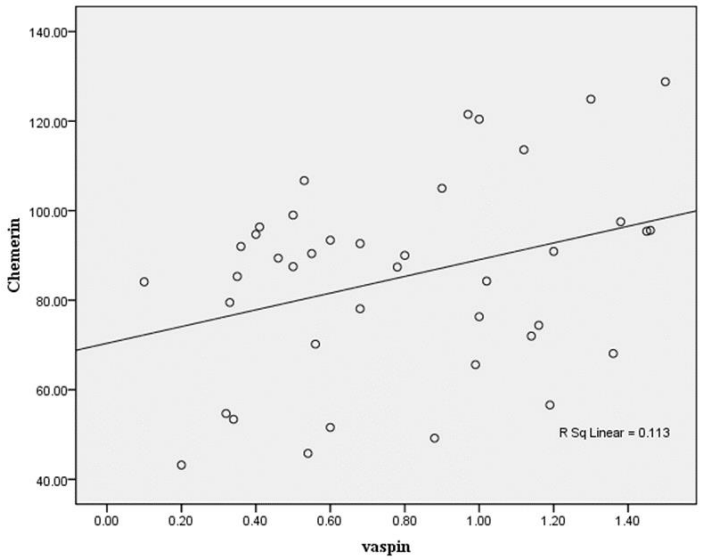


Figure1: The correlation between serum chemerin and vaspin

Furthermore, the characteristics of subjects also could be considered as counting factor. This study included a healthy young male army force without risk factors of cardiometabolic disease, while most other researches were carried out among middle/advanced-aged, overweight/ obese or diabetic [13, 30, 31] subjects who are exposed to high cardiometabolic risk. Further researches are necessary to clarify the impact of training type, frequency, and duration, and participant's health and fitness status on chemerin levels [6]. The mechanical tension leads to cell rupture and bioactive chemokine production to help macrophages for phagocytosis in the initial stage of inflammation [7]. As we observed a weak positive correlation between serum levels of chemerin and vaspin changes in response to one bout of acute exercise activity executed in MANUF test, it seems that there was not deleterious enough alteration in vaspin to induces a significant increase in chemerin. As it found a positive association between chemerin levels with obesity and T2DM and negative association of these diseases with vaspin levels, and low levels of vaspin reported in different stages of cardiovascular disease (CVD) [1], so optimal exercise intervention could be defined when it induced serum vaspin elevation while chemerin did not. In contrast to our results, Motawi et al. (2018) reported a strong negative relationship between chemerin and vaspin in grade I, II CVD that could be related to baseline variance levels of this adipokine in compare with the present study healthy arm force subjects. Subsequently, increased vaspin levels with non-changes in chemerin levels could be ideal regards the protective effects of exercise in CVD that needed to be clarified in further studies.

The result of the present study shown that vaspin levels increased at the end of the combat fitness exercise test. The recorded times to the completion of combat physical fitness tests, which were between 3 to 4 minutes that seems to be adequate to enhance vaspin secretion and augmenting its circulating levels. Base on previously available researches, the data about the response of vaspin after an acute bout of exercise particularly the maneuver under attack fire is still scarce and it is difficult to compare results towards reach a conclusion. The elevated serum level of vaspin seems to be related to the intensity of training. In this regard, Youn et al. 2008 reported that 4 weeks of high-intensity training causes an increase in serum vaspin levels along with weight loss in obese or type 2 diabetics subjects [32]. On the other hand,

Oberbach et al [33] observed a significant decrease in serum vaspin concentration after 4 weeks of high-intensity resistance training in healthy young men. Also in a study conducted by Lee et al [34], vaspin levels in obese children significantly decrease after seven days of intensive lifestyle modification. Elevation in vaspin levels in the present study could be suggested as an optimal anti-obesity strategy as previously reported increase in serum vaspin levels depending on the degree of obesity and reduction in its levels with weight reduction programs [22]. Therefore, it seems that high-intensity aerobic exercise/training intervention induces serum however, it needs to be revealed in future studies.

CONCLUSIONS

These data specified that vaspin serum levels are responsive to short-term maximal power output exercise required in a combat fitness test and positively correlates with chemerin levels changes. However, it appears acute high-intensity exercise induce comparatively moderate post-exercise serum vaspin increment, which appears to be inadequate to stimulate chemerin elevation. It appears that there may be higher metabolic stress thresholds that are required for the activation of the compensatory and positive systemic anti-inflammatory responses and an extended exercise duration is expected to be a crucial element in achieving this, however further studies need to elucidate these.

Acknowledgments:
We appreciate participants four their voluntary attendance in the research. The authors cordially appreciate the Exercise Physiology Research Center of Baqiyatallah University of Medical Sciences.

Authors contribution:
These authors also contributed equally in study conception and design, material preparation. Data collection and analysis were performed by A. Delpasan and B. Bazgir. The first draft of the manuscript was written by A. Delpasand and all authors read and approved the final manuscript.

Conflict of Interest:
The authors declare that there is no conflict of interest regarding the publication of this article.

References:

1. Motawi TMK, Mahdy SG, El-Sawalhi MM, Ali EN, El-Telbany RFA. Serum levels of chemerin, apelin, vaspin, and omentin-1 in obese type 2 diabetic Egyptian patients with coronary artery stenosis. Can J Physiol Pharmacol. 2018;96(1):38-44. doi: 10.1139/cjpp-2017-0272

2. Khan M. JF. Adipose Tissue and Adipokines: The Association with and Application of Adipokines in Obesity. Sci. 2014 1-7. doi:10.1155/2014/328592

3. Serafin DS, Allyn B, Sassano MF, Timoshchenko RG, Mattox D, Brozowski JM, et al. Chemerin-activated functions of CMKLR1 are regulated by G protein-coupled receptor kinase 6 (GRK6) and β-arrestin 2 in inflammatory macrophages. MOL IMMUNOL. 2019;106:12-21. doi:10.1016/j.molimm.2015.03.255

4. Buechler C, Feder S, Haberl EM, Aslanidis C. Chemerin Isoforms and Activity in Obesity. INT J MOL SCI. 2019;20(5):1128. doi:¬10.3390/ijms20051128.

5. Sanchez-Rebordelo E, Cunarro J, Perez-Sieira S, Seoane L, Diéguez C, Nogueiras R, et al. Regulation of Chemerin and CMKLR1 Expression by Nutritional Status, Postnatal Development, and Gender. INT J MOL SCI. 2018;19(10):2905. doi: 10.3390/ijms19102905

6. Vermi W, Riboldi E, Wittamer V, Gentili F, Luini W, Marrelli S, et al. Role of ChemR23 in directing the migration of myeloid and plasmacytoid dendritic cells to lymphoid organs and inflamed skin. INT J EXP MED. 2005;201(4):509-15. doi: 10.1084/jem.20041310

7. Helfer G, Wu Q-F. Chemerin: a multifaceted adipokine involved in metabolic disorders. J ENDOCRINOL. 2018;238(2):R79-R94. doi:10.1530/JOE-18-0174

8. Fu B-D, Yamawaki H, Okada M, Hara Y. Vaspin can not inhibit TNF-α-induced inflammation of human umbilical vein endothelial cells. JVMS. 2009;71(9):1201-7. doi: 10.1292/jvms.71.1201.

9. Phalitakul S, Okada M, Hara Y, Yamawaki H. Vaspin prevents methylglyoxal-induced apoptosis in human vascular endothelial cells by inhibiting reactive oxygen species generation. ACTA PHYSIOL. 2013;209(3):212-9. doi: 10.1111/apha.12139.

10. Heiker JT. Vaspin (serpinA12) in obesity, insulin resistance, and inflammation. J. Pept. Sci. 2014;20(5):299-306. doi: 10.1002/psc.2621.

11. Lin X, Yang Y, Qu J, Wang X. Aerobic exercise decreases chemerin/CMKLR1 in the serum and peripheral metabolic organs of obesity and diabetes rats by increasing PPARγ. NUTR METAB. 2019;16(1):17. doi:10.1186/s12986-019-0344-9

12. Shahraki Z, Eftekhari E. Impact of Aerobic Exercise on Serum Vaspin Level in Female Patients With Type 2 Diabetes Mellitus. CJMB. 2018;5(3):203-8.

13. Zarei F, Shadmehri S, Daryanoosh F, Sherafati Moghadam M, Mahmoodi MT. The effect of eight weeks of high-intensity interval training (HIIT) on the serum levels of chemerin, omentin-1 and apelin on overweight female Sprague-Dawley rats. JSSU. 2018;26(6):473-82.[in persian].

14. Asgari HD, Riyahi MS, Babaei S. Effect of eight weeks high intensity interval training and medium intensity interval training and aloe vera intake on serum vaspin and insulin resistance in diabetic male rats. J Arak Uni Med Sci. 2018; 20 (11) :67-75. [in persian].

15. Kim D-I, Lee DH, Hong S, Jo S-w, Won Y-s, Jeon JY. Six weeks of combined aerobic and resistance exercise using outdoor exercise machines improves fitness, insulin resistance, and chemerin in the Korean elderly: A pilot randomized controlled trial. ARCH

GERONTOL GERIAT. 2018;75:59-64. doi: 10.1016/ j.archger.2017.11.006.

16. Mogharnasi M, TaheriChadorneshin H, Abbasi-Deloei N. Effect of exercise training type on plasma levels of vaspin, nesfatin-1, and high-sensitivity C-reactive protein in overweight and obese women. Obes. Med. 2019;13:34-8. doi:10.1016/j.obmed.2018.12.006.

17. Wadley AJ, Chen Y-W, Lip GY, Fisher JP, Aldred S. Low volume–high intensity interval exercise elicits antioxidant and anti-inflammatory effects in humans. J Sports Sci. 2016;34(1):1-9. doi:10.1080/02640414.2015.1035666.

18. Logan GRM, Harris N, Duncan S, Plank LD, Merien F, Schofield G. Low-active male adolescents: a dose response to high-intensity interval training. Med Sci Sports Exerc. 2016;48(3):481-90. doi: 10.1249/MSS.0000000000000799.

19. Vella CA, Taylor K, Drummer D. High-intensity interval and moderate-intensity continuous training elicit similar enjoyment and adherence levels in overweight and obese adults. EUR J SPORT SCI. 2017;17(9):1203-11. doi: 10.1080/17461391.2017.1359679.

20. Kou Y-x, Wang L, Zhou Z-l. Study of Combat Task Allocation Model in Multi-target Attack Condition [J]. Journal of System Simulation. 2008;16. 4408-4411. [in chinies].

21. Jaworski RL, Jensen A, Niederberger B, Congalton R, Kelly KR. Changes in combat task performance under increasing loads in active duty marines. Mil. Med. 2015;180(suppl_3):179-86. doi: 10.7205/MILMED-D-14-00432.

22. Miyatake N, Wada J, Nakatsuka A, Sakano N, Teshigawara S, Miyachi M, et al. Serum vaspin levels are associated with physical activity or physical fitness in Japanese: a pilot study. Environ Health Prev Med. 2014;19(3):200-6. doi: 10.1007/s12199-013-0375-1.

23. Saremi A, Shavandi N, Parastesh M, Daneshmand H. Twelve-Week Aerobic Training Decreases Chemerin Level and Improves Cardiometabolic Risk Factors in Overweight and Obese Men. Asian J. Sports Med. 2010;1(3):34860. doi: 10.5812/asjsm.34860.

24. Chakaroun R, Raschpichler M, Klöting N, Oberbach A, Flehmig G, Kern M, et al. Effects of weight loss and exercise on chemerin serum concentrations and adipose tissue expression in human obesity. Metabolism. 2012;61(5):706-14. doi: 10.1016/j.metabol.2011.10.008.

25. Aghapour A, Farzanegi P. Effect of six-week aerobic exercise on Chemerin and Resistin concentration in hypertensive postmenopausal women. Electronic physician. 2013;5(1):623. doi: 10.14661/2013.623-630.

26. Venojarvi M, Wasenius N, Manderoos S, Heinonen OJ, Hernelahti M, Lindholm H, et al. Nordic walking decreased circulating chemerin and leptin concentrations in middle-aged men with impaired glucose regulation. Ann Med. 2013;45(2):162-70. doi: 10.3109/07853890.2012.727020.

27. Malin S, Navaneethan S, Mulya A, Huang H, Kirwan JP. Exercise-induced lowering of chemerin is associated with reduced cardiometabolic risk and glucose-stimulated insulin secretion in older adults. J Nutr Health Aging. 2014;18(6):608-15. doi: 10.1007/s12603-014-0459-7.

28. Kim SH, Lee SH, Ahn KY, Lee DH, Suh YJ, Cho SG, et al. Effect of lifestyle modification on serum chemerin concentration and its association with insulin sensitivity in overweight and obese adults with type 2 diabetes. Clin Endocrinol. 2014;80(6):825-33. doi: 10.1111/cen.12249

29. Faramarzi M, Banitalebi E, Nori S, Farzin S, Taghavian Z. Effects of rhythmic aerobic exercise plus core stability training on serum omentin, chemerin and vaspin levels and insulin resistance of overweight women. J Sports Med Phys Fitness. 2016;56(4):476-82.

30. Lloyd JW, Evans KA, Zerfass KM, Holmstrup ME, Kanaley JA, Keslacy S. Effect of an acute bout of aerobic exercise on chemerin levels in obese adults. Diabetes Metab Syndr. 2016;10(1):37-42. doi: 10.1016/j.dsx.2015.04.010.

31. Liu M, Lin X, Wang X. Decrease in serum chemerin through aerobic exercise plus dieting and its association with mitigation of cardio-metabolic risk in obese female adolescents. J Pediatr Endocrinol Metab. 2018;31(2):127-35. doi: 10.1515/jpem-2017-0431.

32. Youn B-S, Klöting N, Kratzsch J, Lee N, Park JW, Song E-S, et al. Serum vaspin concentrations in human obesity and type 2 diabetes. Diabetes. 2008;57(2):372-7. doi:10.2337/db07-1045

33. Oberbach A, Kirsch K, Lehmann S, Schlichting N, Fasshauer M, Zarse K, et al. Serum vaspin concentrations are decreased after exercise-induced oxidative stress. Obes Facts. 2010;3(5):328-31. doi: 10.1159/000321637.

34. Lee MK, Jekal Y, Im J-A, Kim E, Lee SH, Park J-H, et al. Reduced serum vaspin concentrations in obese children following short-term intensive lifestyle modification. Clin Chim Acta. 2010;411(5-6):381-5. doi:10.1016/j.cca.2009.12.003.

The article was received on August 31, 2020, and accepted for publishing on September 23, 2020.

VARIA

Normal pressure hydrocephalus – Diagnosis and therapeutic challenges

Alin V. Chirtes[1], Teofil Mures[1], Marian Mitrică[1]

Abstract: *Normal pressure hydrocephalus (NPH) is a rare pathological condition that generally affects older people (>65 years old), and can take one of two forms: idiopathic or secondary. It is a reversible cause of dementia, and it manifests itself through a very specific triad: gait impairment, urinary incontinence, and dementia. The clinical diagnosis of NPH is particularly difficult to establish due to the association between these symptoms and old age, as well as due to the absence of specific paraclinical markers. Nevertheless, a holistic application of clinical, imagistic, paraclinical criteria, as well as of the various developed scales may, in time, lead to a diagnosis. Moreover, the evolution of magnetic resonance imaging has certainly made easier to establish the condition. The sole therapeutic method proven to be efficient is shunting surgery which has good results in the majority of the cases, showing clear signs of improvement from the very first-day post-surgery.*

Keywords: *normal pressure hydrocephalus, ventriculoperitoneal shunt, aqueductal stenosis, cerebral ventriculomegaly, communicating hydrocephalus, obstructive hydrocephalus*

INTRODUCTION

Normal pressure hydrocephalus (NPH) was firstly recognized by Adams et al. in 1965, by identifying a number of patients suffering from hydrocephalus, but having a normal pressure in the cerebrospinal fluid (CSF) at the lumbar puncture (LP) [1]. This represented a potentially reversible syndrome. The pathology is most often present in older people, and it manifests itself through a gait disturbance, urinary incontinence, and cognitive deficit. It has also been determined that gait impairment, along with one other characteristic element is essential for diagnosis. The clinical assessment demands further examinations, such as brain imagery or draining the CSF, to properly confirm the condition [2].

[1] Department of Neurosurgery, Carol Davila University Central Emergency Military Hospital, Bucharest, Romania

Traditionally, hydrocephalus was divided into two types: communicating hydrocephalus or obstructive hydrocephalus (non-communicating). The former type is characterized by an increase in the volume of CSF without any stenotic lesions in the drainage. In this case, the classification of NPH is still the one being used since 1965: idiopathic NPH (iNPH) – in roughly 50% of all cases, and secondary NPH (sNPH), which comes as a result of either subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), meningitis, intracranial tumors or trauma [1]. While iNPH is generally noticed at adults, sNPH may be present at any age, with both genders being affected equally [3]. Apart from the ventriculomegaly, there are no other observable radiological signs.

Obstructive or non-communicating hydrocephalus comes after the stenosis of the drainage between ventricles and the subarachnoid space, either congenital or acquired. The stenosis of the cerebral aqueduct is a common cause in young adults, although the symptoms are not visible until

adulthood [4].

In the largest study ever conducted on NPH, in Sweden, the results estimated a 0.2% prevalence in the 70-79 age group, and 5.9% in those aged over 80 [5]. In Japan, the results estimated a 0.01% prevalence in the general population and 0.03% in those aged over 60 [6]. In another study on a Finnish cohort, the incidence was 1.58 for every 100.000 persons [7].

The comorbidities associated with NPH are: Alzheimer disease (15%), chronic high blood pressure (50%), hyperlipidemia (14%), and diabetes mellitus (20%) [6, 7]. The latter two factors increase the risk of developing NPH by doubling it, as compared to a normal patient [8]. Similarly, obesity and psychological stress, heart diseases, and strokes have also been named as contributory to the development of this pathology [8, 9].

Unfortunately, the criteria for NPH diagnosis remain uncertain. While some specialists consider it the most common form of hydrocephalus in adults, others contest its very existence [3, 10, 11].

NPH is difficult to diagnose due to its broad and general symptomology, commonly associated with old age. Thus, in individuals aged over 75, urinary incontinence is present in 20 to 30% of them, whereas 20% develop some kind of dementia and 20% show signs of ventriculomegaly [4]. Implicitly, the management of NPH is equally difficult, due to the complications associated with shunting. As such, the morbidity and mortality rates are 20% and 0.2%, respectively [12].

PHYSIOPATHOLOGY

The CSF is mainly secreted by the cells of the choroid plexus, other regions playing mainly a rather insignificant role. CSF's volume is between 125 and 150 ml, and its secretion varies between 400 and 600 ml daily, renewing itself 4 to 5 times every 24 hours in a healthy adult [13]. Its role is vital, namely, the protection and nutrition of the parenchyma [14]. Furthermore, its dynamic is highly dependent on the rate of production and absorption, as well as on the blood-related pulsatile flow through both the subarachnoid and Virchow-Robin spaces to the cerebral parenchyma [15, 16]. According to Adams et al. original theory, NPH develops when the level of CSF's reabsorption diminishes, thus resulting in intracranial hypertension, leading to ventricular dilation as a compensating mechanism [1]. Hence, a larger volume of CSF is redirected to the Virchow-Robin spaces, giving birth to a compression of the parenchyma and ischemia of the white matter.

The specific pathophysiology of iNPH is unclear, yet various mechanisms have been put forward as possibly involved in developing the pathology, such as [2]:

- Reduced compliance of the subarachnoid space
- Reduced reabsorption of CSF in the venous system
- Inadequate expression of TNF-alpha in CSF
- The hyperdynamic flux of CSF in the cerebral aqueduct
- The higher pressure of the CSF
- The reabsorption of CSF through abnormal mechanisms

CLINICAL PRESENTATION

iNPH must be suspected in older patients suffering from abnormal walking, sometimes combined with dementia or urinary incontinence [3].

Symptomatology can vary massively between patients. They may show signs with the classic triad in percentages of 30 to 50 (gait disturbance, urinary incontinence, and cognitive deficit), or only a combination of these: only gait impairment (5%), only dementia (2%), both combined (28%), gait abnormality together with urinary incontinence (4%) and dementia accompanied by urinary incontinence (1%) [6][17]. Approximately half of the patients with iNPH only show signs of a gait disorder, the other two characteristic symptoms being absent [6].

DIAGNOSIS

According to international guides, the imagistic diagnosis is based on the following elements [18]:

- Ventricular dilation with an Evans index > 0.3 [19]
- The absence of a macroscopic obstruction of the dynamics of the CSF
- At least one of the following [20]:
  - o Callosal angle exceeding 40° [21]
  - o Temporary dilated temporal horns of the lateral ventricles, but not fully due to the atrophy of the hippocampus
  - o Changes in the CT and MRI signal caused by the alteration of the content of cerebral water, not fully owed to the microvascular ischemic modifications or demyelination.
  - o Signs of a "flow void" in the MRI in the Sylvian aqueduct

The following imagistic methods can be engaged as well: MR elastography (MRE), glymphatic MRI, or the Silver index [22, 23, 24].

Regarding the Evans index, it is established based on a CT scan in the axial incidence. An index exceeding 0.3 indicates a pathological condition of the ventricles (sensibility of 80%) [19]. The threshold for indicating a pathological component

varies by age, namely: between 65 and 69 years – 0.34; between 70 and 74 years – 0.36; between 75 and 79 years – 0.37; between 80 and 84 years – 0.37 [19].

Callosal angles are measured based on a CT or MRI scan, at the median point of the corpus callosum [21]. Identifying this point necessitates using the sagittal plane, placed parallel to the floor of the fourth ventricle [21]. The limit was 105.4° (42% sensibility, 87% specificity) [21]. It is deemed that, with the decrease of every degree in callosal angles, a patient has a 4% greater chance of benefitting from a shunting surgery [21].

The Japanese guidelines for diagnosing NPH do not regard periventricular changes as relevant. However, they do include two new criteria of diagnosis, i.e. Sylvian fissures and enlarged basal cisterns, as well as the narrowing down of the subarachnoid space and the cerebral sulci at the median level of the brain [25]. In 2017, the efficiency of the two guides was debated, since there are significant discrepancies from the international medical practice, the former being substantially more specific, demanding the presence of at least two symptoms of the classic triad to confidently identify the diagnosis [26]. Furthermore, the study has underlined the necessity of a common system for diagnosis, more objective than the current one [26].

Clinically, several procedures could be executed to diagnose NPH. Firstly, "tap test" or CSF's evacuation test consists in removing 30-50 mL of CSF through a lumbar puncture, to improve the symptomology, the association of the gait function with the frontal assessment battery score, the improvement of verbal fluency and gait [25, 27, 28, 29]. Secondly, different weights can be given to the various markers from CSF, such as the expression of certain isoforms of transferrin, of the tyrosine phosphatase Q-type receptor, or has-miR-4274. Similarly, the correlation between slow vasogenic waves (SWV) and intracranial pressure must be investigated [30].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis must be performed with Alzheimer disease (AD), frontotemporal dementia, dementia with Lewy body, the one from Parkinson disease (PD), the one associated with AIDS, dementia caused through corticobasal degeneration and any other type.

Generally, the level of proteins in the CSF is measured, considered alongside biomarkers of the AD. In this particular case, the level of p-tau and t-tau are high, whereas the level of a β-amyloid peptide (Aβ) is low [4]. In the particular case of NPH, all these parameters are high, going back to normal values after shunting [31].

Apart from the AD, the PD, as well as other parkinsonian syndromes cause gait impairment [4]. Numerous investigations can be carried out, such as SPECT (Single Photon Emission Computed Tomography), this being limited through detecting an exhaustive set of neurodegenerative diseases, or FDG-PET (Fluorodeoxyglucose – Positron Emission Tomography), which can identify caudate hypometabolism, a potential marker of NPH [4].

TREATMENT

The clinical presentation of NPH is insufficient to recommend ventriculoperitoneal shunting surgery (VPS), because either one of the symptoms of NPH may have multiple potential etiologies. The diagnosis must be established clearly through the abovementioned methods in order to recommend surgical treatment.

VPS is the only efficient method of treatment for iNPH, by implanting a ventriculoperitoneal shunt. The international and Japanese guides, as well as AAN (American Academy of Neurology), confirm VPS as the only efficient method of treating iNPH, as opposed to the rather supposedly inefficient endoscopic approach of the third ventricle [25, 32, 33].

The purpose of a shunt is to drain CSF towards space where it may be reabsorbed. A shunt has three components: a proximal catheter, inserted at the level of the right lateral ventricle, a distal catheter in the peritoneal cavity, and a valve of shunting which contains a mechanism opening the valve up when the difference in pressure between the two cavities reaches a pre-established value [3]. Once the valve is open, CSF is drained in the peritoneum. Another approach is represented by lumboperitoneal shunt (LPS), which has the proximal end in the lumbar zone. In a study from Japan, it has been stated that LPS is used in 55% of the cases, whereas VPS is used in 43% of the surgical cases of NPH [6]. Another option of VPS is placing the distal end of the shunt between the two sheets of the greater omentum, the technique is considered as having good results and a low rate of post-surgery complications [34].

Concerning the efficiency of the shunting surgical treatment, in the first three months, in most cases, the headache is gone, and the gait deficit has improved in 85% of the cases, urinary incontinence in 70%, and cognitive functions in 65% [35].

In a study on the efficiency of LPS, it has been concluded that the method is comparable with VPS for patients showing signs of NPH. Nevertheless, the revision of the shunt took place more frequently in patients with LPS than in those with VPS [36].

Regarding the prognostic, 60% of the patients have benefitted from an improvement in symptomatology after the shunting surgery, and 40% have shown signs of significant improvement. These were measured using the mRS scale [9]. Both pre-surgery and post-surgery, patients must be evaluated using the following systems: Japanese NPH scale, Berg scale, DGI (Dynamic Gait Index), FIM (Functional Independence Measure), MMSE (Mini-Mental Status Examination), and TUG (Timed Up and Go) [2].

A series of post-surgery factors can suggest a good prognostic, such as: an aqueduct flux exceeding 42 µl, the absence of lesions of the white matter on MRI, resistance to the CSF debit exceeding 18 mmHg [2]. Antagonistic factors are severe dementia, dementia as a symptom of presentation and MRI abnormalities such as cerebral atrophy or lesions of the white matter [2].

Complications that may arise include:

• Surgical complications of the shunt: the failure of the shunt (3%), under- or over-drainage, subdural hematoma (3-4%), infections (1%) [37];

• Surgical complications unrelated to the shunt: seizures and intracerebral hemorrhage (under 5%) [2];

• Schizophrenia – 3 to 4 times more likely in patients with iNPH than in the healthy population [38];

• Hypertension and diabetes type 2 are frequent in iNPH patients, the latter risk factor causing increased mortality in affected patients [7].

CONCLUSIONS

NPH is a rare, yet treatable disease, and the diagnosis may be difficult to establish due to the rather broad symptoms. Both iNPH and sNPH cause similar features.

The difference between the idiopathic and secondary hydrocephalus has led to a difference in approach in a similar pathology, the latter being labeled as a surgical emergency. Both the concept of NPH, as well as the therapeutic approach retain a status of controversy. The diagnosis of iNPH must be considered when a patient shows signs either of the classic triad, or of some elements of it, or in the case of suggestive imagistic criteria.

Following this evaluation, treatment must be sought only when the risks and benefits of the shunt are carefully balanced. Recent innovations in the field of imaging have greatly improved the identification of patients who may benefit from shunting surgery. Furthermore, it should be also keep in mind that patients suffering from iNPH also present associated comorbidities, such as PD, AD, or other neurodegenerative diseases. Hence, the diagnosis must include tests that draw a clear distinction between NPH and these potentially present diseases. For the same reason, the patient's response to the drainage of CSF can be unpredictable.

NPH must be seen as a reversible cause of dementia. In the future, ample studies must be made to demonstrate the efficiency of shunting surgery.

References:

1. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure. A treatable syndrome. N Engl J Med. 1965 Jul 15;273:117-26. doi: 10.1056/NEJM196507152730301. PMID: 14303656.

2. M Das J, Biagioni MC. Normal Pressure Hydrocephalus. [Updated 2020 Jun 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542247/.

3. Williams MA, Malm J. Diagnosis and Treatment of Idiopathic Normal Pressure Hydrocephalus. Continuum (Minneap Minn). 2016 Apr;22(2 Dementia):579-99. doi: 10.1212/CON.0000000000000305. PMID: 27042909; PMCID: PMC5390935.

4. Graff-Radford NR, Jones DT. Normal Pressure Hydrocephalus. Continuum (Minneap Minn). 2019 Feb;25(1):165-186. doi: 10.1212/CON.0000000000000689. PMID: 30707192.

5. Jaraj D, Rabiei K, Marlow T, Jensen C, Skoog I, Wikkelsø C. Prevalence of idiopathic normal-pressure hydrocephalus. Neurology. 2014 Apr 22;82(16):1449-54. doi: 10.1212/WNL.0000000000000342. Epub 2014 Mar 28. PMID: 24682964; PMCID: PMC4001197.

6. Kuriyama N, Miyajima M, Nakajima M, Kurosawa M, Fukushima W, Watanabe Y, Ozaki E, Hirota Y, Tamakoshi A, Mori E, Kato T, Tokuda T, Urae A, Arai H. Nationwide hospital-based survey of idiopathic normal pressure hydrocephalus in Japan: Epidemiological and clinical characteristics. Brain Behav. 2017 Jan 27;7(3):e00635. doi: 10.1002/brb3.635. PMID: 28293475; PMCID: PMC5346522.

7. Pyykkö OT, Nerg O, Niskasaari HM, Niskasaari T, Koivisto AM, Hiltunen M, Pihlajamäki J, Rauramaa T, Kojoukhova M, Alafuzoff I, Soininen H, Jääskeläinen JE, Leinonen V. Incidence, Comorbidities, and Mortality in Idiopathic Normal Pressure Hydrocephalus. World Neurosurg. 2018 Apr;112:e624-e631. doi: 10.1016/j.wneu.2018.01.107. Epub 2018 Jan 31. PMID: 29374607.

8. Israelsson H, Carlberg B, Wikkelsö C, Laurell K, Kahlon B, Leijon G, Eklund A, Malm J. Vascular risk factors in INPH: A prospective case-control study (the INPH-CRasH study). Neurology. 2017 Feb 7;88(6):577-585. doi: 10.1212/WNL.0000000000003583. Epub 2017 Jan 6. PMID: 28062721; PMCID: PMC5304464.

9. Andrén K, Wikkelsö C, Sundström N, Agerskov S, Israelsson H,

Laurell K, Hellström P, Tullberg M. Long-term effects of complications and vascular comorbidity in idiopathic normal pressure hydrocephalus: a quality registry study. . J Neurol. 2018 Jan;265(1):178-186. doi: 10.1007/s00415-017-8680-z. Epub 2017 Nov 29. PMID: 29188384; PMCID: PMC5760598.

10. Saper CB. Is there even such a thing as "Idiopathic normal pressure hydrocephalus"? Ann Neurol. 2017 Oct;82(4):514-515. doi: 10.1002/ana.25053. Epub 2017 Oct 10. PMID: 28940258.

11. Espay AJ, Da Prat GA, Dwivedi AK, Rodriguez-Porcel F, Vaughan JE, Rosso M, Devoto JL, Duker AP, Masellis M, Smith CD, Mandybur GT, Merola A, Lang AE. Deconstructing normal pressure hydrocephalus: Ventriculomegaly as early sign of neurodegeneration. Ann Neurol. 2017 Oct;82(4):503-513. doi: 10.1002/ana.25046. Epub 2017 Oct 4. PMID: 28892572.

12. Toma AK, Papadopoulos MC, Stapleton S, Kitchen ND, Watkins LD. Systematic review of the outcome of shunt surgery in idiopathic normal-pressure hydrocephalus. Acta Neurochir (Wien). 2013 Oct;155(10):1977-80. . doi: 10.1007/s00701-013-1835-5. Epub 2013 Aug 23. PMID: 23975646.

13. Telano LN, Baker S. Physiology, Cerebral Spinal Fluid (CSF). 2020 Jul 14. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan–. PMID: 30085549.

14. Spector R, Robert Snodgrass S, Johanson CE. A balanced view of the cerebrospinal fluid composition and functions: Focus on adult humans. Exp Neurol. 2015 Nov;273:57-68. doi: 10.1016/j.expneurol.2015.07.027. Epub 2015 Aug 4. PMID: 26247808.

15. Nassar BR, Lippa CF. Idiopathic Normal Pressure Hydrocephalus: A Review for General Practitioners. Gerontol Geriatr Med. 2016 Apr 20;2:2333721416643702. doi: 10.1177/2333721416643702. PMID: 28138494; PMCID: PMC5119812.

16. Brinker T, Stopa E, Morrison J, Klinge P. A new look at cerebrospinal fluid circulation. Fluids Barriers CNS. 2014 May 1;11:10. doi: 10.1186/2045-8118-11-10. PMID: 24817998; PMCID: PMC4016637.

17. Ma TS, Sharma N, Grady MS. A simplified pressure adjustment clinical pathway for programmable valves in NPH patients. Clin Neurol Neurosurg. 2017 Aug;159:83-86. doi: 10.1016/j.clineuro.2017.05.020. Epub 2017 May 30. PMID: 28582688.

18. Damasceno BP. Neuroimaging in normal pressure hydrocephalus. Dement Neuropsychol. 2015 Oct-Dec;9(4):350-355. doi: 10.1590/1980-57642015DN94000350. PMID: 29213984; PMCID: PMC5619317.

19. Brix MK, Westman E, Simmons A, Ringstad GA, Eide PK, Wagner-Larsen K, Page CM, Vitelli V, Beyer MK. The Evans' Index revisited: New cut-off levels for use in radiological assessment of ventricular enlargement in the elderly. Eur J Radiol. 2017 Oct;95:28-32. doi: 10.1016/j.ejrad.2017.07.013. Epub 2017 Jul 20. PMID: 28987681.

20. Oliveira LM, Nitrini R, Román GC. Normal-pressure hydrocephalus: A critical review. Dement Neuropsychol. 2019 Apr-Jun;13(2):133-143. doi: 10.1590/1980-57642018dn13-020001. Erratum in: Dement Neuropsychol. 2019 Jul-Sep;13(3):361. . PMID: 31285787; PMCID: PMC6601311.

21. Grahnke K, Jusue-Torres I, Szujewski C, Joyce C, Schneck M, Prabhu VC, Anderson DE. The Quest for Predicting Sustained Shunt Response in Normal-Pressure Hydrocephalus: An Analysis of the Callosal Angle's Utility. . World Neurosurg. 2018 Jul;115:e717-e722. doi: 10.1016/j.wneu.2018.04.150. Epub 2018 May 1. PMID: 29723726.

22. Perry A, Graffeo CS, Fattahi N, ElSheikh MM, Cray N, Arani A, Ehman RL, Glaser KJ, Manduca A, Meyer FB, Huston J 3rd. Clinical Correlation of Abnormal Findings on Magnetic Resonance Elastography in Idiopathic Normal Pressure Hydrocephalus. World Neurosurg. 2017 Mar;99:695-700.e1. doi: 10.1016/j.wneu.2016.12.121. Epub 2017 Jan 5. PMID: 28063896; PMCID: PMC5357459.

23. Ringstad G, Vatnehol SAS, Eide PK. Glymphatic MRI in idiopathic normal pressure hydrocephalus. Brain. 2017 Oct 1;140(10):2691-2705. doi: 10.1093/brain/awx191. PMID: 28969373; PMCID: PMC5841149.

24. Benedetto N, Gambacciani C, Aquila F, Di Carlo DT, Morganti R, Perrini P. A new quantitative method to assess disproportionately enlarged subarachnoid space (DESH) in patients with possible idiopathic normal pressure hydrocephalus: The SILVER index. Clin Neurol Neurosurg. 2017 Jul;158:27-32. doi: 10.1016/j.clineuro.2017.04.015. Epub 2017 Apr 19. PMID: 28448824.

25. Mori E, Ishikawa M, Kato T, Kazui H, Miyake H, Miyajima M, Nakajima M, Hashimoto M, Kuriyama N, Tokuda T, Ishii K, Kaijima M, Hirata Y, Saito M, Arai H; Japanese Society of Normal Pressure Hydrocephalus. Guidelines for management of idiopathic normal pressure hydrocephalus: second edition. Neurol Med Chir (Tokyo). 2012;52(11):775-809. doi: 10.2176/nmc.52.775. PMID: 23183074.

26. Andersson J, Rosell M, Kockum K, Söderström L, Laurell K. Challenges in diagnosing normal pressure hydrocephalus: Evaluation of the diagnostic guidelines. eNeurologicalSci. 2017 Apr 11;7:27-31. doi: 10.1016/j.ensci.2017.04.002. . PMID: 29302622; PMCID: PMC5746061.

27. Ko PW, Lee HW, Kang K. Frontal Assessment Battery and Cerebrospinal Fluid Tap Test in Idiopathic Normal-Pressure Hydrocephalus. Eur Neurol. 2017;77(5-6):327-332. doi: 10.1159/000472712. Epub 2017 May 5. PMID: 28472801.

28. Liouta E, Gatzonis S, Kalamatianos T, Kalyvas A, Koutsarnakis C, Liakos F, Anagnostopoulos C, Komaitis S, Giakoumettis D, Stranjalis G. Finger tapping and verbal fluency post-tap test improvement in INPH:. its value in differential diagnosis and shunt-treatment outcomes prognosis. Acta Neurochir (Wien). 2017 Dec;159(12):2301-2307. doi: 10.1007/s00701-017-3301-2. Epub 2017 Aug 21. PMID: 28828534.

29. Wolfsegger T, Topakian R. Cognitive impairment predicts worse short-term response to spinal tap test in normal pressure hydrocephalus. J Neurol Sci. 2017 Aug 15;379:222-225. doi: 10.1016/j.jns.2017.06.028. Epub 2017 Jun 19. PMID: 28716246.

30. Spiegelberg A, Krause M, Meixensberger J, Seifert B, Kurtcuoglu V. Significant Association of Slow Vasogenic ICP Waves with Normal Pressure Hydrocephalus Diagnosis. . Acta Neurochir Suppl. 2018;126:243-246. doi: 10.1007/978-3-319-65798-1_49. PMID: 29492569.

31. Jeppsson A, Zetterberg H, Blennow K, Wikkelsø C. Idiopathic normal-pressure hydrocephalus: pathophysiology and diagnosis by CSF biomarkers. Neurology. 2013 Apr 9;80(15):1385-92. doi: 10.1212/WNL.0b013e31828c2fda. Epub 2013 Mar 13. PMID: 23486875.

32. Halperin JJ, Kurlan R, Schwalb JM, Cusimano MD, Gronseth G, Gloss D. Practice guideline: Idiopathic normal pressure hydrocephalus: Response to shunting and predictors of response: Report of the Guideline Development, Dissemination,. and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2015 Dec 8;85(23):2063-71. doi: 10.1212/WNL.0000000000002193. Erratum in: Neurology. 2016 Feb 23;86(8):793. PMID: 26644048; PMCID: PMC4676757.

33. Tudor KI, Tudor M, McCleery J, Car J. Endoscopic third ventriculostomy (ETV) for idiopathic normal pressure hydrocephalus (iNPH). Cochrane Database Syst Rev. 2015 Jul 29;(7):CD010033. doi: 10.1002/14651858.CD010033.pub2. PMID: 26222251.

34. Grigorean VT, Sandu AM, Popescu M, Florian IS, Lupascu CD, Ursulescu CL. Our initial experience with ventriculo-epiplooic shunt in treatment of hydrocephalus in two centers. Neurol Neurochir Pol. 2017 Jul-Aug;51(4):290-298. doi: 10.1016/j.pjnns.2017.04.007. Epub 2017 May 11. PMID: 28528738.

35. Bayar MA, Tekiner A, Celik H, Yilmaz A, Menekse G, Yildirim T, Alagoz F, Guvenc Y, Erdem Y. Efficacy of Lumboperitoneal Shunting in Patients with Normal Pressure Hydrocephalus. Turk Neurosurg. 2018;28(1):62-66. doi: 10.5137/1019-5149.JTN.18702-16.1. PMID: 27858384.

36. Miyajima M, Kazui H, Mori E, Ishikawa M; , on behalf of the SINPHONI-2 Investigators. One-year outcome in patients with idiopathic normal-pressure hydrocephalus: comparison of lumboperitoneal shunt to ventriculoperitoneal shunt. J Neurosurg. 2016 Dec;125(6):1483-1492. doi: 10.3171/2015.10.JNS151894. Epub 2016 Feb 12. PMID: 26871203.

37. Kiefer M, Unterberg A. The differential diagnosis and treatment of normal-pressure hydrocephalus. Dtsch Arztebl Int. 2012 Jan;109(1-2):15-25; quiz 26. doi: 10.3238/arztebl.2012.0015. Epub 2012 Jan 9. PMID: 22282714; PMCID: PMC3265984.

38. Vanhala V, Junkkari A, Korhonen VE et al. Prevalence of Schizophrenia in Idiopathic Normal Pressure Hydrocephalus. Neurosurgery. 2019 Apr 1;84(4):883-889. doi: 10.1093/neuros/nyy147. PMID: 29741669; PMCID: PMC6417909.

The article was received on August 3, 2020, and accepted for publishing on September 23, 2020.

VARIA

The seasonal incidence of intracranial hemorrhages

Marian Mitrică[1], Răzvan I. Dumitru[2], Carmen A. Sîrbu[2,3], Minerva C. Ghinescu[2]

Abstract: *Objective: Cerebrovascular Accidents (CVAs) represent the second most prominent cause of death globally, surpassed only by ischemic heart diseases, thus constituting a significant economic burden for healthcare systems. Despite this, little is known about the correlation between the different times of the year and intracerebral hemorrhages. This review investigates said link, as well as seek to identify whether vascular risk factors (i.e. diabetes and high blood pressure) vary through seasons.*

Method: This paper undertakes the study of 97 patients, all of whom have suffered a hemorrhagic CVA and were hospitalized and treated within the Central Military Emergency University Hospital's Department of Neurology in Bucharest, in the period between 29th of June, 2017 and 29th of July, 2019. The scope of this study is to optimize prophylaxis within the groups most susceptible to the imminent danger of an intracranial hemorrhage during a certain season.

Results: Our study has shown that the season with the highest values of morbidity and mortality is autumn, followed closely by spring.

Conclusion: Given the set of yielded data, which is mirrored in the case of risk factors, we conclude that the results vary slightly from those put forward in the literature. Therefore, whilst hemorrhaging CVAs have a consequential impact upon society, both through the disastrous effects of the incident per se, and its disabling nature in the long-term, a positive percentage of them could be avoided by changing one's behavior during the high-risk periods.

Keywords: *intracranial hemorrhages, subarachnoid hemorrhage, subdural hematoma, hypertension, diabetes mellitus*

INTRODUCTION

Intracranial hemorrhage (ICH) is caused either by tearing apart several small penetrating vessels or as a result of some vascular anomalies. Risk factors such as high blood pressure (HBP) or diabetes mellitus (DM) are frequently associated with ICHs [1, 2]. While in developed countries, the incidence of this pathological condition has reduced due to better control of HBP, in developing countries, it has remained alarmingly constant for the past decades [3].

According to the WHO (World Health Organization), approximately 6 million deaths were attributed globally to ICH in 2016 [4]. In the context of its economic impact, in the US alone, in 2012, the total costs of stroke patients reached USD 71.5 billion, according to the AHA/ASA (American Heart

[1] Department of Neurosurgery, Carol Davila University Central Emergency Military Hospital, Bucharest, Romania
[2] Department of Medical-Surgical and Prophylactic Disciplines, Faculty of Medicine "Titu Maiorescu" University, Bucharest, Romania
[3] Department of Neurology, Carol Davila University Central Emergency Military Hospital, Bucharest, Romania

Corresponding author: Sirbu Carmen Adella
sircar13@yahoo.com

Association/American Stroke Association). By 2030, these costs are estimated to reach USD 240 billion [5].

Intracerebral hemorrhages account for approximately 10 to 20% of all strokes [3]. The main cause of developing ICH is the alteration of the structure of the blood vessel caliber as a result of an untreated or inadequately treated chronic high blood pressure (HBP). Other incriminating causes include amyloid angiopathy and vascular malformations. It has been observed that the frequency of ICHs in developing countries is almost double that of developed countries, progressively growing with aging. Ergo, it has been determined that for the 35-54 age group, the incidence is of 6 cases for every 100,000 people, for the 54-74 age group, it increases to 37 for every 100,000 people, and, for the 75-94 age group, it peaks at 176 for every 100,000 people.

For young patients, the main cause of hemorrhages is represented by vascular malformations. In adults, this is represented by chronic HBP, whereas in the elderly, it is amyloid angiopathy. Moreover, it has been shown that, on average, regardless of age, the incidence of ICH is higher in men than in women [6].

Concerning chronic HBP, this leads, eventually, to hypertensive angiopathy which, in turn, causes degenerative modifications within the caliber of the small and medium penetrating vessels, modifications known as lipohyalinosis. Regarding chronic hypertension, it has been ascertained that degeneration takes place at the muscular layer, together with the fibrinoid necrosis of the subendothelial layer, accompanied by micro-aneurysms.

Amyloid angiopathy is characterized by deposits of β-amyloid peptide (βA) in the capillaries, arterioles, and, generally, in all small and medium vessels in the cerebral cortex, leptomeninges, and cerebellum [6]. Secondly, amyloid angiopathy is portrayed through deposits of intravascular βA in the leptomeningeal collaterals and small intracortical vessels. Although the mechanism of depositing and accumulating βA is unknown, its consequence is the degeneration of the blood vessel caliber through, more specifically, losing smooth muscle fibers, thinning the caliber, narrowing the lumen, and leading to aneurisms, the latter further giving birth to diffuse micro-hemorrhages [7].

Furthermore, apart from HBP, other causes include the dysfunction of self-regulating with excessive cerebral blood flow, arteriovenous malformations, ruptured aneurysms, cerebral angiopathy, hemorrhagic necrosis, cerebral venous thrombosis, and modified hemostasis.

The overflow of the resulting blood from the bursting of the caliber leads to a sudden increase of intracranial pressure, which brings about diffuse vasospasm, followed by the acute ischemia of the parenchyma – a mechanism which is frequently present in the potential vasospasm after subarachnoid hemorrhage [8, 9]. The BBB permeability heightens, thus aggravating the metabolic disorders of the brain, giving birth to the cerebral edema [10]. Despite the advancements in medicine, cerebral bleedings have retained a status of high morbidity and incremental mortality, unaddressed properly by the modern therapeutic methods developed hitherto. This is partly due to the complex, irreversible pathophysiology processes which occur the moment blood makes contact with the cerebral parenchyma. Understanding this phenomenon and ICH's evolution would allow identification of the potential therapeutic targets.

METHODS

A retrospective study has been conducted which includes patients who have had non-traumatic hemorrhaging vascular accidents, hospitalized and treated in the period between June 2017 and July 2019 within the "Carol Davila" Central Military Emergency University Hospital's Department of Neurology.

The selected patients have been diagnosed with non-traumatic intracerebral hemorrhage by a neurologist, subsequently confirmed through a CT scan. The patients' age varied between 23 and 97 years, with provenance from both countryside and urban environment, with diverse professional occupations. We have investigated the three main types of non-traumatic bleedings, namely, intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), and subdural hematoma (SDH).

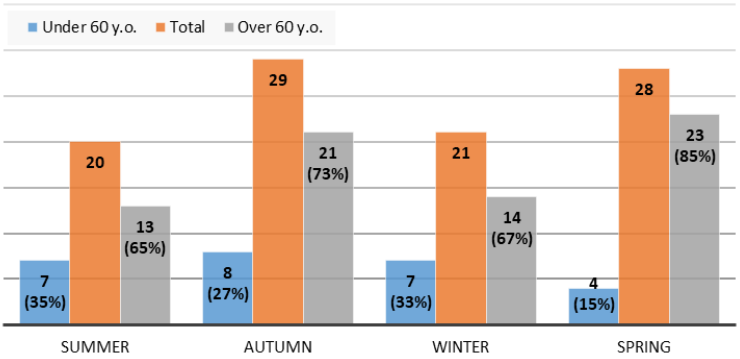
RESULTS

Out of the 97 patients, 67% were male and 33% female. Out of these, as many as 77% have presented non-traumatic IPH, 13% SAH, and 10% SDH. 17% of the patients have deceased during hospitalization. The average age was 67 years old, 72% of those placed in medical care being older than 60 years old (Figure 1). The average period of hospitalization was 21 days, with a minimum of 2 days and a maximum of 587.

Seasons were defined in the same way as in the rest of the studies, to have a consistency between these, for the sake of comparing them and display our research as suitable, i.e. summer: 1st of June – 31st of August, autumn: 1st of September – 30th of November, winter: 1st of December – 28/29th of February, spring: 1st of March – 31st of May.

We have identified an incremental occurrence of the cases

of cerebral hemorrhages in transitional seasons, namely, autumn and spring. Similar results have been produced in most of the past studies, regardless of whether, in some situations, these have shown a larger incidence in winter (based on the geographical areas where these have been carried out) due to the physiological differences of organisms at low temperatures [11, 12, 13].

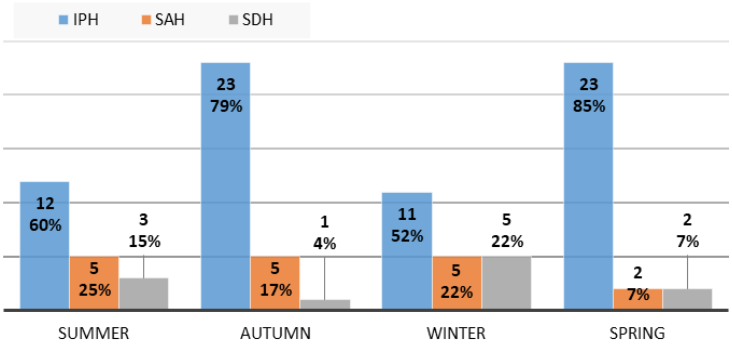


Legend: blue – the incidence of intracerebral hemorrhage (ICH) in the under 60 age group; orange – total incidence of both age groups; grey – the incidence of ICH in the over 60 age group

Figure 1: Number of cases (percentage) of ICH's seasonal incidence

Concerning the seasonal incidence of each type of hemorrhage (Figure 2), we observe an increase in IPH in autumn and spring, a constant incidence in SAH in summer, autumn, and winter, with a lower number of cases in spring, and a relatively constant number for SDH, with a maximum and a minimum number of cases in winter and autumn, respectively.

It is widely accepted that the main risk factor of ICH is represented by chronic HBP, corroborated with a hypertensive leap exceeding the limit of cerebral vascular resistance. The risk of hemorrhage in hypertensive patients is 1.5 times for BP ~ 140 mmHG and three times for BP > 180 mmHg than it is for normotensive patients [14].

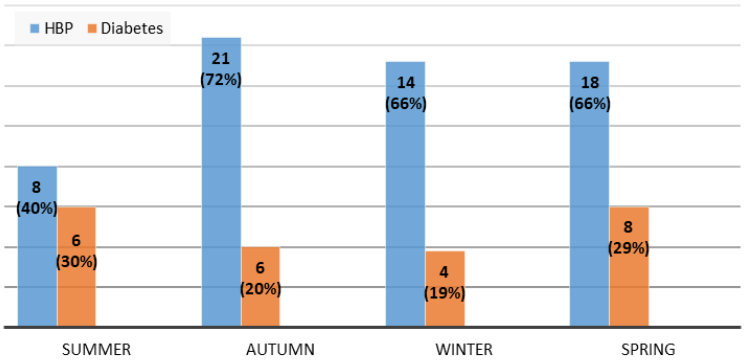


Legend: blue – frequency of intraparenchymal hemorrhage (IPH), orange – the incidence of non-traumatic subarachnoid hemorrhage (SAH); grey – the incidence of subdural hematoma (SDH)

Figure 2: Seasonal incidence of hemorrhages

Out of all diagnosed with IPH, 27% out of the 73 patients have had no associated diabetes mellitus (DM) or chronic HBP, 70% suffered from chronic HBP, 20% from diabetes, and 18% from both. In the context of SAH, 61% had no associated comorbidities, 31% had chronic HBP, 15% DM, and 7% both chronic HBP and DM. Out of those who have been hospitalized from non-traumatic SDH, 36% have not shown any of the abovementioned risk factors, 54% have shown HBP, 27% DM and 18% have shown both. In the analyzed lot, 61 patients suffered from HBP in different degrees, this number representing 62% of the hospitalized patients. The highest rate of cerebral bleedings associated with chronic HBP was registered in autumn, followed by spring (Figure 3). Besides this, we have also evaluated the association between DM and cerebral hemorrhage, as DM may determine an unpropitious prognostic in the case of ICH. Persons with diabetes have a 20% increased risk of suffering from cerebral bleeding, as opposed to a person not afflicted, as well as over a 50% chance of dying within 30 days after the hemorrhage [15]. In our study, we have identified

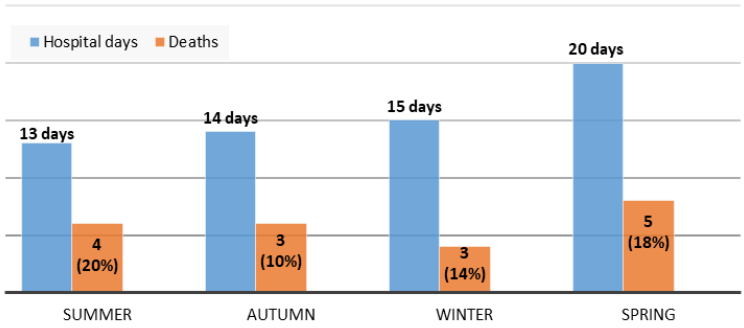
a prevalence of diabetes of 29% among hospitalized patients.



Legend: blue – the prevalence of high blood pressure (HBP) at ICH patients; orange – the prevalence of diabetes mellitus (DM) at ICH patients.

Figure 3: HBP and DM

According to this data, we observe that, indeed, diabetes does not seem to play an important role in contributing to ICH, yet there is high morbidity during summer and winter, seasons with extreme temperatures, and low morbidity during the transitional seasons, spring and autumn. Moreover, there is a higher risk of cerebral hemorrhaging during winter and summer, for those who have diabetes as an associated pathological condition. Apart from a heightened incidence of ICH in spring, we emphasize the more severe nature of these through lengthy hospitalizations periods, hence the increased economic burden on healthcare systems (Figure 4). Considering the number of days of hospitalization as an indicator of the gravity of the hemorrhage, as well as its occurrence in critical areas or through associated complications, we must submit a longer period of recovery for these patients and a lower degree of autonomy and social reintegration. Concerning deaths, we observe a relatively constant rate throughout the entire year, thus barring us from claiming any one risk factor in particular increases ICH's mortality. Apart from the increased morbidity, spring also registers the highest rates of mortality.



Legend: blue – the average number of hospital days; orange – number of deaths

Figure 4: Hospitalization and deaths

DISCUSSIONS

The results of this study show a variety of the incidence of hospitalization, in-hospital mortality, duration of hospitalization, and patients' prognostic throughout the year, in Bucharest, a region with a temperate continental climate. The data is new for this geographic zone, as, hitherto, there have been no recorded statistical studies (at least recent) to quantify the seasonal incidence of ICH in this area. Consequently, this research tackles on a novel theme, representing a pilot study. For the patients included in this study, the highest incidence was observed during the transitional seasons, especially during autumn, whereas the lowest was during summer. The yielded results contradict the larger part of studies available in the specialized literature, which have either failed to find a variety of incidence or claimed a heightened incidence in other seasons, particularly in winter and spring [12, 13, 16, 17]. Nonetheless, there are also similar results [11].

Regarding the seasonal distribution on age groups, the current study has registered a constant tendency of ICH debuting at patients under 60 throughout the year, apart from spring, when it has decreased, contrary to the constant incidence in the year evaluated by other studies [11, 12]. Conversely, regarding patients over 60, the seasons corresponding to high risk are spring and autumn, with two minimums registered during winter and summer, data which is in line with the results of other comparative studies [11, 12].

When the assessment also includes comorbidities, data is similar to that obtained in other research papers. Diabetes does not seem to play a decisive role in how a hemorrhage comes to be, but it may exacerbate the prognostic [15]. On the other hand, concerning HBP, this is seen as being the most important risk factor for hemorrhage and it has implications both for the prognostic and survival [18]. The mechanisms underlying these seasonal varying conditions are not clear, but it is probable for the latter to be associated with seasonal variations in biological factors, such as the level of serum lipids, some components of the blood, and a hypercoagulable state [19]. Concerning the number of deaths, we have not observed a significant variation in the year, thus being relatively constant, similar data having been obtained by other authors as well [12, 13].

The reason why the risk of ICH is modified throughout the year is not entirely known. The dysfunction of the environmentally adaptive physiological processes may be the underlying cause of hemorrhages. Variations in temperature and atmospheric humidity are considered the main catalyst for hemorrhaging events [20]. Low temperatures and low atmospheric humidity can increase evaporation, leading to an increased demand for salt, thus constituting HBP [20].

CONCLUSIONS

ICH is one of the most important neurological pathological conditions. Even though incidence is lower than it is in the case of ischemic strokes, morbidity and mortality are higher. There is still an ongoing need for thorough studies regarding the seasonal incidence of cerebral hemorrhages, as there is a subset of modifiable factors related to behavior and lifestyle which can potentially contribute to avoiding a hemorrhagic episode in either one of the seasons.

In this study, we have noticed a heightened tendency to cerebral bleeding during autumn and spring, as compared to other geographic zones or climates. Moreover, we have seasonally classified the type of ICH patients in this study were subject to, observing the predominant IPH throughout the entire year. We have also determined the average number of necessary hospital days for each season, emphasizing that spring is associated with the highest morbidity. Furthermore, in the context of this study, we have also found a significant correlation between chronic HBP and the incidence of cerebral hemorrhages, confirmed prior data that DM is a risk factor for triggering a hemorrhagic stroke, but with no real influence on mortality, as well as defined seasonal risk of ICH groups based on age and comorbidities.

In the future, it is paramount that we understand better the physiopathological process underlying cerebral hemorrhages to develop efficient methods with therapeutic potential. Although this may seem ideal, reducing seasonal incidence in risk groups through educating patients is particularly difficult to achieve. Until then, developing methods of treatment that focus on slowing down or completely barring the inflammation's progress and, implicitly, that of neurological deficits, is a short-term objective.

References:

1. Hesami O, Kasmaei HD, Matini F, Assarzadegan F, Mansouri B, Jabbehdari S. Relationship between intracerebral hemorrhage and diabetes mellitus: a case-control study. J Clin Diagn Res. 2015 Apr;9(4):OC08-10. doi: 10.7860/JCDR/2015/12226.3741. Epub 2015 Apr 1. PMID: 26023579; PMCID: PMC4437093.

2. Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, Rosand J. Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. JAMA. 2015 Sep 1;314(9):904-12. doi: 10.1001/jama.2015.10082. PMID: 26325559; PMCID: PMC4737594.

3. An SJ, Kim TJ, Yoon BW. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J Stroke. 2017 Jan;19(1):3-10. doi: 10.5853/jos.2016.00864. Epub 2017 Jan 31. PMID: 28178408; PMCID: PMC5307940.

4. The top 10 causes of death. 24 May 2018. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.

5. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, Lackland DT, Lichtman JH, Mohl S, Sacco RL, Saver JL, Trogdon JG; American Heart Association Advocacy Coordinating Committee and Stroke Council. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke. 2013 Aug;44(8):2361-75. doi: 10.1161/STR.0b013e31829734f2. Epub 2013 May 22. .

6. Qi XM, Ma JF. The role of amyloid beta clearance in cerebral amyloid angiopathy: more potential therapeutic targets. Transl Neurodegener. 2017 Aug 17;6:22. doi: 10.1186/s40035-017-0091-7.

PMID: 28824801; PMCID: PMC5559841.

7. Charidimou A, Boulouis G, Gurol ME, Ayata C, Bacskai BJ, Frosch MP, Viswanathan A, Greenberg SM. Emerging concepts in sporadic cerebral amyloid angiopathy. Brain. 2017 Jul 1;140(7):1829-1850. doi: 10.1093/brain/awx047. PMID: 28334869; PMCID: PMC6059159.

8. Rajashekar D, Liang JW. Intracerebral Hemorrhage. [Updated 2020 Mar 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553103/.

9. Liebeskind, David S. Hemorrhagic Stroke. Medscape Apr 22, 2019.

10. Lim-Hing K, Rincon F. Secondary Hematoma Expansion and Perihemorrhagic Edema after Intracerebral Hemorrhage: From Bench Work to Practical Aspects. Front Neurol. 2017 Apr 7;8:74. doi: 10.3389/fneur.2017.00074. PMID: 28439253; PMCID: PMC5383656.

11. Jin H, Xu Z, Li Y, Xu J, Shan H, Feng X, Xie Y, Bian K, Qin D. Seasonal variation of stroke incidence in Wujin, a city in southeast China. Health Sci Rep. 2018 Mar 9;1(4):e29. doi: 10.1002/hsr2.29. PMID: 30623065; PMCID: PMC6266434.

12. Wang K, Li H, Liu W, You C. Seasonal variation in spontaneous intracerebral hemorrhage frequency in Chengdu, China, is independent of conventional risk factors. J Clin Neurosci. 2013 Apr;20(4):565-9. doi: 10.1016/j.jocn.2012.02.052. Epub 2013 Jan 12. . PMID: 23317754.

13. Telman G, Sviri GE, Sprecher E, Amsalem Y, Avizov R. Seasonal variation in spontaneous intracerebral hemorrhage in northern Israel. Chronobiol Int. 2017;34(5):563-570. doi: 10.1080/07420528.2016.1278223. Epub 2017 Feb 3. PMID: 28156174.

14. Du X, Wang C, Ni J, Gu H, Liu J, Pan J, Tu J, Wang J, Yang Q, Ning X. Association of Blood Pressure With Stroke Risk, Stratified by Age and Stroke Type, in a Low-Income Population in China: A 27-Year Prospective Cohort Study. . Front Neurol. 2019 May 29;10:564. doi: 10.3389/fneur.2019.00564. PMID: 31191445; PMCID: PMC6548813.

15. Boulanger M, Poon MT, Wild SH, Al-Shahi Salman R. Association between diabetes mellitus and the occurrence and outcome of intracerebral hemorrhage. Neurology. 2016 Aug 30;87(9):870-8. doi: 10.1212/WNL.0000000000003031. Epub 2016 Jul 29. PMID: 27473136; PMCID: PMC5035156.

16. Bahonar A, Khosravi A, Khorvash F, Maracy M, Saadatnia M. Seasonal and Monthly variation in stroke and its subtypes-10 Year Hospital-Based Study. Mater Sociomed. 2017 Jun;29(2):119-123. doi: 10.5455/msm.2017.29.119-123. PMID: 28883775; PMCID: PMC5544452.

17. Anand Patel, Archana Hinduja, Jamil Dibu, Eugene Achi, Rajan Patel. Seasonal Variation In The Incidence And Mortality Of Intracerebral Hemorrhage. Neurology Apr 2014, 82 (10 Supplement) P7.144.

18. Chiquete E, Ruiz-Sandoval MC, Alvarez-Palazuelos LE, Padilla-Martínez JJ, González-Cornejo S, Ruiz-Sandoval JL. Hypertensive intracerebral hemorrhage in the very elderly. Cerebrovasc Dis. 2007;24(2-3):196-201. doi: 10.1159/000104477. Epub 2007 Jun 27. PMID: 17596688.

19. Kumar P, Kumar A, Pandit AK, Pathak A, Prasad K. Seasonal Variations in Stroke: A Study in a Hospital in North India. J Stroke. 2015 May;17(2):219-20. doi: 10.5853/jos.2015.17.2.219. Epub 2015 May 29. PMID: 26060810; PMCID: PMC4460342.

20. Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. Circulation. 2006 Oct 24;114(17):1863-72. doi: 10.1161/CIRCULATIONAHA.105.596189. PMID: 17060396.

Guidelines for authors

Thank you for your interest in the *Romanian Journal of Military Medicine*. Please read the complete Author Guidelines carefully before submission, including the section on copyright.
To ensure fast peer review and publication, manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.
Note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. Once you have prepared your submission following the Guidelines, manuscripts should be submitted online at rjmilmed@yahoo.com.
We look forward to your submission.

EDITORIAL AND CONTENT CONSIDERATIONS

Aims and Scope

Romanian Journal of Military Medicine (RJMM) is the official journal of the Romanian Association of Military Physicians and Pharmacists. The Journal publishes peer-reviewed original papers, reviews, meta-analyses, and systematic reviews, and editorials concerned with clinical practice and research in the fields of medicine.
Papers cover the medical, surgical, radiological, pathological, biochemical, physiological, ethical, and historical aspects of the subject areas.
Clinical trials are afforded expedited publication if deemed suitable. RJMM also deals with the basic sciences and experimental work, particularly that with clear relevance to disease mechanisms and new therapies. Case reports and letters to the Editor will not be considered for publication.

Editorial Review and Acceptance

The acceptance criteria for all papers and reviews are based on the quality and originality of the research and its clinical and scientific significance to our readership. All manuscripts are peer-reviewed under the direction of an Editor. The Editor reserves the right to refuse any material for review that does not conform to the submission guidelines detailed throughout this document, including ethical issues, completion of an Exclusive License Form, and stipulations as to length.

ETHICAL CONSIDERATIONS

Principles for Publication of Research Involving Human Subjects

Manuscripts must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed following the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013) (http://www.wma.net/en/30publications/10policies/b3/index.html).
It should also state clearly in the text that all persons gave their informed consent before their inclusion in the study. Details that might disclose the identity of the subjects under the study should be omitted. Photographs need to be cropped sufficiently to prevent human subjects from being recognized (or an eye bar should be used).

Registration of Clinical Trials

We strongly recommend, as a condition of consideration for publication, registration in a public trials registry. Trials register at or before the onset of patient enrolment. This policy applies to any clinical trial. We define a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase 1 trials) are exempt.
We do not advocate one particular registry, but registration with a registry that meets the following minimum criteria:
(1) Accessible to the public at no charge;
(2) Searchable by standard, electronic (Internet-based) methods;
(3) Open to all prospective registrants free of charge or at minimal cost;
(4) Validates registered information;
(5) Identifies trials with a unique number; and
(6) includes information on the investigator(s), research question or hypothesis, methodology, intervention and comparisons, eligibility criteria, primary and secondary outcomes measured, date of registration, anticipated or actual start date, anticipated or actual date of the last follow-up, the target number of subjects, status (anticipated, ongoing or closed) and funding source(s).

Plagiarism Detection

The journal employs a plagiarism detection system. By submitting your manuscript to this journal you accept that your manuscript may be screened for plagiarism against previously published works.

Committee on Publication Ethics

The journal subscribes to the principles of the Committee on Publication Ethics (COPE).

MANUSCRIPT CATEGORIES AND SPECIFICATIONS

All articles, except for Editorials, must contain an abstract of no more than 250 words. Abstracts for original articles should be formatted into subheadings, as detailed below. Titles must not be longer than 120 characters (including spaces).

Editorials

These are invited by the Editor-in-Chief or their delegated editor and should be a brief review of the subject concerned, regarding and commentary about one or more articles published in the same issue of RJMM. Editorials are generally 1200–1500 words, may contain one table or figure, and cite up to 15 references, including the source article [this should be cited as Rom J Mil Med (year); (vol): [this issue].

Review Articles

RJMM welcomes reviews of important topics across the scientific basis of medicine and advances in clinical practice. Most published reviews are in response to the editorial invitation, including thematically related "mini-series" of reviews. Authors considering submitting a review for RJMM are advised to canvas their possible review with the Editor-in-Chief or a colleague editor; this avoids early rejection if the subject matter is not deemed a high priority for the Journal at the time of submission. Reviews are limited to 3500–5000 words, with an abstract of up to 250 words and up to 75 references and 3–7 figures or tables.

Meta-Analyses or Systematic Reviews

RJMM particularly welcomes the submission of Meta-Analyses and Systematic Reviews, which underpin evidence-based medicine. Guidelines for the preparation of Meta-Analysis and Systematic Reviews are similar to other reviews, and articles are subject to the usual peer-review process. Meta-Analyses and Systematic Reviews have a word limit of 3500–5000 words, with an abstract of up to 250 words and up to 75 references, and 3–7 figures or tables.

Original Articles (including clinical trials)

RJMM welcomes original articles concerned with clinical practice and research in the fields of medicine. Papers can cover the medical, surgical, radiological, pathological, biochemical, physiological, ethical, and/or historical aspects of the subject areas. Clinical trials are afforded expedited publication if deemed suitable. RJMM also deals with the basic sciences and experimental work, particularly that with clear relevance to disease mechanisms and new therapies. Original articles are limited to 3000 words, with an abstract of up to 250 words and up to 50 references and 3–7 figures and tables.

Education and Imaging

The Editors welcome contributions to the Education and Imaging section. The purpose is to present imaging for the evaluation of unusual features of common conditions or diagnosis of unusual cases. Contributions will be reviewed by the Education and Imaging Coordinating Editors. The format of the Images pages involves two parts, each of which will occupy up to one journal page. In part 1, a case will be described briefly, including a summary of the presentation, clinical features, and key laboratory results. One to two key images will then be presented. It is helpful to the reader if the author responds to questions that follow from the images of the case, such as 'What is your diagnosis? What are the features indicated on the CT scan? What is the differential diagnosis?' Part 2 will briefly describe the imaging features, particularly those that lead to a diagnosis or which are critical for management. Differential diagnosis should be mentioned. It will be useful to include either further images or pathological details that validate the imaging diagnosis. Occasionally, the presentation of analogous cases or related images from a similar case might be appropriate. Please include between one and three references to definitive studies and appropriate reviews of the subject. The format of the Images page involves a brief background to and description of the disorder of interest together with two figures of high quality. Colored photographs are encouraged. The submission may take the form of a case report or may illustrate particular features from more than one patient.

MANUSCRIPT PREPARATION

Style

Manuscripts should follow the style of the Vancouver agreement detailed in the International Committee of Medical Journal Editors' revised 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication', as presented at http://www.ICMJE.org/.

Spelling. The journal uses US spelling and authors should, therefore, follow the latest edition of the Merriam-Webster's Collegiate Dictionary.

Units. All measurements must be given in SI units as outlined in the latest edition of Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Royal Society of Medicine Press, London).

Abbreviations should be used sparingly and only where they ease the reader's task by reducing repetition of long technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation.

Trade names should not be used. Drugs should be referred to by their generic names, rather than brand names.

Parts of the Manuscript

The manuscript should be submitted in separate files: title page; main text file; figures.

Title page

The title page should contain (i) a short informative title that contains the major keywords. The title should not contain abbreviations; (ii) the full names of the authors (if possible, not more than 5 authors per title); (iii) the author's institutional affiliations at which the work was carried out; (iv) the full postal and email address, plus telephone number, of the author to whom correspondence about the manuscript should be sent; (v) disclosure statement; and (vi) acknowledgments. The present address of any author, if different from that where the work was carried out, should be supplied in a footnote.

Disclosure statement

The source of financial grants and other funding should be acknowledged, including a frank declaration of the authors' industrial links and affiliations. In the case of clinical trials or any article describing the use of a commercial device, therapeutic substance or food must state whether there are any potential conflicts of interest for each of the authors: failure to make such a statement may jeopardize the article being sent out for peer-review.

Acknowledgments

The contribution of colleagues or institutions should also be acknowledged. Thanks to anonymous reviewers are not allowed.

Main text

As papers are double-blind peer-reviewed the main text file should not include any information that might identify the authors. The main text of the manuscript should be presented in the following order: (i) abstract and keywords, (ii) text, (iii) references, (iv) tables (each table complete with title and footnotes), (vii) figure legends. Figures and supporting information should be submitted as separate files. Footnotes to the text are not allowed and any such material should be incorporated into the text as parenthetical matter.

Abstract and keywords

Original articles must have a structured abstract that states in 250 words or less the purpose, basic procedures, main findings, and principal conclusions of the study. Divide the abstract with the headings: *Background and Aim, Methods, Results, Conclusions*. The abstracts of reviews need not be structured. The abstract should not contain abbreviations or references. Three to five keywords should be supplied below the abstract and should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser—(http://www.nlm.nih.gov/mesh/meshhome.html).

Text

Authors should use subheadings to divide the sections of their manuscript: *Introduction, Methods, Results, Discussion Acknowledgments, and References*.

References

The Vancouver system of referencing should be used. In the text, references should be cited using superscript Arabic numerals in the order in which they appear. If cited only in tables or figure legends, number them according to the first identification of the table or figure in the text. In the reference list, the references should be numbered and listed in order of appearance in the text. Cite the names of all authors when there are six or less; when seven or more list the first three followed by et al. Names of journals should be abbreviated in the style used in MEDLINE. Reference to unpublished data and personal communications should appear in the text only.

References should be listed in the following form:

Number references in the order cited as Arabic numerals in parentheses on the line. Only literature that is published or in press (with the name of the publication known) may be numbered and listed; abstracts and letters to the editor may be cited, but they must be less than 3 years old and identified as such. Refer to only in the text, in parentheses, other material (manuscripts submitted, unpublished data, personal communications, and the like) as in the following example: (Chercheur X, unpublished data). If the owner of the unpublished data or personal communication is not an author of the manuscript under review, a signed statement is required verifying the accuracy of the attributed information and agreement to its publication. Use Index Medicus as the style guide for references and other journal abbreviations. List all authors up to six, using six and "et al." when the number is greater than six.

Tables

Tables should be self-contained and complement, but not duplicate, the information contained in the text. Number tables consecutively in the text in Arabic numerals. Type tables on a separate page with the legend above. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. Vertical lines should not be used to separate columns. Column headings should be brief, with units of measurement in parentheses; all abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶ should be used (in that order), and *, **, *** should be reserved for *P*-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure legends

Type figure legends on a separate page. Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement Indicate the stains used in histopathology. Identify statistical measures of variation, such as standard deviation and standard error of the mean.

Figures

All illustrations (line drawings and photographs) are classified as figures. Figures should be numbered using Arabic numerals, and cited in consecutive order in the text. Each figure should be supplied as a separate file, with the figure number incorporated in the file name.

Preparation of Electronic Figures for Publication: Although low-quality images are adequate for review purposes, publication requires high-quality images to prevent the final product from being blurred or fuzzy.

SUBMISSION REQUIREMENTS

Manuscripts should be submitted online at rjmilmed@yahoo.com

A cover letter containing an authorship statement should be included.

The cover letter should include a statement covering each of the following areas:

1. Confirmation that all authors have contributed to and agreed on the content of the manuscript, and the respective roles of each author.

2. Confirmation that the manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere.

3. A statement outlining how ethical clearance has been obtained for the research, particularly concerning studies involving human subjects, and animal experimentation. The institutional ethics committees approving this research must comply with acceptable international standards (such as the Declaration of Helsinki) and this must be stated.

4. For research involving pharmacological agents, devices, or medical

technology, a clear Conflict of Interest statement concerning any funding from or pecuniary interests in companies that could be perceived as a potential conflict of interest in the outcome of the research.
5. For clinical trials, these have been registered in a publically accessible database.
If the above items are not included in the cover letter, manuscripts cannot be sent for review.
Please also note that the cover letter does not require a detailed or lengthy description of the content or structure of the manuscript itself.
Two Word-files need to be included upon submission: A title page file and the main text file that includes all parts of the text in the sequence indicated in the section 'Parts of the manuscript', including tables and figure legends but excluding figures which should be supplied separately.
The main text file should be prepared using Microsoft Word, double-spaced. The top, bottom, and side margins should be 30 mm. All pages should be numbered consecutively in the top right-hand corner, beginning with the first page of the main text file.
Each figure should be supplied as a separate file, with the figure number incorporated in the file name. For submission, low-resolution figures saved as .jpg or .bmp files should be uploaded, for ease of transmission during the review process. Upon acceptance of the article, high-resolution figures (at least 300 d.p.i.) saved as .eps or .tif files will be required.

PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted papers will be passed to the production team for publication. The author identified as the formal corresponding author for the paper will receive an email, being asked to complete an electronic license agreement on behalf of all authors on the paper.

Accepted Articles

The accepted 'in press' manuscripts are published online very soon after acceptance, before copy-editing or typesetting. Accepted Articles are published online a few days after final acceptance, appear in PDF format only, are given a Digital Object Identifier (DOI), which allows them to be cited and tracked. After print publication, the DOI remains valid and can continue to be used to cite and access the article. Given that copyright licensing is a condition of publication, a completed copyright form is required before a manuscript can be processed as an Accepted Article.

Proofs

Once the paper has been typeset, the corresponding author will receive an e-mail alert containing instructions on how to provide proof corrections to the article. It is therefore essential that a working e-mail address is provided for the corresponding author. Proofs should be corrected carefully; the responsibility for detecting errors lies with the author. The proof should be checked, and approval to publish the article should be emailed to the Publisher by the date indicated; otherwise, it may be signed off on by the Editor or held over to the next issue.

Offprint

A PDF reprint of the article will be supplied free of charge to the corresponding author. Additional printed offprints may be ordered for a fee.

COPYRIGHT, LICENSING AND ONLINE OPEN

Details are on the Copyright Agreement Form that must be completed and signed when the Article is accepted.

ROMÂNIA
MINISTERUL APĂRĂRII NAȚIONALE

Atestat

Ministrul apărării naţionale

dorind a răsplăti meritele

redacției pubilcației „Revista de Medicină Militară",

în semn de apreciere a contribuţiei avute la creşterea prestigiului structurilor medicale din Armata României, cu ocazia aniversării a 120 de ani de la înfiinţare,

conferă ***Emblema de Onoare a Armatei României***
-cu însemn de pace-

Acordat în Bucureşti, 15 Noiembrie 2017

Ministrul apărării naţionale

Mihai-Viorel Fifor

Ordinul nr.M.P.3 din 15.11.2017
Atestat E.O.A.R./nr.1

Nr.crt. 21

Romanian Journal of

Military Medicine

New Series, Vol. CXXIII, No 4/2020, November
ISSN-L 1222-5126; eISSN 2501-2312; pISSN 1222-5126