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ARTICLE

A conceptual analysis of loneliness in military personnel and suggested directions of therapeutic intervention

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Abstract: Loneliness is receiving more and more attention for being an important psychosocial contributor to the deterioration of quality of life, psychological well-being, onset of mental health disorders, but also to the increased mortality and morbidity, through the mediation of general health problems and suicide. While studies on the impact of loneliness in the civilian population have been steadily increasing in number over the past decade, research on the same phenomenon in military settings has progressed at a comparatively slower pace. This article is a two-stage analysis of the perceived lack of social connectedness among active-duty and former military personnel, including (1) a conceptual exploration and literature review based on searches in three electronic databases (PubMed, Google Scholar, and Web of Science/Clarivate), and (2) a pragmatical set of recommended strategies to reduce the impact of loneliness in these populations. Based on the review of 42 primary and secondary sources, the paper explores the prevalence, risk and protective factors, characteristics, and consequences of loneliness, with particular attention to various minorities, female military personnel experiencing motherhood during active duty, civilian spouses of deployed service members, and other significant subgroups. Recommended directions of interventions are threefold, i.e., screening for loneliness and its risk factors, initiation of prophylactic strategies and therapeutic interventions targeting this phenomenon in vulnerable categories. In conclusion, further research on loneliness in both active and former military personnel is strongly warranted, given its significant consequences for multiple dimensions of health and overall functioning.

Keywords: loneliness; social isolation; thwarted belongingness; active military personnel; veterans; PTSD; combat stress reactions; prisoners of war; military spouses; female military personnel

INTRODUCTION

Loneliness is a phenomenon with high incidence in adults, and the estimate of this subjective emotional state (i.e., the feeling of being alone) in an analysis conducted by the Centers for Disease Control and Prevention (CDC) in the US shows high values, of 32%, among adults in 2022 [1]. According to the same report, 24% of the US adults perceived a lack of social and emotional support, which is another important indicator of social disconnection, and the values were the highest for individuals aged between 18 and 34 years old, for both variables [1]. The third indicator that should be explored in this context is social isolation (an objective variable, this time, defined by lack of interpersonal interactions) in the adult population, which has a prevalence ranging from 15 to 40% [2-4]. According to another report published in 2020, when loneliness and social isolation were analyzed by age group, more than 33% of adults aged 45 years and older reported feeling lonely, while over 25% of

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adults aged 65 years and older were considered socially isolated, based on assessments using a validated instrument, such as the UCLA Loneliness Scale [2-4].

The exploration of loneliness and social isolation is not limited to psychosocial factors alone, as the impact of these phenomena on overall health, quality of life, and psychological well-being is substantial and cannot be overstated (Fig.1). For example, loneliness has been linked to higher rates of heart disease, lung illnesses, stroke, and metabolic disorders [5]. More specifically, this feeling of being alone and the lack of social contacts were independently associated with a diagnosis of cardiovascular disease and type 2 diabetes after 5-year follow-up, in a study that paired the results of a survey (N=24687 participants) with data collected from the National Danish Patient Registry [6]. Loneliness was significantly associated with a higher probability of metabolic syndrome, not moderated by age or central obesity, in a population-based survey in England (N=3211 patients aged 52 to 79 years old) [7].

Also, loneliness is an essential predictor of psychological difficulties and psychiatric symptoms, such as depressed mood and anxiety, and it is linked to overall morbidity and mortality in the adult population [5]. A systematic review that included 32 reports concluded that most studies focused on depressive disorders were able to detect an association between the new onset of depression during the patients' evolution and loneliness at baseline, and similar correlations were reported for anxiety and self-harm [8]. The adjusted odds ratio for new-onset depression in adults who had significant levels of loneliness was 2.33 when compared to those who were not feeling lonely [8]. Moderate to severe loneliness predicted higher depression scores six months later, and higher depression and anxiety scores at baseline predicted social isolation at follow-up [9].

Figure 1: Loneliness and its negative consequences [5-15]
CVD=cardio-vascular diseases, SC=social cognition

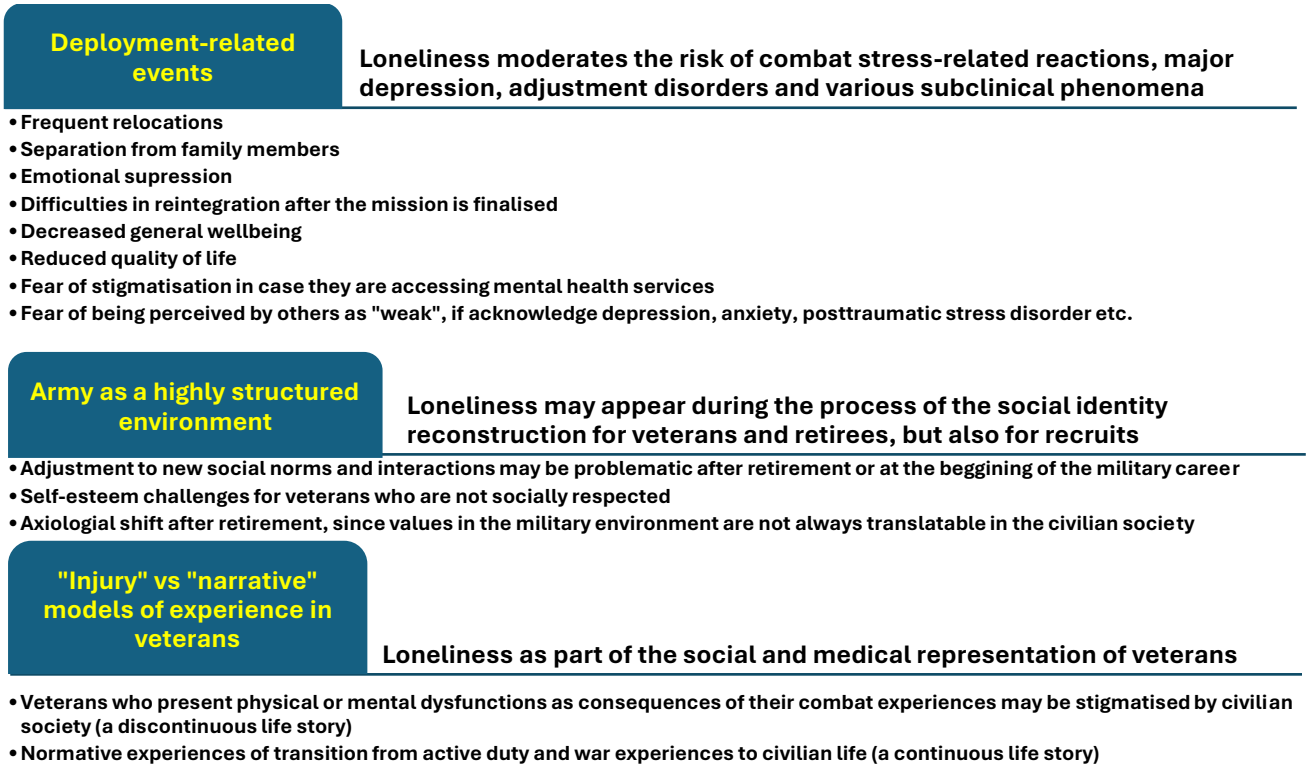
Loneliness was involved in the all-cause mortality increase in a meta-analysis (n=86 studies), and equivalent correlations were found for social isolation and living alone (HR=1.14, 1.35, and 1.21, respectively) [10]. The negative consequences of loneliness were related to hypervigilance for social threats that alter psychological functioning, reduced quality of sleep, and increased morbidity [9]. Loneliness also had a negative impact on cognition, with lower overall cognitive performance, faster cognitive decline, poorer executive functioning, more negativity and depressive cognition, heightened sensitivity to social threats, and biases in social cognition

[11,12]. These cognitive differences modulate emotions, decision-making process, behavior, and social interactions, all of which play a role in linking loneliness to cognitive decline and increased risk of illness [12].

Social isolation and loneliness were also associated with a poor quality of life [13]. Loneliness was proven to be an independent determinant of poor health, quality of life, and psychological well-being in home-dwelling older adults (N=989) [14]. Individuals who were lonely also presented social inactivity and social isolation (38% of the cases), were widowed or lived alone, and had the lowest levels of health-related quality of life and psychological well-being, compared to other groups [14]. Loneliness significantly reduced the physical and mental health components of quality of life and patient satisfaction with medical services in a survey-based study (N=2756 adult participants) [15].

Loneliness among military personnel possesses distinct characteristics that set it apart from the general population, being influenced by deployment-related events and the highly structured military environment, both of which shape the way this phenomenon is experienced [16]. The exploration of loneliness in military personnel is necessary in active-duty members, veterans or former service members without combat experience, since factors like frequent relocations, separation from family members, emotional suppression due to professional circumstances, difficulties in reintegrating into civilian life may significantly reduce their quality of life and their general well-being through the mediation of social isolation, dispositional negativity, stress, and feelings of being alone [17,18]. Loneliness also represents an essential factor shaping the reintegration of veterans and other former military personnel into civilian society after retirement. A sizeable minority of veterans in the US are returning from deployment with psychiatric or physical injuries, but even in the absence of clear illnesses, many experience functional problems that interfere with full reinsertion into civilian life [19]. Also, many service members and veterans with reintegration difficulties have significant challenges in receiving adequate treatment, raising the topic of a necessary comprehensive approach to the psychosocial aspects, like loneliness and ignored, subclinical mental health problems, in these cases [19]. An estimated 60% of military personnel who experience psychopathological manifestations do not seek help, regardless of their active or veteran status, mainly due to worries related to stigma [20]. A systematic review and meta-analysis (n=20 papers) highlighted the two most commonly reported fears of stigma in active-duty military personnel, i.e., that of being treated differently by unit leadership and of being perceived by others as “weak” [20].

Figure 2: Loneliness and challenges in the military active personnel and veterans [16-26]



The military environment is highly structured and integrates healthcare, housing, welfare, and social support, with a very well-organized daily program and clearly defined professional rules, all of these creating an identity difficult to translate into civil society after retirement [21-23]. The transition into retirement involves a complex process of identity reconstruction, which includes changes

in social roles, the loss of former professional responsibilities, the formation of new support systems and social networks, and the need to adapt to new rules, norms, and a different daily rhythm [22]. All of these shifts demand substantial psychological resources from the retiree and may lead to a heightened perception of loneliness, alienation, or mis-adjustment to the new stage of life. The axiological shift is another important factor that should be taken into consideration when discussing loneliness in retired military personnel. Values like camaraderie, courage, discipline, loyalty, integrity, honour, commitment, and selfless service may not be translatable into civilian life to the same extent and with the same intensity as they were inculcated in the active duty. When veterans return from active duty, they may feel disconnected from civilians, who often lack understanding of the realities of war and the suffering it involves; this gap in knowledge can lead to a perceived lack of respect for the veterans' personal struggles and experiences [24].

Multiple models have been suggested to explain difficulties in the adjustment of veterans to civilian life. One of these is the “injury model”, which focuses on veterans who are unemployed or have various service-related health conditions, facing difficult challenges to civilian life [25]. Narrative models approach this sensitive topic from normative experiences of transition from active duty and war experiences to civilian life, in an attempt to create a continuous life story [22,26]. Regardless of the preferred model, the importance of investigating loneliness as a mediator of the adjustment problems in this population, together with the need to find prophylactic interventions for such psychosocial phenomena, justifies further explorations in this field (Fig.2).

MATERIALS AND METHODS

The primary objective of this article was to explore the currently available data on the loneliness phenomenon in the military personnel (active duty and retirees), and also its possible causes and consequences. The secondary objective was to identify potential intervention directions that could be helpful in the management of loneliness in this population.

An initial review of literature was a conceptual analysis based on a search in three main electronic databases (PubMed, Google Scholar, and Web of Science/Clarivate) for primary and secondary reports published in any language, with no temporal limitations, using the keywords “military”, “recruits”, “officers”, “veterans” AND “loneliness”, “social isolation”, “quality of life”, “well-being”, “health status”. The second stage of the research involved developing intervention strategies, based on the collected data and a conceptual analysis, to support the prevention and treatment of loneliness among military personnel.

RESULTS

A total number of 42 reports (most of them studies based on surveys, but also reviews and meta-analyses) were reviewed and clustered in eight categories, according to their main focus and potential to stimulate further directions of interventions (Table 1).

Analysis of risk and protective factors for loneliness among military personnel

Seven primary and secondary reports were included in this section, based on their common focus on the exploration of potential vulnerability and protective factors, and triggers for loneliness and social isolation in active military or veteran populations. The identified factors in these categories were related to social descriptors (e.g., interpersonal engagement, comradeship, social support), psychological (e.g., mental skills, self-esteem, attachment styles), psychiatric (e.g., anxiety, depression, stress-related reactions), engagement in armed conflicts (e.g., deployment, war experience), early traumas (e.g., childhood abuse), economic (e.g., income level), and demographic (e.g., marital status, age).

A study evaluated the factors related to loneliness and social isolation in ex-military personnel (who served in the British Armed Forces), starting from their discharge until the time of evaluation (N=11 participants) and found three main themes of interest, i.e., a “sense of loss”, difficulty in connecting during civilian life, and seeking out familiarity [27]. These results show that switching from a highly connected network of relationships during the active duty, i.e., close bonds through significant and prolonged interpersonal contact, to retirement leads to intensely unfavourable perceived feelings of loneliness in this second phase [27]. The strong sense of belonging associated with active duty constituted a significant factor that complicated the transition to retirement, as it impeded the development of connections with the civilian community [27]. A study in Dutch veterans (N=2643 retired military personnel with combat experience) reported that in 27% of the cases, at least a mild level of loneliness, and in 13% of them, severe levels could be detected [16]. Factors mitigating loneliness were social support, perceived comradeship during deployment, and a feeling of positive effect of deployment on current life [16]. A young age, living alone, unemployment or work disability, needs of care (either general or related to deployment causes), perceived frustration related to deployment, and longing back to the time of deployment were correlated with a higher level of loneliness [16]. This study highlighted the need for more attention to the deployment-related experiences and their consequences, including loneliness, that could be identified even at long distances after the event [16].

Table 1: Analysis of the reports on loneliness in active-duty military and related categories

Type of report	Number of participants	Outcomes	Results	Conclusions
Factors contributing to loneliness in military personnel				
Survey-based investigation [16]	2643 veterans from the Dutch Armed Forces	Prevalence of loneliness and its relationships with deployment-associated factors	27% - at least a mild level of loneliness, 13% - severe levels could be detected. Various protective and risk factors have been identified for loneliness	More attention is needed to the deployment-related experiences and their consequences, including loneliness, that could be identified even at long distances after the event
Qualitative, phenomeno-logical study (semi-structured interviews) [27]	11 British Armed Forces ex-members (Army, Royal Navy, Royal Air Force)	Factors related to loneliness and social isolation, identified from discharge to the present day	4 themes have been identified- a "sense of loss", difficulty in connecting during civilian life, and seeking out familiarity	A strong sense of belonging during active duty interferes with adjustment to the retirement period
Cross-sectional observational study [28]	662 soldiers from the US Army	Distal to proximal risk factors in active duty soldiers	A set of factors associated with loneliness was found, including demographic, relational, personal traumas, and professional-related elements	Unique predictors of loneliness in the military environment were found, besides those shared by civilians
Cross-sectional observational study [29]	2025 US veterans aged ≥60 years	Loneliness assessment using UCLA-LS	44% - feelings of loneliness at least some of the time, 10.4% - often feeling lonely. Multiple factors were associated with loneliness, including PTSD, depressive symptoms, and lifetime traumas	Loneliness is associated with the existence of multiple psychopathological phenomena
Cross-sectional observational study [30]	78000 respondents, veterans and civilians without prior military service	Volunteering behaviour (presence/absence, number of hours dedicated to volunteering activities, and type of such activity/organization)	↑ volunteering rates for veterans overall, but especially for those who served during wartime, had higher education levels, and were married; ↑ number of hours for volunteering in veterans vs. non-veterans	Veterans had a higher involvement in volunteer activities vs. the civilian population without military experience
Cross-sectional observational study [31]	427 male soldiers from the US Army	Psychosocial characteristics and level of intrinsic motivation	Stronger mental skills correlated with lower levels of loneliness	Screening for types of mental skills may be helpful in detecting the risk of loneliness in soldiers
Exploratory qualitative study [32]	1000 recruits in the British Army Infantry	Causes for attrition	The cumulative effect of stressors and disruption of the previous supportive network explains early discontinuation	Screening for stressful factors, including loneliness, is needed in the population of Army recruits
Impact of loneliness on the health status of military personnel				
Longitudinal observational study [33]	100 veterans, aged ≥62 years	Mood, loneliness, and activity levels before and during the COVID-19 pandemic	"Blued mood" and loneliness were at significantly higher levels during the COVID-19 pandemic vs. before the pandemic	Vulnerable populations were at higher risk for low mood due to movement restriction rules during the pandemic
Cross-sectional observational study [34]	1562 UK Armed Forces veterans	Relationship between structural and functional support during the COVID-19 pandemic	Single individuals, living alone and experiencing loneliness, had worse mental health and well-being	High association between feelings of loneliness and low levels of perceived support
Longitudinal observational study [35]	112 Italian Army cadets	Relationship between personality features, stressful	A high rate of infections was detected in relation to a	There is a complicated relationship between

		events, and the onset of illnesses	higher number of stressful events and a set of psychological characteristics	immunity, stress and psychological factors that needs further exploration
Cross-sectional study [36]	4069 US veterans, mean age 62 years	Relationship between loneliness and physical and mental health, overall functionality and suicidal ideation	Significant correlations between loneliness and the other mentioned variables were detected	More than 50% of the veterans in the US report loneliness, which predisposes them to health problems and suicidal ideation
Particularities of loneliness in military spouses				
Cross-sectional observational survey study [37]	~2300 Army spouses during the Iraq war period	Mental health, physical health, overall health status, functioning and coping	Mental well-being, household strains, and aspects related to their jobs were more affected in spouses who were exposed to extensions of deployments	Deployment extensions had a clear negative impact on the health and well-being of Army spouses
Quasi-experimental study [38]	231 military wives	Improvements in mental health, including loneliness, through therapeutic interventions	No difference between the two interventions was found, but both were efficient	Educational and theory-based interventions may mitigate loneliness in military wives
Cross-sectional observational survey study [39]	400 civilian wives of enlisted soldiers during the Somalia peacekeeping mission	The perceived impact of stressors experienced during brief deployments	Experiencing a pregnancy during deployment, facing loneliness, confronting the death of a close friend or relative, and/or having problems communicating with one's spouse were identified as main stressors	The perceived impact of stressors experienced during brief deployments was found to be less detrimental to marital satisfaction than commonly presumed
Cross-sectional observational survey [40]	500 civilian wives of enlisted US Army soldiers during the Somalia Operation Restore Hope deployment	The self-reported impact of rumours on the spouses' levels of stress	The perceived stressfulness of rumors was mitigated by effective unit leadership, strong family support networks, and greater emotional adaptability to deployment	Significant correlations were found between the experience of rumors as problematic and wives' fears regarding their soldier's safety or uncertainty about his current status
Qualitative observational study [41]	18 spouses of deployed military (Guard/Reserve service members)	Analysis of major stressors during the deployment of their partners	Worrying, waiting, going through it alone, pulling double duty, and loneliness were identified as stressors during this period	There is a very complex role for loneliness as part of a larger set of variables that model the resilience vs. vulnerability dynamics in this population
Qualitative study [42]	15 Israeli bereaved girlfriends of fallen soldiers	The impact of the event on psychological status	Loneliness was experienced both among peers and within close family relationships	Loneliness is an important variable during the grieving period in this population
Literature review [43]	9 papers focused on military widow/ers	The themes most frequently identified in the literature regarding social isolation and loneliness	The four themes identified were: experiences of loneliness and social isolation", "the uniqueness of the military", "access to social support", and "the importance of peer support"	Loneliness has a central role in the life of military widow/ers
Quantitative observational longitudinal study [44]	4003 participants (59% nonveterans, 31% served in the military but without exposure to death, 10% veterans and exposed to death)	Exploration of adjustment to widowhood and loneliness among older men	A significantly lower level of feeling lonely among veterans exposed to death vs. civilians who become widowed, but veterans without such experience had a similar level of loneliness to the civilian widowers	The training of new skills and strategies to cope with challenging life events that imply death, in the case of widowed military may have a protective role in the case of widowhood
Cross-sectional observational study [45]	122 participants, students	Psychological distress and physiological stress	Psychological distress was correlated to personal history	↑emotional and physiological stress appear in

			of trauma, lower levels of social support and high media exposure. No prior bereavement individuals had ↑ hair cortisol levels vs. those with 1-2 prior bereavements	response to repeated peer deaths. Although no military personnel was involved in this study, its conclusions may be relevant due to the exposure of participants to peer loss.
Long-term observational study [46]	~35000 Union Army veterans	The effect of wartime stress on old-age mortality, and the impact of unit cohesion as a buffer	↑ Wartime mortality rates are associated with ↑mortality in old age, while ↑unit cohesion decreased the negative effect of wartime stress on later-life mortality	Wartime stress harms long-term health, but strong social bonds within military units can buffer these effects, improving survival decades after service.
Loneliness and post-traumatic stress reactions				
Longitudinal observational study [47]	225 Israeli ex-POWs	Marital adjustment, PTSD symptoms, loneliness	Lower levels of marital adjustment and higher levels of PTSD in POWs than in controls	Loneliness was a mediator of the relationship between PTSD, 18-year post-war experience, and marital adjustment, at 30 years post-war
Longitudinal observational study [48]	83 Israeli ex-POWs	Relationship between loneliness and perceived social support and TL length 18 years after repatriation	The psychological variables predicted, each, shorter TL in later life, and when combined, they explained 26% of the overall variance	There is a long-term impact of the extreme stress on a defined biological parameter, namely the TL length
Longitudinal quasi-experimental design study [49]	79 Lebanon War soldiers with CSRs and frontline treatment, 156 soldiers with CSRs but without frontline treatment, and 194 soldiers without CSRs	PTSD and general psychiatric symptoms, loneliness, and social functioning	20 years after the war, traumatized soldiers who received frontline treatment had lower rates of posttraumatic and other psychiatric symptoms, experienced less loneliness, and better social functioning than similarly traumatized soldiers who did not receive such treatment	A cumulative effect of the application of frontline treatment principles was documented
Longitudinal observational cohort study [50]	382 Israeli soldiers	Relationship between CSRs and other psychosocial factors	CSRs were worsened by perceived lack of support from officers, leading to ↑feelings of loneliness and stress reactions in soldiers	Both battle intensity and perceived support from officers directly modelled the onset of CSRs and indirectly influenced feelings of loneliness
Loneliness as a mediator of depression and suicide in military personnel				
Cross-sectional observational study [51]	301 US veterans with symptoms of depression	Depression severity, suicidal ideation, health-related behaviors, help-seeking intention, and patient activation	Loneliness was associated with ↑ levels of depression and suicidal ideation, ↓ patient activation and help-seeking intentions, while social support and social norms about depression treatment were associated with ↑ patient activation and help-seeking intentions	Loneliness is a strong and independent correlate of depression severity and suicidal ideation among military veterans in primary care
Cross-sectional observational study [52]	443 US Navy recruits	Depression severity, loneliness, sense of belonging	49% of the variance in depressive symptoms was explained by loneliness and sense of belonging	Interventions targeting the sense of belonging applied in high-risk depression recruits to decrease their feeling of loneliness and depression

				could be helpful for them not to discontinue their basic training
Cross-sectional observational study [53]	32, 38, 33 military suicide attempters, non-suicidal psychologically treated peers and controls	Problem-solving capacity, emotion regulation, perceived burdensomeness, loneliness, suicidal ideation	Loneliness and burdensomeness together explained 65% of the variance in suicidal ideation in the stage prior to the suicide attempt.	Loneliness is a significant contributor to the suicide risk
Retrospective observational study (psychological autopsy) [54]	100 US Air Force married vs. unmarried suicide decedents	Impact of life stressors on suicide intent	Married decedents were twice as likely to have had documented interpersonal conflict 24 hours prior to suicide and communicated suicide intent to peers or professionals	Loneliness + frustrated belongingness + rejection were the interpersonal factors most frequently detected in this population
Cross-sectional observational study [55]	937, 3386, and 417 US military service members and veterans	Insomnia symptoms, thwarted belongingness, and suicidal ideation	Thwarted belongingness significantly mediated the relationship between insomnia and suicidal ideation	Chronic insomnia is a significant predictor of suicidal ideation within this population, and it can also be an essential contributor to feelings of hopelessness
Cross-sectional observational study [56]	443 US Navy recruits with depression	Depressive symptoms during basic training (self-report), loneliness, life-change events, stress levels, sense of belonging, coping styles	Loneliness was a frequently reported concomitant factor, together with higher levels of stress, life change events, lower sense of belonging, more emotion-oriented coping, and less task-oriented coping in recruits with depressive symptoms vs. controls	Interpersonal dysfunction, including loneliness, is a factor reported in the depression onset in recruits
Particularities of loneliness in minorities within the military personnel				
Cross-sectional observational survey study [57]	640 active duty US soldiers	Behavioral health outcomes, behavioral health care utilization, and psychological factors, including loneliness	↑% of LGB soldiers than heterosexual soldiers had a higher load of anxiety, PTSD, and suicidality than heterosexual soldiers, but no differences between groups in the use of health care services were detected. No difference between the loneliness in the two groups was found, while the perceived prejudice was higher for the LGB soldiers, and perceived support was lower	Organizational barriers appear to still exist for sexual minority soldiers
Qualitative study [58]	12 post-9/11 racial minority ex-service members	Thematic areas of cultural identity among the Black minority related to the service post-9/11 event	Four main themes of interest were identified by the respondents, reflecting emotional restraint, limited self-disclosure, discrimination, and deindividuation	A phenomenological sensitivity when approaching the world of minorities from the perspective of mental health specialists is recommended
Mixed-methods observational study [59]	15 LGBT+ in semi-structured interviews veterans and 101 LGBT+ veterans in online survey	Emotional and psychological impact of serving under the UK “gay ban”; experiences of discrimination, harassment and identity concealment;	LGBT+ veterans reported feelings of losing their identity and inability to foster relationships after being discharged due to this law,	Long-term unfavorable psychological consequences may still be detected in stigmatised minorities

		barriers to help-seeking; measures of social isolation and loneliness	and also mentioned emotional distress, mental illnesses, social isolation, and limited access to appropriate support, due to harassment and discrimination	
Motherhood during military service, loneliness and mental health				
Cross-sectional study [60]	750 female Army veterans	The impact of having a first child while being on active duty on the mothers' health status, well-being, and service separation	The most frequent health-related outcomes were low social support, loneliness, and common mental health problems	Female Army veterans who had a first child born during active military duty had poorer outcomes, including leaving the service non-voluntarily
Therapeutic and prophylactic interventions targeting loneliness and social isolation in military personnel				
Longitudinal observational study [61]	212 military caregivers	Perceived social isolation, depressive symptoms	Caregivers in the online peer group experienced less perceived social isolation after three months, but not at six months	Joining and actively engaging with an online peer support group helped reduce perceived social isolation among military caregivers, but it did not lead to improvements in depressive symptoms
Cluster-randomized controlled trial [62]	99 active-duty US Army platoon leaders + 118 service members supervised in the intervention group + 158 service members in the control group	Levels of loneliness	This supportive-leadership training proved itself beneficial in reducing the loneliness reports for service members (N=118) vs. the control group (N=158), and higher baseline loneliness severity was associated with more positive effects of the intervention	The intervention was especially impactful for those already feeling lonelier at baseline, demonstrating how workplace leadership training can contribute meaningfully to improving social connection and well-being
RCT [63]	48 Army platoons participating in social resilience training vs. cultural awareness training	Social cognition, loneliness, unit-level attitudes, mental health outcomes, effectiveness of cultural awareness training	Social resilience training produced small but significant improvements in social cognition and reduced loneliness. Cultural awareness training specifically increased cultural knowledge and reduced outgroup prejudice	An increase in empathy and perspective taking was observed as a result of the training, but benefits for the training outside the training foci were not observed
Prospective RCT [64]	801 Navy recruits receiving BOOTSTRAP intervention vs. non-intervention at-risk recruits vs. comparison group of recruits	Sense of belonging, loneliness, problem-solving skills, attachment security, and training performance	An increase in the sense of belonging, a lowering of loneliness feelings, a more frequent use of problem-solving coping skills, and a decrease in insecure attachment were observed in "at-risk" recruits for depression by the end of the 9-week training period	The intervention significantly enhanced recruits' sense of belonging, reduced loneliness, improved coping skills, and led to higher completion rates of basic training
Systematic literature review [65]	28 studies	Social connection, social isolation, loneliness	A direct focus upon social reintegration and engagement, psychosocial functioning, building trust, peer support, group cohesiveness and empowerment through a sense of purpose and learning new skills could decrease	Interventions emphasizing social reintegration, peer engagement, group cohesion, empowerment through purpose, and the rebuilding of trust appear most effective at reducing loneliness and social isolation among military veterans with PTSD

			loneliness and social isolation in this population	
Systematic narrative review [66]	17 papers	Prevalence of loneliness in the veteran population, contribution of military service experiences to loneliness/social isolation, and the impact of loneliness on mental health	The uniqueness of the loneliness and social isolation post-deployment in the military involves the need for tailored psychosocial interventions	Military veterans experience unique and persistent challenges with loneliness and social isolation, indicating that tailored interventions beyond general population campaigns are necessary
Mixed-method, pilot feasibility study [67]	200 veterans (phase 1), 19 veterans (exposed to the CONNECTED intervention)	Social isolation, social support, anxiety and depression symptoms	Significant reductions of social isolation, an increase of social support, and a decrease of anxiety and depression were recorded due to the intervention	This is a feasible, acceptable, and promising intervention for reducing social isolation and improving social support, anxiety, and depression among veterans

BOOTSTRAP= Building Our Opportunities to Strengthen Trust, Respect, and Purpose; CONNECTED= Creating Networks of Necessity by Engaging in Community-Based Telehealth to Enhance Connectedness and Decrease Isolation; CSR= combat stress reaction; POW= prisoners of war; PTSD= post-traumatic stress disorder; RCT= randomised controlled trial; TL=telomere; UCLA-LS= University of California, Los Angeles- Loneliness Scale

An exploration of the distal (such as demographic and socio-economic factors) and proximal factors (for example, platoon relationships and their quality) associated with loneliness in active duty soldiers in the US Army revealed a set of factors associated with loneliness, i.e., age, frequency of contact with friend and family by phone, childhood trauma, self-reported overall emotional health, intra-platoon harassment, perceived stress, perceived platoon cohesion and support, organizational citizenship behavior, relationship satisfaction with friends, and relationship satisfaction with platoon members [28]. The association between loneliness, perceived stress, and relationship satisfaction with platoon members demonstrated a moderate effect size [28].

Combat experience was also associated with lower levels of loneliness among older veterans, in an extensive study (N=2025 US veterans aged ≥60 years) [29]. Loneliness was found to be higher among individuals who were older, had disabilities affecting daily activities, experienced lifetime traumas, reported greater perceived stress, or were currently experiencing depression or posttraumatic stress disorder (PTSD) [29]. In contrast, loneliness was lower among those who were married, had higher incomes, demonstrated better cognitive functioning, received social support, had secure attachment styles, expressed greater dispositional gratitude, and attended religious services more frequently [29]. Also, volunteering is more frequently reported in individuals who had military service, especially married veterans and those who had served during wartime, which signals a higher level of social interest in this group [30]. A high interest in social activities that are normative, such as voting, was also linked to military service, especially in the case of ethnic minorities [30]. The cultivation of civic responsibility, social resources, and social skills is commonly observed in military personnel and may be extremely helpful in reducing the risk of loneliness in veterans [30].

An observational, cross-sectional study examined the psychosocial characteristics and levels of intrinsic motivation among U.S. Army soldiers with varying mental skills profiles [31]. Findings indicated that soldiers with stronger mental skills profiles exhibited higher intrinsic motivation and better psychological health compared to those with weaker profiles [31]. Strong mental skills were correlated with higher self-esteem scores, lower hopelessness, loneliness, depression, anxiety, stress, and anger scores [31]. Therefore, it could be inferred that strong mental skills may be considered protective factors against the feelings of being lonely and the associated psychological and psychopathological negative consequences.

A study that investigated the causes for attrition in British Army Infantry (N=1000 recruits) found the cumulative effect of stressors, combined with the severing of the recruit support established network, as the core of the failure phenomenon among this population [32]. Homesickness ("I miss my friends and family"), the loss of freedom ("I feel trapped…I have lost my freedom"), inability to cope psychologically with physical demands ("I find the training hard…discipline hard…I don't fit in"), and relationship deficits, all these lead to early discontinuation from the training program [32]. A very competitive environment was considered by some recruits an obstacle to making new friends and, therefore, a trigger for loneliness [32].

Impact of loneliness on the health status of military personnel

The four reports in this section are dedicated to the negative effects of loneliness and social isolation on the general health status of military personnel, including some observations that were made during the COVID-19 pandemic. The interplay between loneliness, mental health, and susceptibility to physical illnesses represents an important area of inquiry that warrants further investigation, including in research involving military personnel.

A study examined the changes in mood and activity during the COVID-19 pandemic in veterans, aged ≥62 years, who were asked to complete online health forms, and the results collected from 100 participants reflected "blued mood" and loneliness at significantly higher levels than before the pandemic [33]. A study explored the relationship between structural and functional support and mental

health and wellbeing in 1562 UK Armed Forces veterans during the COVID-19 pandemic and reported a high association between feelings of loneliness (27%) and low levels of perceived support (28%) when functional social support was assessed [34]. Individuals who were single, lived alone and experienced loneliness had worse mental health and psychological well-being [34]. On the contrary, those who lived with other adults and had high levels of perceived social support also had better mental health and well-being [34].

A study involving 112 Italian Army cadets, who completed a series of personality assessments and reported stress-related events from the previous year, found that individuals experiencing a higher number of stressful events also reported significantly more total health episodes, particularly infections [35]. These associations were moderated by factors such as attitudes toward parental figures, psychological hardiness, feelings of loneliness, and alienation [35]. Additionally, younger age was a significant predictor of increased total episodes and infections, both as an independent factor and in interaction with attitudes toward the mother, hardiness, and alienation [35].

A cross-sectional study explored the feelings of loneliness in US veterans (N=4069, mean age 62 years) and their relation with mental and physical health [36]. Almost 57% of the veterans reported feeling lonely at some point or often, and these feelings were independently associated with a wide range of mental health problems (OR=1.21-33.3), somatic diseases (OR=1.21-6.80) and functional difficulties [36]. Current suicidal ideation was also associated with feeling lonely often or sometimes, with a 12- and, respectively, 3-time higher risk, even after adjustment for multiple variables [36].

Particularities of loneliness in military spouses

Ten sources reviewed here investigated the characteristics of loneliness as an existential crisis in spouses of military personnel, a critical, although less researched, topic. The consequences of partners ' deployment, or of losing them in battle, and the impact of being a widow/er on mental health, all of these aspects are explored, based on evidence derived from studies involving spouses or bereaved unmarried partners of military personnel.

The military spouses commonly report feelings of loneliness and isolation, due to their partners' deployments, and variables such as mental well-being, household strains, and aspects related to their jobs were more affected in spouses who were exposed to extensions of deployments [37]. In a quasi-experimental study, an online standard educational intervention was compared to an interactive, theory-based intervention for exploring their comparative effects on the health of military spouses (N=231 participants) [38]. Although no major difference was observed between the effects of the two interventions, both improved significantly in all the mental health outcomes, i.e., loneliness, stress, anxiety, depression, self-esteem, physical activity, and diet [38]. The scores of the UCLA Loneliness Scale in this study supported significant differences between the intensity of this feeling in the explored groups ($p=0.05$ for the control group and 0.03 for the active group) [38]. The importance of determining the presence of loneliness, high levels of stress and depression in this population derives from the fact that they were unlikely to take the initiative to enrol in therapy, leading to the possibility of gradual worsening of their status [38].

In a study involving 400 civilian wives of enlisted soldiers, the perceived impact of stressors experienced during brief deployments was found to be less detrimental to marital satisfaction than commonly presumed, even among marriages characterized by low stability [39]. Among Army wives of soldiers deployed overseas, the perceived stressfulness of rumors was mitigated by effective unit leadership, strong family support networks, and greater emotional adaptability to deployment [40]. In contrast, reliance on surface mail was associated with increased stress from rumors [40]. Furthermore, significant correlations were found between the experience of rumors as problematic and wives' fears regarding their spouse's safety or uncertainty about his current status [40].

An interview with the spouses of deployed military personnel (N=18) acknowledged five major stressors during deployment of their partners- worrying, waiting, going it alone, pulling double duty, and loneliness [41]. These results suggest a very complex role for loneliness as part of a larger set of variables that model the resilience vs. vulnerability dynamics in this specific, vulnerable population. Also, the practical implication would be the need to explore loneliness, together with the other four major stressors in spouses of deployed personnel, and to find the most adequate strategies to reduce their influence on daily life.

A qualitative study investigated the loss experience effect of 15 Israeli bereaved girlfriends of fallen soldiers, and the results supported a multidimensional experience, which includes personal, interpersonal and social components, each ranging from a sense of acceptance to a sense of exclusion [42]. Informants reported experiencing loneliness both among peers and within close family relationships [42]. Feelings of loneliness and a lack of social support were frequently described (e.g., "I was very lonely… I felt lonesome´), with this phenomenon situated on a continuum ranging from emotional or intimate loneliness to social loneliness [42]. Additionally, avoidance of discussing such sensitive topics was noted within the informants' network groups [42]. Therefore, the results of this study show the importance of personal resilience factors, since the support group may fail to provide the necessary safeguards in such difficult situations.

A review (n=9 papers) focused on the exploration of social isolation and loneliness in military widow/ers, identified four themes related to loneliness in military personnel from the US and Israel, i.e., "experiences of loneliness and social isolation", "the uniqueness of the military", "access to social support", and "the importance of peer support" [43]. These themes reflect the central role of

loneliness in military widow/ers and the potential directions of therapeutic interventions aiming at mitigating this outcome, i.e., enhancing peer support and creating specialised services within the health system for this vulnerable population.

The exploration of adjustment to widowhood and loneliness among older men, with a focus on the military service, showed a significantly lower level of feeling lonely among veterans exposed to death vs. civilians who become widowed, but veterans without such experience had a similar level of loneliness to the civilian widowers [44]. The basics of this observation may reside in the training of new skills and strategies to cope with challenging life events that imply death, in the case of widowed war veterans [44,45]. Another possible explanation would be the construction of stronger networks of relationships during military service that could represent a buffer for further adverse life events [44,46]. Also, the training of social skills and the opportunity to understand the importance of meaningful relationships throughout life may contribute to better resilience capacity, a phenomenon that could be inferred in the widowhood military population [44].

Loneliness and post-traumatic stress reactions

Four reports, all studies with significant participation, signal the existence of relationships between loneliness and combat stress reactions. The significance of loneliness in the development of PTSD is considerable, as it should be incorporated into screening and therapeutic interventions, given its role as a moderating factor in the emergence of clinically significant stress reactions.

A prospective study investigated the contribution of loneliness and PTSD to marital adjustment in Israeli veterans (N=225 participants) and found that ex-POWs (prisoners of war) had lower levels of marital adjustment and higher levels of PTSD than controls [47]. Loneliness was a mediator of the relationship between PTSD, 18-year post-war experience, and marital adjustment, at 30 years post-war [47]. In former ex-POWs, loneliness was found to contribute to marital adjustment independently of the effects of PTSD, even when assessed 30 years after the war [47].

A study involving Israeli former prisoners of war (ex-POWs; N=83) examined the associations between loneliness and perceived social support, assessed 18 years after repatriation, and telomere (TL) length, used as a biomarker of cellular aging [48]. The psychological variables predicted, each, shorter TL in later life, and when combined, they explained 26% of the overall variance, thus proving the long-term impact of the extreme stress on this biological parameter [48].

A longitudinal quasi-experimental design study recruited participants with combat stress reaction (N1=79), comparable combat stress reaction casualties who did not receive frontline treatment (N2=156), and matched soldiers who did not experience combat stress reaction (N3=194) [49]. The study reported that 20 years after the war, traumatized soldiers who received frontline treatment had lower rates of posttraumatic and psychiatric symptoms, experienced less loneliness, and better social functioning than similarly traumatized soldiers who did not receive such treatment [49]. A cumulative effect of the application of frontline treatment principles was documented, which supports its importance and suggests the need for further exploration of its effects on medium and long term [49].

Combat stress reactions in a sample of 382 Israeli soldiers could be worsened by the perceived lack of support from officers, which triggered greater feelings of loneliness and a greater likelihood of stress reactions in soldiers [50]. Higher levels of loneliness were associated with reduced social support from comrades, while greater battle intensity was linked to increased loneliness and a higher likelihood of combat stress reactions [50]. In a path analysis, both battle intensity and perceived support from officers directly contributed to combat stress reactions and indirectly influenced feelings of loneliness [50].

Loneliness as a mediator of depression and suicide in military personnel

The six reviewed studies in this section approach the sensitive topic of loneliness in relation to depression and suicide. The results of this line of research highlight the role of loneliness as a predisposing or even causal factor for depression and suicidal ideation, therefore inviting the early detection of this variable in military personnel exposed to stressful situations.

The influence of social relationships on mental health has been explored intensively, and a study that recruited veterans (N=301 participants) from the US, presenting symptoms of depression, confirmed this correlation [51]. Loneliness was associated with higher levels of depression and suicidal ideation, lower patient activation and help-seeking intentions, while social support and social norms about depression treatment were associated with higher patient activation and help-seeking intentions [51].

A relational model for depression in the US Navy was constructed based on a theory-testing analysis (N=443 recruits) and 49% of the variance in depressive symptoms was explained by loneliness and sense of belonging [52]. Therefore, interventions targeting the sense of belonging applied in high-risk depression recruits to decrease their feeling of loneliness and depression could be a helpful strategy in order for them not to discontinue their basic training [52].

Military suicide attempters were compared to non-suicidal psychologically treated peers and controls (N=32, 38, and 33, respectively), and the study showed that the first group presented more difficulties in problem-solving, negative emotion regulation, and burdensomeness compared to their peers [53]. Loneliness and burdensomeness together explained 65% of the variance in suicidal ideation in the stage prior to the suicide attempt [53].

In a sample of US Air Force married vs. unmarried suicide decedents (N=100), the analysis of the impact of life stressor precipitants and communications of distress and suicide intent showed that married decedents were twice as likely to have had documented interpersonal conflict 24 hours prior to suicide and communicated suicide intent to peers or professionals [54]. Loneliness, together with frustrated belongingness and rejection, were the interpersonal factors most frequently detected in this population [54].

Across three groups of U.S. military service members and veterans (N = 937, 3386, and 417), thwarted belongingness significantly mediated the relationship between insomnia and suicidal ideation [55]. These findings indicate that chronic insomnia is a significant predictor of suicidal ideation within this population, and it can also be an essential contributor to feelings of hopelessness [55]. The same study showed that loneliness, social isolation, and social connectedness among service members and veterans with sleep problems may need to be assessed in order to determine the risk of insomnia and its complications [55].

Depressed recruits in the US Navy were more likely not to finish their training, had more predisposing factors regarding family history of mental illness, alcohol abuse, and personal history of psychiatric problems, in a study with 443 participants [56]. Loneliness was a frequently reported concomitant factor, together with higher levels of stress, life change events, lower sense of belonging, more emotion-oriented coping, and less task-oriented coping in recruits with depressive symptoms vs. controls [56]. Therefore, interpersonal dysfunction, including loneliness, is a factor reported in the depression onset in recruits [56].

Particularities of loneliness in minorities within the military personnel

The importance of exploring the mental health status in a culturally sensitive manner, including within the military setting, is supported by the reviewed studies in this section (n=3). It can be easily seen that research on this topic remains limited, despite its high relevance given the negative consequences it may entail within the highly regulated organizational context of the military environment.

The assessment of well-being in sexual minority soldiers in a Military Academic institution (N=640 active duty US soldiers) showed that a higher proportion of LGB soldiers than heterosexual soldiers had positive results on anxiety, PTSD, and suicidality, but no differences between groups in the use of health care services were detected [57]. No difference between the loneliness in the two groups was found, while the perceived prejudice was higher for the LGB soldiers, and perceived support was lower [57]. Therefore, organizational barriers appear to still exist for sexual minority soldiers [57].

The provision of culturally sensitive and appropriate mental health care for Black veterans has been the focus of a study that involved an assessment of 12 post-9/11 racial minority ex-service members [58]. These participants identified four key thematic domains: (1) “keep pushing/suck it up” - reflecting emotional restraint and limited self-disclosure regarding deployment experiences and systemic discrimination; (2) “family oriented/communalism” - denoting the expression of communal or familial identity; (3) “seeing green/colorblindness” - referring to a deindividuation process, and (4) “no protective cloak/microcosm of American society” - indicating experiences of significant discrimination [58]. Loneliness, but also confusion and anxiety, were reported within this group of Black former service members, and a lack of “cultural fluency” was considered important as a generator for these negative emotions [58]. A phenomenological sensitivity when approaching the world of minorities (e.g., women, ethnic minorities, LGBTIQA+) from the perspective of mental health specialists was recommended by the authors of the respective study [58].

The effects of the exemptive military laws in the UK that banned LGBT individuals from the respective professional environment were explored in an empirical study (N=101 participants, veterans), focused on emotional impact, adapting to change, and aftermath (barriers to help-seeking) [59]. LGBT+ veterans reported feelings of losing their identity and inability to foster relationships after being discharged due to this law, and also mentioned emotional distress, mental illnesses, social isolation, and limited access to appropriate support, due to harassment and discrimination [59]. Although this law was cancelled, the long-term unfavorable psychological consequences may still be detected; therefore, further exploration of such subclinical psychological phenomena is needed, and it can be extrapolated to different minorities that have been historically neglected or mistreated, including in the military environment. An increase in the awareness of such phenomena is a step forward in the creation of possible policies destined to prevent and mitigate the negative consequences of discrimination and stigmatization, loneliness and social isolation included.

Motherhood during military service, loneliness, and mental health

Although a provocative topic, only a single study employing a scientific approach was identified in the literature that examined the impact of motherhood in this specific environment. The cross-sectional study was based on self-report surveys (N=750 participants, female Army veterans) and explored the impact of having a first child while being in active duty [60]. The results showed that the most frequent health-related outcomes were low social support, loneliness, and common mental health problems [60]. Female Army veterans who had a first child born during active military duty had poorer outcomes, including leaving the service non-voluntarily [60]. Although none of the health or well-being outcomes remained statistically significant after adjustment, the observed trends still highlight the need to further investigate this under-researched population segment [60].

Identifying early factors for mood disorders, such as insufficient social support and loneliness, can be of interest for improving female Army personnel's quality of life, general well-being and mental health in vulnerable periods, such as having a first child. Also, the

impact of these variables on the professional trajectories was identified as significant by this study, and counselling in the perinatal period may decrease the risk of premature military service withdrawal.

Therapeutic and prophylactic interventions targeting loneliness and social isolation in military personnel

The effects of interventions focusing on preventing and approaching feelings of loneliness and mitigating the impact of social isolation were reviewed based on the results of seven primary and secondary reports. The range of explored interventions is not large; still, individual and group therapies and training programs, both online and in-person, have been identified. It can be observed that interventions targeting specifically loneliness as an outcome are very few, most data being derived from studies that enrolled military personnel with PTSD, who also reported loneliness or social isolation as a contributing factor.

A longitudinal questionnaire study investigated the effects of the participation of 212 military caregivers in an online peer support community program vs. those who were members of other military caregiver groups [61]. Caregivers in the online peer group experienced less perceived social isolation after three months, but not at six months [61]. Both groups (active controls and main intervention) had, over time, less perceived social isolation and increased interactions with other military caregivers, mediated by this phenomenon [61]. There was no significant effect on the depressive symptoms of the participants, indicating that such support groups are not sufficient for this purpose [61].

The efficacy of evidence-based supportive leadership training interventions targeting active-duty US Army platoon leaders, including destigmatisation techniques and proactive support behaviors, was explored in a study with 99 trainees (both in-person and computer-based training sessions) [62]. This intervention proved itself beneficial in reducing the loneliness reports for service members (N=118) vs. the control group (N=158), and higher baseline loneliness severity was associated with more positive effects of the intervention [62].

A randomized controlled study explored the short-term effect of social resilience training vs. cultural awareness (as a control group) in 48 Army platoons, and the results showed that the active intervention produced small but significant improvements in social cognition and decreased loneliness [63]. An increase in empathy and perspective taking was observed as a result of the training, but benefits for the training outside the training foci were not observed [63].

A prospective study investigated the effects of a survival training for Navy recruits (N=801), and an increase in the sense of belonging, a lowering of loneliness feelings, a more frequent use of problem-solving coping skills, and a decrease in insecure attachment were observed in “at-risk” recruits for depression by the end of the 9-week training period [64].

A systematic review dedicated to interventions for military veterans with a PTSD diagnosis (N=28 studies) found that a direct focus upon social reintegration and engagement, psychosocial functioning, building trust, peer support, group cohesiveness and empowerment through a sense of purpose and learning new skills could decrease loneliness and social isolation in this population [65]. Another review (n=17 papers) supported the uniqueness of the loneliness and social isolation post-deployment in the military, which involves the need for tailored psychosocial interventions [66]. A study that enrolled veterans with social isolation showed positive results for a targeted intervention based on group support and individual counselling delivered by peers via telehealth (CONNECTED), with significant reductions of social isolation, an increase of social support, and a decrease of anxiety and depression [67].

DISCUSSION

Loneliness is a multifaceted phenomenon with an impact larger than just its psychosocial negative effects, as was stated in the introductory part of this article and supported by evidence in the “Results” section. The detrimental effects of loneliness have been demonstrated by numerous studies in various populations and on a range of outcomes. For example, insomnia was related to loneliness and a review and meta-analysis that explored various groups (undergraduates, Army recruiters, adults with suicidality history and/or depression, adult psychiatric outpatients, young adults at elevated risk of suicide) concluded that more severe insomnia symptoms were significantly associated with feelings of loneliness, while depression was a moderator of this relationship [68]. Loneliness also exerts a negative influence on eating behaviors through the mediation of negative interpersonal relationships, both individual and skewed individual perceptions, which is an interesting phenomenon, due to the rising incidence of eating disorders in the post-modernistic society [69-73]. Loneliness was also associated in older individuals with a higher risk of dementia (OR=1.64) in a cohort study (N=2173 community-living persons), when compared to people without such feelings, thus showing another essential negative consequence of this phenomenon [74].

The need to train the coping mechanisms in recruits, in order to strengthen their abilities to face loneliness and changes in lifestyle when compared to civilian norms, can not be overemphasized. Studies have shown that lonely service members are more likely to experience suicidal ideation and reduced coping mechanisms [75]. The reports reviewed in this article support the positive role of a prophylactic strategy, but also of therapeutic interventions targeting dysfunctional coping mechanisms that may foster loneliness and social isolation in the military environment and in veterans and retirees. For older former military personnel, psychotherapy aimed at

enhancing cognitive skills may be beneficial in strengthening their capacity to cope with retirement and, potentially, the transition to widowerhood [76].

Exploration of minorities, for example, female military personnel, or ethnic, cultural, gender/sexual or religious subgroups, is another topic of interest from the perspective of loneliness research in the military environment. The existing data are too few to support clear directions for interventions, although training in cultural sensitivity may be of some use in this environment. However, there is room for optimism when data from civilian society is analysed, because interventions targeting loneliness in various minority groups may lead to positive results [77,78].

The analysis of risk and protective factors for loneliness in military personnel is essential because this variable is a stage in the process of development of mental disorders, like depression, anxiety disorders, or PTSD. Therefore, screening for such factors may help in creating policies for early intervention and prophylaxis, as well as therapy of vulnerable subgroups. The investigation of the relationship between loneliness and physical and mental disorders is bidirectional, because researchers may start from the diagnosis of a particular illness and, when constructing the image of potential causal factors, identify loneliness and social isolation among them. Loneliness has been associated with multiple organic diseases; therefore, interventions targeting its prevention may have beneficial effects far beyond the psychological well-being [79-83].

Military spouses are an insufficiently explored vulnerable population to loneliness, due to their partners' deployment, frequent relocations and absences, or being killed in action. Extensive exploration of their quality of life and health status is granted based on the existing data, reviewed in this article. The importance of this topic's exploration is further enhanced by the existence of factors that may represent barriers to mental health services for military wives, such as inability to attend daytime appointments, incapacity to find a counselor who understands the specifics of military families, concerns about confidentiality, and lack of knowledge on where to find specialised services [84]. Phases of their partners deployment associate specific challenges that require targeted approaches from counsellers, such as facing the news of deployment and making preparations (during the first phase), shifting focus, emotional and physical turmoil, staying strong (during spartners' deployment), and property of time span, themes of absence and reestablishing roles (after deployment) [85].

Other topics of interest may be the relationship between loneliness and difficulties faced by female military personnel during motherhood, the problems confronted by military families who may have children with severe and incapacitating illnesses, or the challenges of military personnel enduring physical disabilities or mental disorders [86-89].

Direction of intervention for prophylaxis and therapy of loneliness in military personnel

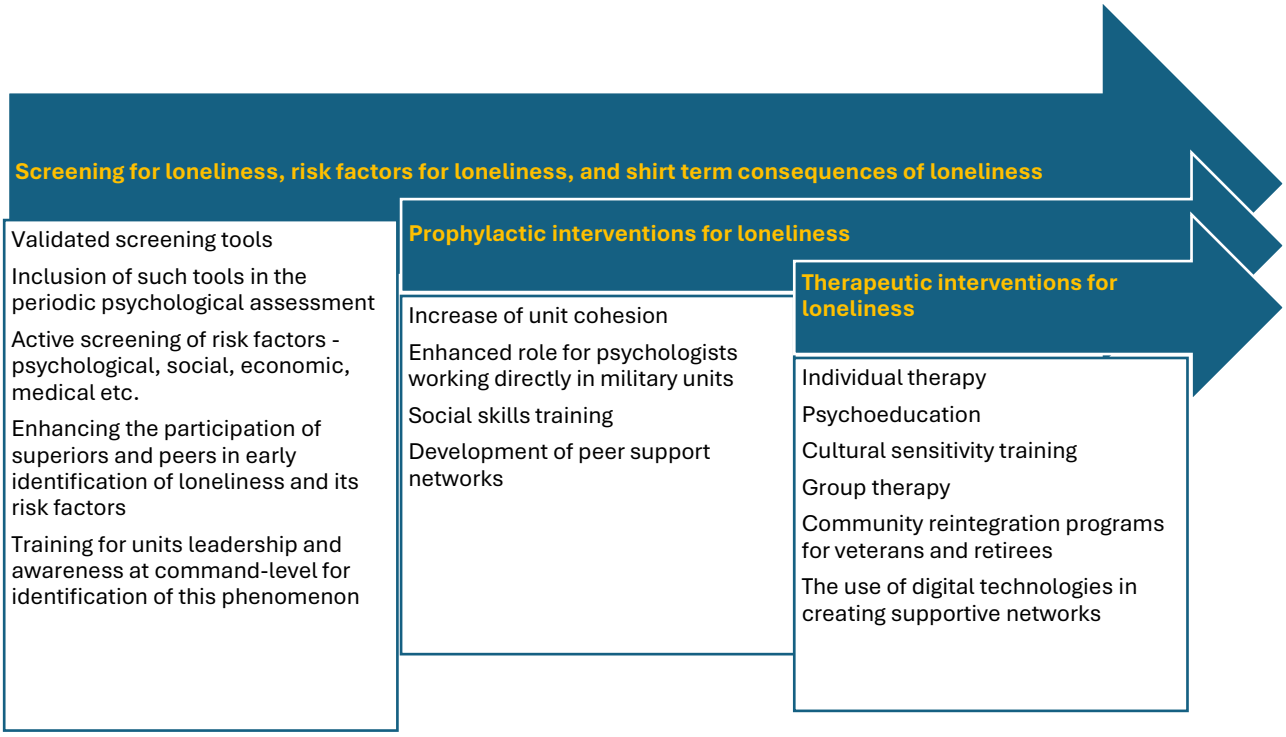
The importance of loneliness and social isolation (the latter being considered the objective equivalent of the former) in military environments, but also in veterans and retirees, supported by a large volume of data in the reviewed literature, indicates the urgency to find adequate methods aimed at controlling these two phenomena.

Based on the reviewed data, the core interventions aimed at improving the level of loneliness detection in military personnel refer to (1) the use of validated screening tools, the most commonly used, although not specific for the military environment, being the UCLA Loneliness Scale; (2) such instruments need to be developed and adjusted to the characteristics of armed forces setting; (3) the use of these tools need to be included in the annual check-ups of the psychological status of active military personnel and periodical evaluations for veterans and retirees, due the signifiant impact of loneliness on the general health; (4) identifying risk factors for loneliness, some of them being presented in this article, such as childhood traumas, low self-esteem, or lack of social skills; (5) use of behavioral indicators, as provided by direct superiors and peers; (6) initiation of digital platforms that are secured and confidential, for self-report of loneliness-related components, in order to avoid stigmatisation; (6) training of leadership and command-level awareness, especially regarding the vulnerable minorities, individuals with risk factors, and early signs of mental health problems.

Prophylactic interventions for loneliness in a military setting may include (1) measures to increase unit cohesion, by fostering trust and camaraderie; (2) enhancing the role of the psychologists in military units to initiate training for military leadership focused on cultural sensitivity, enhancing coping skills and capacity to detect vulnerability factors in recruits; (3) social skills training targeting communication and general coping abilities; (4) developing peer support networks.

Therapeutic interventions aimed at reducing loneliness in military settings should envisage (1) individual therapy, especially cognitive-behavioral therapy, but also (2) group therapy, for mutual support, and (3) psychoeducation programs conducted by psychologists; (4) community reintegration programs for veterans and retirees; (5) the use of digital technologies in creating networks for military personnel during their transition to civilian life, during deployment or prolonged isolation.

Figure 3: Directions of intervention targeting loneliness in military active personnel and ex-members



Synthesized in Fig.3, these three directions of interventions represent the foundation for further research in the field of loneliness in military active and retired personnel and of possible policies destined to decrease the medical and social impact of this phenomenon.

Limitations of the article

There are some limitations that need to be acknowledged by the readers, the most important one being the fact that the first part, consisting of the literature overview, was not conceived as a systematic search; therefore, relevant sources might have been missed. It is also noteworthy to consider other pertinent components of the three strategies focused on reducing the phenomenon of loneliness and its negative impact on active and former members of the military, which could have been overlooked. It is also important to adapt the conclusions and recommendations of this research to the specific military traditions and cultural contexts of each country, and to address sensitive issues, such as the situation of minorities in the Army, with care, avoiding pre-determined or inflexible solutions.

CONCLUSION

Loneliness constitutes a prevalent and consequential psychosocial phenomenon, characterized by its association with a wide range of health-adverse outcomes in both civilian and military communities. Within the military context, its impact can be particularly pronounced, contributing to premature attrition from training programs, diminished quality of learning and skill acquisition, reduced morale, and an impaired sense of cohesion and connectedness with peers and unit members. These effects not only undermine individual well-being but may also compromise operational readiness and the overall effectiveness of military training environments.

Data reviewed in this article suggest the importance of analysing risk factors for loneliness and for its consequences on mental and physical health in active military personnel and ex-service members. Improving the level of loneliness detection, initiating prophylactic interventions for loneliness, and therapeutic interventions aimed at this phenomenon are of significant importance within military settings. Further research in this field is urgently needed, in order to find the most validated instrument for loneliness and social isolation detection, to explore the specific consequences of loneliness on general health, quality of life, psychological well-being, and

combat readiness, and also to examine the risk of loneliness in spouses of military personnel, vulnerable sub-groups, and veterans who were exposed to prolonged deployments.

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Authors' contribution

Conceptualization, O.V., B.M.P., A.G.M., and O.M.S.; methodology, O.V., A.P., and D.G.V.; software, O.V.; validation, O.V., C.A.C., A.P., O.M.S., and A.G.M.; formal analysis, O.V., A.G.M.; investigation, O.V., A.G.M., A.P., and B.M.P.; resources, O.V., O.M.S, and D.G.V.; data curation, O.V.; writing—original draft preparation, O.V.; writing—review and editing, O.V., A.G.M., B.M.P, D.G.V, A.P., and O.M.S.; visualization, O.V., C.A.C. and A.P.; supervision, O.V. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

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ORIGINAL ARTICLE

Analysis of Gene Expression in Synovial Tissue from Patients with Knee Osteoarthritis

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Abstract: Knee osteoarthritis (KOA) is a chronic, degenerative disease that affects not only the bone and cartilage but also all periarticular soft tissues. Transcriptomic investigations in osteoarthritis have recently advanced due to the introduction of RNA sequencing, which has been used to elucidate significant molecular differences between groups of patients with KOA. A total of 29 patients with knee pain were selected and divided into two groups. Group 1 comprised 26 patients, who were diagnosed with stage four KOA according to the Kellgren and Lawrence (KL) classification and were scheduled for total knee arthroplasty. Group 2 consisted of three patients who constituted the control group. The main objective of this study is to analyze gene expression in suprapatellar synovial tissue using the RT-PCR technique in patients with knee osteoarthritis. The promising results of gene expression analysis highlight the complex transcriptomic profile of synovial tissue in patients with stage IV KL KOA who required TKA after conservative treatments failed. The analysis of the expression of four genes indicates that compensatory mechanisms are either insufficient or exhausted due to the chronic proinflammatory status. Pro-inflammatory transcription factors (JUN, MYC) and feedback regulators (DUSP1, NFKBIA) require extensive clinical trials for the use of disease-modifying drugs.

Keywords: Knee osteoarthritis, Gene expression, Rt-PCR, Synovium, Transcriptomics

INTRODUCTION

Knee osteoarthritis (KOA) is a chronic, degenerative disease that affects not only the bone and cartilage but also all periarticular soft tissues such as menisci, ligaments, synovial tissue, tendons, and muscles. Osteoarthritis most commonly affects the knee, followed by the hip joint. Pain dominates the symptomatology, leading to a progressive limitation of joint mobility and an increase in patient morbidity. In the context of an increase in life expectancy and an ageing population, knee osteoarthritis is becoming a public health problem both through the complications caused by the disease and through the high costs associated with care and treatment. Approximately 240 million people worldwide suffer from osteoarthritis, which makes understanding the pathogenic mechanisms, identifying risk factors and identifying disease-modifying drugs a priority[1]. For patients with a significantly impaired quality of life, total knee arthroplasty is recommended. The identification of effective biomarkers is essential for the early diagnosis and treatment of knee osteoarthritis. Recent studies have shown that osteoarthritis is not just a disease induced by mechanical destruction of articular cartilage, and the main pathogenic mechanisms involved are the immune system and inflammatory mechanisms[2-4]. Imaging, pathological, and clinical results suggest that synovial alterations manifest prior to the pathological deterioration of cartilage, while synovitis, characterized by the recruitment of immune cells, is present throughout the entire developmental course of osteoarthritis[5,6]. Transcriptomic investigations in osteoarthritis have recently advanced due to the introduction of RNA sequencing. RNA sequencing has been used to elucidate significant molecular differences between groups of patients with knee osteoarthritis. In patients with KOA who experience significant pain, transcriptomic analysis of synovial tissue from those undergoing total knee arthroplasty reveals differential regulation of 32 genes

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(mRNA), two long non-coding RNAs (lncRNAs) and 35 micro-RNAs (miRNAs). This regulation appears independently of radiological severity or gender[7]. Fisch et al. have identified a series of transcription factors, prioritising eight as high-priority candidates for therapeutic intervention. Among these, JUN, JUND, FOS and FOSL2 encode different subunits of AP-1. The role of AP-1 in chondrocytes requires further elucidation. Studies suggest that IL-1 promotes the synthesis of MMP13 proteases via activation of JUN/FOS heterodimers[8-10]. The expression of growth and differentiation factor 5 (GDF5) poses a significant risk for the development of osteoarthritis of the knee.

Murakami T et al. showed that GDF5 expression was amplified in post-injury articular cartilage of the medial meniscus and was increased in human articular cartilage of patients with KOA, according to the findings obtained via immunohistochemistry and microarray analysis[11].

Zhang Q. et al. identified a diagnostic model based on the expression of four genes, which shows significant predictive performance in knee osteoarthritis. The identified genes are implicated in the TNF signalling pathway and the IL-17 signalling pathway, along with their roles in the response to steroid hormones, glucocorticoids and corticosteroids. Notably, four of these genes- MYC, JUN, DUSP1, and NFKBIA- are specifically expressed in the immune system.

Clinical studies have demonstrated a consistent change in these four genes in synovial tissue obtained from patients with KOA[12].

Gene expression analysis allows the comprehension of the pathophysiological mechanisms, the identification of potential therapeutic targets, and the detection of patients at risk of adverse outcomes requiring total knee arthroplasty. Genetic studies have prompted a trend to classify knee osteoarthritis from a molecular perspective, rather than merely on osteocartilaginous lesions.

MATERIALS AND METHODS

A total of 29 patients were selected who presented to the orthopedics and traumatology department of the University Emergency Hospital of Bucharest with knee pain and were divided into two groups. Group 1 comprised 26 patients, aged between 59 and 81 years, who were diagnosed with stage four KOA according to the Kellgren and Lawrence (KL) classification and were scheduled for total knee arthroplasty. Group 2 consisted of three patients who constituted the control group. These patients, aged between 30 and 45 years, did not manifest any radiological or MRI signs of knee osteoarthritis. They required arthroscopic surgery for pathologies associated with the meniscus or anterior cruciate ligament. The study was conducted from January 1, 2023, to March 31, 2024. The inclusion criteria for group 1 comprised patients aged over 45 with knee pain and radiographic evidence of KOA. The exclusion criteria included patients with recent trauma, signs of active osteoarticular infection, a lack of radiological changes in KOA demanding a differential diagnosis, individuals with known rheumatological conditions, and those for whom complete required data could not be obtained.

The main objective of this study is to analyze gene expression in suprapatellar synovial tissue using the RT-PCR technique in patients with knee osteoarthritis. Five genes with the potential to show expression changes in synovial tissue were selected, according to the data available to date in articles retrieved from PubMed/MEDLINE (https://pubmed.ncbi.nlm.nih.gov) and EMBASE (https://www.embase.com), focusing on studies published between January 2005 and January 2023. The five selected genes are represented by GDF5, MYC, JUN, DUSP1, and NFKBIA.

Synovial tissue harvesting in patients who required total knee arthroplasty was done through an anterior internal parapatellar approach and harvesting from the suprapatellar region of synovial tissue using a cold scalpel, in order not to alter the quality of the sample. In the case of the control group, synovial tissue harvesting was done during arthroscopic surgery, using a grasper and harvesting fragments of synovial tissue with a diameter of approximately 1 centimeter, then immersed in RNA preservation fluid. Fresh synovial tissue harvested during the surgical procedure was immediately immersed in RNAprotect Tissue stabilization reagent (Qiagen, Hilden, Germany) to prevent RNA degradation, and the sample was stored at -20°C until further processing. For each sample, approximately 30 mg of synovial tissue was cut into cubes of approximately 3 mm. Total RNA extraction from synovial tissue was performed using the RNeasy Fibrous Tissue Mini kit (Qiagen), which uses silica membrane column purification technology. The stabilised fragment of synovial tissue was placed into a homogenisation tube containing Buffer RLT (Qiagen), which was supplemented with 14.3 M β-mercaptoethanol. Tissue homogenization and complete mechanical disaggregation were performed using a TissueLyser II (Qiagen) with stainless steel beads at optimal parameters (2 × 2 minutes at 20 Hz) to ensure complete tissue lysis. RNA concentration and purity were determined spectrophotometrically using the Infinite 200 PRO multimodal plate reader (Tecan Group Ltd., Switzerland) with the NanoQuant plate. The absorbance ratio at 260 and 280 nm was between 2.0 and 2.2, indicating adequate purity of the isolated RNA. Each PCR reaction was performed in triplicate for each gene used in the experiment. Tissue homogenisation and complete mechanical disaggregation were performed using a TissueLyser II (Qiagen) with stainless steel beads at optimal parameters (2 × 2 minutes at 20 Hz) to ensure complete tissue lysis. The NanoQuant plate was utilized to determine the RNA concentration and purity spectrophotometrically using the Infinite 200 PRO multimodal plate reader (Tecan Group Ltd., Switzerland). The isolated RNA was of sufficient purity, as evidenced by the absorbance ratio of 2.0 to 2.2 at 260 and 280 nm. Each gene utilized in the experiment was subjected to a triplicate PCR reaction. A separate plate was designated for each gene, and all reactions for the samples included in the experiment were conducted on the same plate to ensure consistency and comparability in the results. The amplification efficacy

of each gene was determined by utilizing the standard curve, which was generated from serial dilutions (1:10) of the amplified product. The efficacy of the dilutions was automatically determined by the LightCycler® 480 software through linear regression, utilizing the Ct values and $\log_{10}$ of the initial concentration. Efficiency values of over 96% were observed for all genes examined, with the exception of the GDF5 gene, which had an efficiency value of 91%. Two reference genes were employed to analyze the expression of the genes of interest (NFKBIA, DUSP1, JUN, MYC, GDF5): β-glucuronidase (GUSB) and β-actin (ACTB). These genes were chosen based on their expression stability under varying experimental conditions. The technical replicates of each gene were tested in triplicate for each sample. For each sample and gene, the average Ct value from the three replicates was calculated to provide a robust estimate and reduce technical variability. The variability among the replicates was minimal, with the maximum difference between the Ct values obtained in the replicates not exceeding 0.5 cycles, thereby confirming the reproducibility of the measurements. Relative gene expression levels were determined using the E-ΔCt analysis method. To compare gene expression between the disease group (osteoarthritis) and the healthy control group (control), the relative expression values E-ΔCt were used. These values represent the expression of the genes of interest normalized to the 2 reference genes (GUSB and ACTB), in each sample, without using a separate calibrator. Thus, E-ΔCt allows for direct comparison of gene expression between groups (Disease vs Control).

Statistical analysis was performed using IBM SPSS Statistics 27, MedCalc Software Ltd. (Version 23.2.1), Excel 2019 MSO (Version 2503) and GraphPad Prism version 10.4.1.

Differences in gene expression were identified using the nonparametric Mann-Whitney U test, where p-values ≤ 0.05 were considered significant. The Pearson coefficient (r) was used to measure the strength and direction of the linear relationship between genes. The value of the coefficient varies between 0 and +1, with a value of 0 indicating the absence of a linear relationship between the analyzed genes. To quantify the magnitude of rise or decrease in a gene's expression on a logarithmic scale, hence aiding in the understanding of significant variations, we used log10 fold change. To effectively visualize the expression of genes of interest and to discern significant changes in gene expression, as well as to detect patterns and clusters, we employed a heatmap.

Study approval was obtained from the local ethics committee of the University Emergency Hospital of Bucharest, and informed consent was obtained from all participants, ethical approval code 40525 / 2023.

RESULTS

Dendrogram analysis (Fig. 1) revealed a clear separation of the investigated genes (JUN, NFKBIA, DUSP1, MYC, GDF5) into two major groups: (i) a core formed by JUN, DUSP1 and NFKBIA, which exhibited high correlations among them, and (ii) MYC and GDF5, of which GDF5 showing the most distinct expression profile. The dendrogram of the samples (Fig. 2) indicated the clustering of osteoarthritis patients into several subclusters, with pairs or groups of extremely similar samples. DUSP 1 has been identified as overexpressed in the synovial tissue of the patients with KOA. DUSP1 may indirectly regulate JUN/AP-1 activity by functioning as a phosphatase on MAPKs, which activate JUN through phosphorylation.

Figure 1: Hierarchical clustering dendrogram for the genes of interest

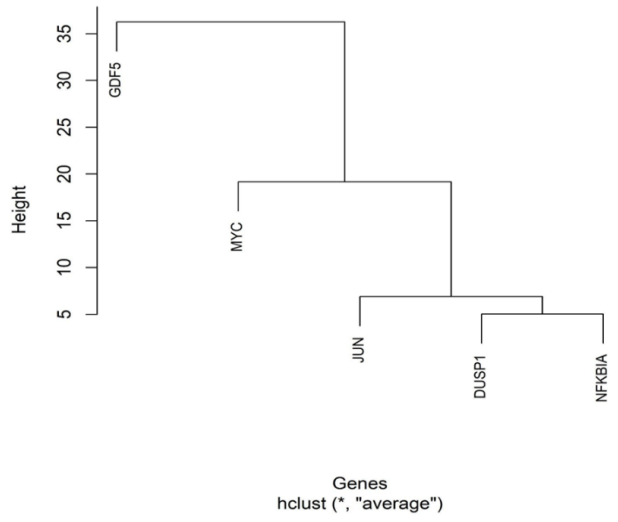
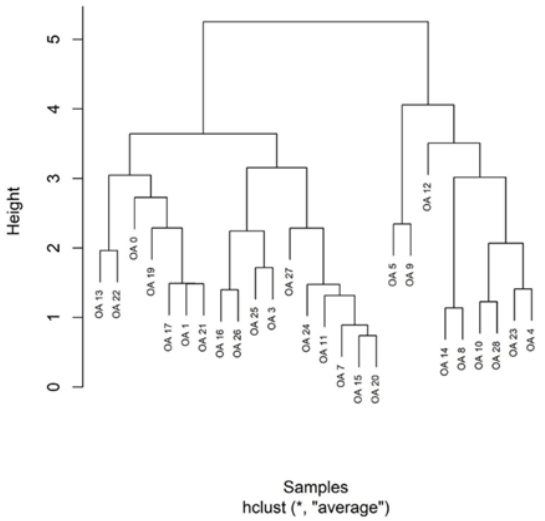
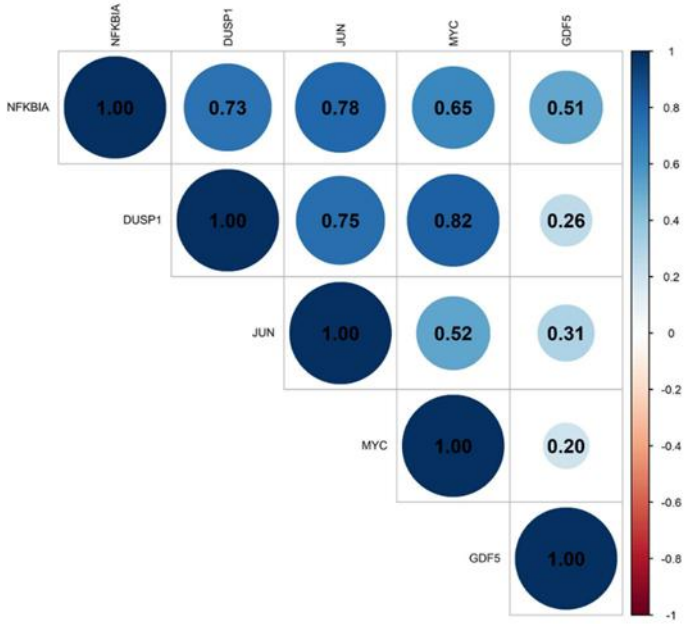


Figure 2: Hierarchical clustering dendrogram for patient samples



The Pearson correlation plot (Fig. 3) showed strong associations between: DUSP1–MYC (r=0.82), NFKBIA–JUN (r=0.78), DUSP1–JUN (r=0.75) and NFKBIA–DUSP1 (r=0.73). Correlations with GDF5 were weak (r=0.20–0.51), confirming the distinct profile of this gene. These findings indicate a coordinated transcriptional mechanism linking the MAPK/AP-1 and NF-κB pathways. At the same time, the positive correlation between NFKBIA and DUSP1 rather suggests a chronic inflammatory process that is self-regulating.

Figure 3: Correlation plot

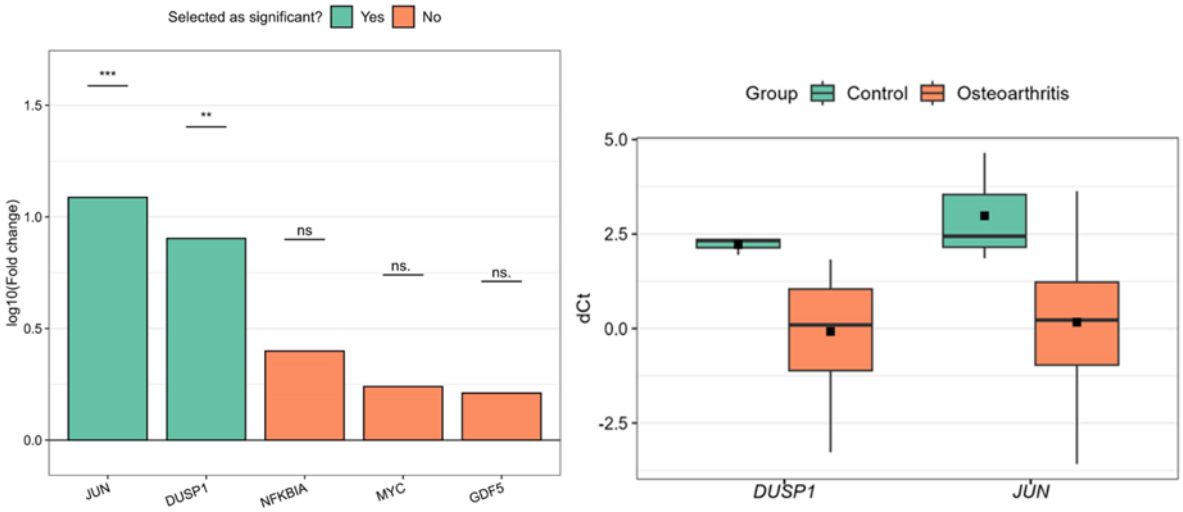


The dCt represents the discrepancy between the Ct value of the target gene and the Ct value of the reference gene. The gene's expression is reduced when the dCt value is higher.

JUN and DUSP1 exhibit substantial fold alterations, with JUN exhibiting a greater change than DUSP1. The absence of substantial fold changes in MYC and GDF5 between the two groups implies that these genes may not be as pertinent to osteoarthritis as JUN and DUSP1.

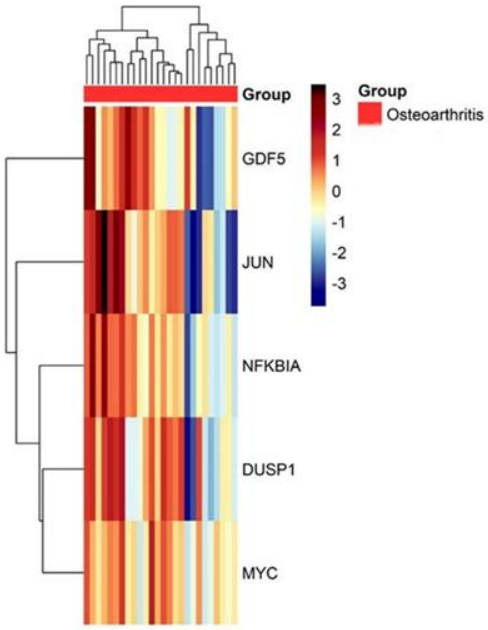
The dCt values of DUSP1 and JUN are both higher in the control group, whereas their expression is substantially lower in the osteoarthritis group. This suggests that the expression of these genes in the synovial tissue of patients with osteoarthritis who require total knee arthroplasty has increased.

Figure 4: A(left)Log10 Fold Change between groups. B(right) Boxplot for DUSP1 and JUN



The utility of the heatmap, besides the visual representation of the results, is to observe large differences in expression between conditions to identify patterns and clusters (genes that behave similarly). The heatmap (Fig. 5) revealed clear blocks of co-regulation: JUN, DUSP1 and NFKBIA demonstrated similar patterns, MYC showed an intermediate expression, while GDF5 presented a distinct profile, characterized by considerable variations between samples.

Figure 5: Heatmap of Gene Expression



DISCUSSION

The functions of several immune cells are essential in the onset and advancement of osteoarthritis. The timely use of diagnostic and therapeutic biomarkers could greatly improve the prognosis for osteoarthritic patients; however, there are currently few molecular candidates that meet the standards for high sensitivity and specificity.

In this study, we examined the alterations in gene expression and immune cell infiltration within osteoarthritic synovial tissue in comparison to normal control. The analysis of gene expression for JUN, DUSP1, NFKBIA, GDF5, and MYC demonstrated heterogeneous expression patterns in the synovial tissue of patients suffering from knee osteoarthritis relative to those in the control group without any signs of arthritis.

One study indicates that synovitis exacerbates pain and contributes to cartilage degradation; for every 0.1 mm of lost cartilage over a 24-month period, a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score of 0.32 (95% CI: 0.21–0.44) is obtained[13].

The role of JUN in knee osteoarthritis appears to be complex and varies from case to case. Recent research suggests that elevated levels of JUN in the synovium contribute to inflammation, angiogenesis, and synovial proliferation. This process may occur through the activation of the MAPK/JNK pathways, which stimulate pro-inflammatory or degradative genes. The overexpression of JUN in the patients enrolled in the study, who are part of the group of patients with stage IV knee osteoarthritis according to Kellgren and Lawrence, is consistent with available data in previously published literature[14].

Moreover, DUSP 1 has also been found to be overexpressed in the synovial tissue of patients with KOA. Due to its role as a phosphatase on MAPKs (which activate JUN by phosphorylation), DUSP1 may indirectly regulate JUN/AP-1 activity. Thus, under conditions where DUSP1 is low, JUN activation may be more intense, favoring pro-inflammatory/degenerative phenotypes. The concomitant overexpression of JUN and DUSP1 in the synovium of patients with advanced gonarthrosis (KL IV) suggests a chronic activation of the MAPK–AP-1 pathways, alongside an anti-inflammatory compensatory feedback response through DUSP1 induction. However, the increased level of DUSP1 appears insufficient to restore synovial homeostasis, allowing for the progressive perpetuation of inflammation and contributes to the progressive degradation of the joint tissue.

Pearson correlation analysis demonstrated robust positive correlations between DUSP1–MYC (r = 0.82), NFKBIA–JUN (r = 0.78), and NFKBIA–DUSP1 (r = 0.73). These results indicate a synchronized transcriptional program that connects the MAPK/AP-1 and NF-κB pathways. The connection between DUSP1 and MYC suggests that MAPK-dependent proliferative and metabolic signaling is intertwined with feedback inhibitory mechanisms within the same cellular environment. The concurrent activation of NF-κB and AP-1, two critical transcriptional pathways implicated in osteoarthritic inflammation, is reflected in the positive correlation between NFKBIA and JUN. Additionally, the correlation between NFKBIA and DUSP1 underscores the concurrent activation of feedback inhibitors—IκBα for NF-κB and MKP-1 for MAPK—which implies a chronic, self-regulating inflammation rather than an acute activation..

This expression pattern indicates a dysregulated inflammatory milieu in the end-stage synovium of osteoarthritis that is highly active. It is distinguished by the co-expression of feedback regulators (DUSP1, NFKBIA) and pro-inflammatory transcription factors (JUN, MYC). This co-activation is likely indicative of an adaptive response that is designed to reduce the excessive signaling of MAPK and NF-κB. Nevertheless, this response does not achieve homeostasis; rather, it exacerbates the persistence of synovitis and tissue remodeling that are indicative of advanced KOA[12, 16].

The inconsistent expression and weak correlations of GDF5 with inflammatory markers (JUN, DUSP1, MYC, and NFKBIA) corroborate the unique profile of this gene. In contrast to genes associated with MAPK/NF-B signaling and the inflammatory response, GDF5 is involved in the processes of chondrogenic differentiation and tissue regeneration. In the synovium of patients with advanced KOA (KL IV), where chronic inflammation is predominant and regenerative processes are fragmented, GDF5 expression is heterogeneous and lacks functional coherence.

This indicates the loss of or dysregulation of local anabolic potential. Consequently, the lack of significant correlations supports the idea that GDF5 belongs to a distinct regulatory axis, separate from the proinflammatory JUN–MYC–DUSP1–NFKBIA networks. Furthermore, its role in advanced OA is likely residual or compensatory, not significantly influencing the inflammatory synovial phenotype[16].

CONCLUSION

The promising results of gene expression analysis highlight the complex transcriptomic profile of synovial tissue in patients with stage IV KL KOA who required total knee arthroplasty after conservative treatments failed. The complex changes in synovial tissue highlight the proinflammatory status of synovial tissue, leading to damage to articular cartilage. The analysis of the expression of four genes indicates that compensatory mechanisms are either insufficient or exhausted due to the chronic proinflammatory status. Pro-inflammatory transcription factors (JUN, MYC) and feedback regulators (DUSP1, NFKBIA) require extensive clinical trials for the use of disease-modifying drugs. The limitations of the study are induced by the limited number of patients and the limited number of the

control group. Conducting a study with a large number of participants across multiple centres is also necessary to validate the statistical data obtained.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

"Conceptualization, S.A.I., and C.F.C.; methodology E.R; software, D.G.M.; validation, C.F.C., D.G.M., and A.C.; formal analysis, M.C.; investigation, B.C.; resources, M.I.G.P.; data curation, B.S.; writing—original draft preparation, S.A.I.; writing—review and editing, S.A.I.; visualization, D.G.M.; supervision, C.F.C.; project administration, E.R; funding acquisition, A.C. All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of University Emergency Hospital of Bucharest (protocol code 40525/2023.

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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REVIEW

Brain [^{18}F]FDG PET/CT in Clinical Practice: Indications, Methodological Considerations and Metabolic Patterns

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Abstract: [^{18}F]FDG PET/CT enables in vivo quantification of cerebral glucose metabolism, revealing functional abnormalities before morphological changes on CT or MRI. This review summarizes major clinical indications, methodological aspects, and key metabolic patterns. In cognitive impairment, [^{18}F]FDG PET is a core biomarker within the amyloid/tau/neurodegeneration (A/T/N) framework, predicting conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) and differentiating AD, dementia with Lewy bodies (DLB), frontotemporal lobar degeneration (FTLD), vascular dementia, and atypical parkinsonian syndromes (APS). In movement disorders, it distinguishes Parkinson's disease (PD) from APS – including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS) – and supports prognosis in amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). In epilepsy, interictal hypometabolism aids localization of the epileptogenic zone, especially in MRI-negative cases, while in neuro-oncology, [^{18}F]FDG PET assists in primary central nervous system lymphoma (PCNSL), glioma grading, and recurrence assessment. The review also highlights roles in inflammatory and infectious diseases, such as autoimmune encephalitis, neurosarcoidosis, and post-coronavirus disease 2019 (COVID-19) sequelae. Standardized preparation, glucose control, and statistical comparison with normal databases remain essential for accurate interpretation.

Keywords: Brain [^{18}F]FDG PET/CT; neurodegeneration; mild cognitive impairment); atypical parkinsonian syndromes; epilepsy localization; primary central nervous system lymphoma; autoimmune encephalitis; metabolic brain imaging.

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INTRODUCTION

Glucose accounts for up to 95% of ATP production required to sustain neuronal and synaptic function. [18F]FDG – a radiolabeled glucose analog – serves as an indicator of neurosynaptic activity and neuronal density, enabling in vivo quantification of regional cerebral glucose metabolism. Resembling endogenous glucose, intracellular

accumulation of [18F]FDG depends on the integrity of glucose transporters, hexokinase availability, and astrocyte-neuron metabolic dynamics[1, 2].

Physiologically, [18F]FDG uptake is greater in regions characterized by high baseline synaptic and functional activity – such as the basal ganglia, frontal eye fields, posterior cingulate cortex, and visual cortex- and lower in areas with reduced resting metabolic demand – such as the medial temporal cortex[3]. Notably, [18F]FDG PET imaging in control populations has demonstrated region-specific age-associated declines in cerebral glucose metabolism, primarily involving the anterior cingulate, frontolateral cortex, and perisylvian regions[4].

Leveraging the neurometabolic coupling between cerebral activity and metabolic demand, alterations in [18F]FDG uptake can exemplify abnormal functional patterns before morphologic presentation is seen on CT and MRI scans.

CLINICAL INDICATIONS

Cognitive Impairment and Dementia

Neurodegenerative dementias are usually preceded by a prodromal phase – mild cognitive impairment (MCI) – characterized by subtle clinical-neuropsychological changes that do not yet interfere with daily life activities. Related to synaptic dysfunction and long-lasting pathological deposition of toxic proteins in the brain, M

Within the A/T/N framework of Alzheimer's disease biomarkers – amyloid (A), tau (T), and neurodegeneration (N) – [^{18}F]FDG PET serves as a well-established marker of neurodegeneration and disease progression. It independently predicts conversion from mild cognitive impairment (MCI) to AD, irrespective of hippocampal volume or amyloid status. [^{18}F]FDG PET complements amyloid and tau biomarkers, whether derived from cerebrospinal fluid analysis or PET imaging, and is recommended to support early diagnosis of Alzheimer's disease (AD) in mild cognitive impairment (MCI), Lewy body dementia (DLB), and frontotemporal lobar degeneration (FTLD). Furthermore, [^{18}F]FDG PET aids in differentiating AD from FTLD, DLB, vascular dementia, and atypical Parkinsonian syndromes associated with cognitive decline, particularly when clinical evaluation and MRI are inconclusive. Consensus algorithms now endorse [^{18}F]FDG PET as a first-line tool when non-AD etiologies are suspected. Characteristic topographic hypometabolic patterns have been described for AD, FTLD, and DLB, with spatial patterns correlating strongly with clinical phenotypes. Importantly, a normal [^{18}F]FDG PET scan at the MCI stage has a high negative predictive value, with fewer than 10% of patients progressing to dementia three years[1, 5-8].

Movement Disorders

[^{18}F]FDG PET supports the differentiation of Parkinson's disease (PD) from atypical Parkinsonian syndromes (APS) – including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), and dementia with Lewy bodies (DLB). [^{18}F]FDG PET is also useful in imaging prodromal α-synucleinopathies, such as idiopathic REM sleep behavior disorder, where metabolic patterns partially overlap with PD and related disorders[1, 6, 9, 10].

The clinical utility of [^{18}F]FDG PET extends to several motor neurodegenerative disorders beyond Parkinsonian syndromes, notably amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD). In ALS, [^{18}F]FDG PET is primarily employed to evaluate extra-motor cortical involvement and to better characterize patients within the ALS–frontotemporal dementia spectrum. As extensive frontotemporal involvement is associated with a more aggressive clinical course, [^{18}F]FDG PET may also be useful for prognostic assessment in ALS. In HD, [^{18}F]FDG PET can assist in differentiating early psychiatric or behavioral manifestations from other neurodegenerative disorders with overlapping clinical features. Notably, presymptomatic carriers of pathogenic Huntington's mutations may exhibit region-specific metabolic alterations detectable by [^{18}F]FDG PET well before the onset of motor symptoms[1, 6, 11].

Epilepsy

The primary objective of [^{18}F]FDG PET in this setting is to localize the epileptogenic zone (EZ), thereby guiding surgical planning when conventional imaging modalities (such as MRI) are inconclusive or when multiple structural lesions are present. Interictally, epileptogenic foci typically manifest as hypometabolic regions that may extend beyond the seizure onset zone, reflecting both primary pathology and propagation networks. This finding reflects underlying neuronal dysfunction and uncoupling between cerebral glucose metabolism and blood flow, which is frequently observed in epilepsy.

In MRI-negative epilepsy, [^{18}F]FDG PET can uncover hypometabolic regions not visible on structural imaging. These findings may direct the placement of intracranial electrodes for invasive electroencephalographic monitoring and improve overall surgical strategy. Notably, patients with negative MRI but positive PET findings demonstrate postoperative seizure-free rates comparable to those with clear structural lesions.

In extratemporal lobe epilepsy, the detection rate of the EZ is comparatively lower (38–67%) than that observed in temporal lobe epilepsy (~80%); nevertheless, the technique remains clinically valuable, especially for identifying subtle cortical malformations such

as focal cortical dysplasia. While the examination is conventionally performed during the interictal period to detect hypometabolism, ictal [^{18}F]FDG administration – although rare – can highlight hypermetabolic foci corresponding to seizure onset. [^{18}F]FDG PET/CT offers strong prognostic value, with a more restricted pattern of hypometabolism predicting better postsurgical seizure control and cognitive outcomes[1, 12-15].

Neurooncology

Increased [^{18}F]FDG uptake on PET images reflects the intense glycolytic activity of neoplastic cells, aiding detection of certain viable tumor tissue. Physiologically high glucose metabolism in cortical gray matter and nonspecific [^{18}F]FDG uptake in inflammatory lesions limit tumor-to-background contrast and reduce sensitivity compared to amino acid PET tracers, which are preferred when available. Systematic employment of whole-body [^{18}F]FDG PET/CT is of limited value for detecting unsuspected cerebral metastases in cancer patients.

In primary central nervous system lymphoma (PCNSL), [^{18}F]FDG PET demonstrates consistently high and homogeneous tracer accumulation. This allows reliable differentiation from non-neoplastic processes such as opportunistic infections in immunocompromised patients. Pooled sensitivity and specificity have been reported to exceed 84%, with baseline uptake intensity correlating with both therapeutic response and overall prognosis. Whole-body [^{18}F]FDG PET is additionally used for staging, with extracranial lymphoma detection characterized by low false-positive rates.

In gliomas, [^{18}F]FDG PET has a limited role due to substantial overlap between low-grade tumor uptake and that of normal white matter, as well as potential uptake in inflammatory tissue. Nevertheless, when amino acid tracers are not available, [^{18}F]FDG PET may be used in initial tumor characterization, with increased uptake generally associated with higher histologic grade and poorer prognosis. Follow-up studies can also assist in detecting malignant transformation and provide prognostic information at recurrence. Post-treatment imaging represents another indication. [^{18}F]FDG PET/CT can help distinguish recurrent tumor from radiation necrosis, typically performed no earlier than 6–8 weeks after radiotherapy, with reported sensitivity and specificity of approximately 84%[1, 16-18].

Cerebral Infectious and Inflammatory Diseases

Brain [^{18}F]FDG PET offers valuable insights in various cerebral infectious diseases, primarily aiding in differential diagnosis, while assessing disease activity. In evaluating alveolar echinococcosis (AE), strong correlations have been observed between Echinococcus serology and [^{18}F]FDG tracer uptake. [18F]FDG PET can analyze immune cell activity at the parasite-host interface, assessing disease progression and treatment response. This is critical for guiding treatment intensity in inoperable patients and appraising the safety of structured treatment interruptions. In immunocompromised individuals, [18F]FDG PET/CT can assist in distinguishing between cerebral toxoplasmosis and CNS lymphoma, which may present similar MRI patterns. For rare CNS infections, [18F]FDG PET/CT has correctly identified unusual cases, such as suppurative meningomyelitis and ventriculitis. While their low incidence limits prospective studies, these findings can have clinical value by guiding treatment changes and improving outcomes, especially in patients with unexplained fever and neurological signs[19-21].

Autoimmune encephalitis (AIE) represents the primary inflammatory indication for cerebral [^{18}F]FDG PET. Displaying higher sensitivity compared to MRI - particularly in N-methyl-D-aspartate receptor (NMDAR) encephalitis – [^{18}F]FDG PET is particularly relevant when MRI findings are negative or inconclusive. While aiding early diagnosis, this hybrid imaging technique can also help evaluate therapeutic efficacy on follow-up scans. Beyond AIE, [^{18}F]FDG PET provides diagnostic support in neurosarcoidosis, enabling visualization of both cerebral granulomatous lesions and extra-neural manifestations - even without corresponding MRI abnormalities - particularly when CNS biopsy is difficult. In neuropsychiatric systemic lupus erythematosus (NPSLE), while MRI detects macrovascular damage, [^{18}F]FDG PET can reveal alterations related to microvascular damage and antibody-mediated injury undetectable on MRI. Employed to evaluate post-COVID-19 (neuro-COVID) sequelae, [^{18}F]FDG PET allows for the assessment of specific neuronal impairments and time-dependent metabolic alterations at an individual level. The severity of its distinct hypometabolic pattern correlates with cognitive and neuropsychiatric deficits[1, 21, 22].

CONTRAINDICATIONS AND CAUTIONS

- Uncontrolled hyperglycemia – blood glucose levels above 150 mg/dL (~8.3mmol/L) can significantly reduce cerebral [^{18}F]FDG uptake through increased competition between elevated plasma glucose and FDG for GLUT transporters and hexokinase; stochastic noise would also be enhanced, further degrading lesion-to-background contrast.

- Pregnancy – judicious clinical judgment is imperative to determine whether anticipated benefits sufficiently outweigh potential risks of harm.

- Breastfeeding – mothers should interrupt breastfeeding for 24h following PET examination.

- Recent seizure activity – interictal scans performed less than 24 hours after the last seizure can lead to transient perfusion and metabolic changes, challenging interpretation.

- Inability to remain still during image acquisition (30-60 minutes) – leads to blurring of tracer activity across cerebral structures, resulting in a significant decrease of spatial resolution, thus rendering image interpretation challenging, if not entirely unfeasible.
- Lack of cooperation [1, 2, 6, 23].

PROCEDURE AND PATIENT PREPARATION

Patients should fast for 4-6 hours prior to the injection, though encouraged to maintain hydration with water, for serum glucose levels not interfere with cerebral [^{18}F]FDG uptake. Parenteral feeding or intravenous fluid containing dextrose should also be withheld for 4-6 hours before injection, for the same reason. Also, caffeine, alcohol and other drugs that may affect cerebral glucose metabolism should be avoided on the day of the PET examination. Medication for diabetes does not need to be discontinued on the day. It is preferred to schedule the study 4-6 weeks after radiation therapy, where appropriate.

The patient must be exposed to external stimuli as little as possible, before and after [^{18}F]FDG injection. The cannula for intravenous administration should be placed at least 10 minutes before the [^{18}F]FDG. Patients should be resting in a quiet and dimly lit room with their eyes open, without speaking, reading, or engaging in major movements or anything cognitively challenging, several minutes before [^{18}F]FDG administration as well as during the uptake phase of [^{18}F]FDG, which lasts around 20 minutes. Before the scanning procedure is started, patients should void their bladders for maximum comfort during the study. It is recommended that the patient void the bladder again after the scan in order to minimize radiation exposure. If sedation is necessary, it is recommended to be done as late as possible, at least 20 minutes after the [^{18}F]FDG injection. For preoperative evaluation of epilepsy, a continuous EEG recording is required. Monitoring should start before injection (ideally 2 hours before) in order to ensure that [^{18}F]FDG is not administered in a postictal situation, and should be maintained at least until 20 min after injection[1, 2, 6, 23].

MEDICAL INFORMATION NECESSARY FOR AN ACCURATE PROCEDURE AND INTERPRETATION

- Patient identification and demographics (age, sex, handedness, body weight, height)
- Primary diagnosis and specific clinical indication for the PET/CT study
- History of neurological and psychiatric disorders, as well as past surgery, trauma or radiation to the brain
- History of diabetes and fasting status.
- Current neurological and psychiatric status and relevant symptoms.
- Current and recent medications, particularly those influencing cerebral metabolism (e.g., benzodiazepines, antiepileptics, neuroleptics, corticosteroids, levodopa, insulin).
- Prior structural neuroimaging (CT, MRI) and functional brain examinations (EEG).
- The patient's ability to lie still for 30 minutes to 1h. If sedation is necessary, [^{18}F]FDG should be administered prior to it[1, 2, 6].

INTERPRETATION

Acquisition images should first be carefully checked for movement or attenuation artefacts, as well as possible misalignments of the head. Knowledge of normal glucose brain metabolism variations, especially age-dependent changes, as well as medication-related changes, is mandatory for accurate interpretation and reporting. A normal database should be available, preferably obtained with the same type of camera, under the same acquisition circumstances and using the same type of reconstruction and attenuation correction. Matching spatial resolution is the most important parameter needed for optimal database use. This allows assessment of normal variability of regional [^{18}F]FDG uptake and improves diagnostic accuracy[1, 2].

Cognitive Impairment and Dementia

Different neurodegenerative diseases preferentially involve distinct brain regions, resulting in reproducible [^{18}F]FDG PET uptake patterns that can now be quantitatively assessed through statistical mapping technologies. Differentiating AD, FTLD, and DLB with [^{18}F]FDG PET has become standard practice. As the nosology of FTLD evolves, encompassing behavioral variant FTD, the three clinical subtypes of primary progressive aphasia, and movement disorders such as progressive supranuclear palsy and corticobasal degeneration, disease-specific metabolic signatures have been delineated. The recognition of mixed dementias and coexisting pathologies, particularly in the elderly, has shifted interpretation from a binary AD versus non-AD framework toward identifying the predominant pathology most consistent with clinical presentation[1, 6, 8].

In Alzheimer's disease, hypometabolism is typically observed in the parietotemporal and posterior cingulate cortex – and, with disease progression, in the frontal lobe and hippocampus – while the primary sensorimotor and primary visual cortices, striatum, thalamus, pons, and cerebellum are usually spared. Notably, reductions in glucose metabolism often exceed the degree of structural atrophy observed in most affected brain regions, with the exception of the hippocampus. This discrepancy suggests the existence of synaptic compensatory mechanisms that sustain neuronal activity despite ongoing tissue damage, particularly in younger patients. However, hippocampal hypometabolism becomes more prominent in late-onset AD. Although frontal hypometabolism is also commonly associated with advanced stages of AD, frontal lobe involvement can be distinguished early in a fraction of patients with prominent behavioral symptoms (behavioral variant of AD [bvAD]), thus challenging differential diagnosis. Remarkably, frontal lobe metabolic impairment has been more frequently reported in female patients with AD suspicion, compared to their male counterparts. AD subtypes with visual symptoms (posterior cortical atrophy) show distinct bilateral occipitoparietal hypometabolism. The logopenic variant of primary progressive aphasia (lvPPA) shows decreased [^{18}F]FDG uptake typically in the posterior temporal cortex and inferior parietal lobule, with the left hemisphere often more severely affected, which is similar to AD findings and often reflects underlying AD pathology. Posterior cortical atrophy (PCA) – an atypical variant of AD – is characterized by often asymmetric parietotemporal and occipital hypometabolism, the latter aiding differentiation from typical AD[1, 5, 7, 8, 24, 25].

Lewy body dementia (DLB) and Alzheimer's disease have a similar hypometabolic cerebral distribution with marked decreases in association cortices and relative sparing of subcortical structures and primary somatomotor cortex. However, metabolic reduction in the occipital cortex is the key feature of supporting the diagnosis of DLB, often described as the “occipital tunnel” sign. Additional differentiating characteristics of DLB versus AD include relatively preserved metabolism in the posterior cingulate gyrus (compared with the precuneus) – “cingulate island” sign – as well as generally preserved hippocampal [^{18}F]FDG uptake. Crossed cerebellar diaschisis (CCD) may accompany posterior cortical hypometabolism due to deactivation of cortico-ponto-cerebellar projections. While CCD occurs across neurodegenerative syndromes and is reported most frequently in corticobasal syndrome and primary progressive aphasia, isolated reports document CCD in DLB as well. Accordingly, cerebellar hypometabolism on FDG PET should be interpreted as a non-specific remote effect, integrated with the characteristic DLB pattern (occipital hypometabolism with cingulate-island sign) and clinical data[6-8, 24, 26, 27].

Frontotemporal degeneration (FTLD) encompasses the behavioral variant frontotemporal dementia (bvFTD), the primary progressive aphasia (PPA) spectrum (semantic, non-fluent/agrammatic, and logopenic variants), and FTLD-spectrum movement disorders (e.g., corticobasal syndrome, progressive supranuclear palsy). The canonical pattern of behavioral variant FTD (bvFTD) shows hypometabolism in the frontal association cortices (dorsolateral, medial and orbitofrontal), and the anterior temporal lobes, with progressive involvement of the caudate nuclei and thalami. The bilaterally involved frontomedial cortex of bvFTD is typically well demarcated – a feature originally described on CT and MRI as “lobar atrophy”. In semantic variant PPA (svPPA), [^{18}F]FDG uptake typically demonstrates asymmetric anterior temporal hypometabolism, most often with left-predominant – reflecting language-dominant hemisphere involvement. The nonfluent variant of PPA (nfvPPA) is often associated with hypometabolism affecting the left posterolateral frontal and superior medial frontal cortices, and inferofrontal regions (insula). In logopenic variant PPA (lvPPA), [^{18}F]FDG PET typically reveals asymmetric hypometabolism of the left posterior perisylvian cortex (posterotemporal and inferoparietal lobes), a pattern that aids differentiation from svPPA and nfvPPA and supports its frequent association with underlying AD pathology. In corticobasal syndrome (CBS), hypometabolism often involves the frontoparietal cortex, basal ganglia, and thalamus, often most pronounced in the hemisphere contralateral to the clinically predominant symptoms. The characteristic [^{18}F]FDG uptake pattern of progressive supranuclear palsy (PSP) typically involves the medial frontal cortex, anterior cingulate, and midbrain, frequently extending to the thalamus and basal ganglia[6-8, 24, 25].

Vascular dementias show no signature patterns of cortical hypometabolism; uptake abnormalities mirror the topography of vascular injury and its remote network effects – including crossed cerebellar diaschisis after supratentorial infarction. These changes are often heterogeneous and multifocal, often asymmetric across cortical and subcortical territories – although they may appear more symmetric in diffuse small-vessel disease. Particularly in older patients, vascular dementia frequently coexists with other neurodegenerative pathologies – most commonly Alzheimer’s disease – in what is termed “mixed dementia”. Interpretative cues, in a top-down approach, include the absence of expected neurodegenerative patterns (e.g., parietal hypometabolism with preserved precuneus) or, conversely, an atypical pattern such as precuneus involvement with relative sparing of the temporal lobes[1, 2, 8, 25].

Movement Disorders

At first glance, brain [^{18}F]FDG PET scans in Parkinson's disease (PD) often appear unremarkable. On closer inspection – particularly using voxel-based statistical mapping – PD shows posterior temporo-parietal and occipital hypometabolism, sometimes extending to the frontal lobes in patients with cognitive impairment. In parallel, there is relative hypermetabolism of the basal ganglia (putamen and pallidum), thalamus, sensorimotor cortex, pons, and cerebellum; this network expression can be attenuated under dopaminergic treatment. Unlike the striatal hypometabolism characteristic of atypical parkinsonian syndromes (APS), patients with PD usually show preserved or relatively increased [^{18}F]FDG uptake, compared with cortical regions. This reflects compensatory activity in the striato-pallidal-thalamic circuit in the setting of nigrostriatal degeneration.

By contrast, multiple system atrophy (MSA) is associated with bilateral reductions in putaminal uptake, progressive supranuclear palsy (PSP) most often demonstrates caudate hypometabolism, and corticobasal syndrome (BCS) typically displays asymmetric striatal reductions accompanied by concordant cortical asymmetry. MSA is characterized by hypometabolism involving the (posterior) putamen, pons and cerebellum. The pattern of [^{18}F]FDG uptake reduction in MSA varies with the clinical subtype: in MSA with predominant parkinsonism (MSA-P), changes are more pronounced in the striatum, whereas in the cerebellar variant (MSA-C), hypometabolism is more prominent within the pontocerebellar structures. PSP displays consistent regional hypometabolism in the medial, dorsal, and ventrolateral frontal areas – including the anterior cingulate gyrus, supplementary motor area, precentral gyrus, and premotor–to–posterior prefrontal areas – with additional involvement of the caudate, thalamus and upper brainstem. A distinct focal decrease in midbrain [^{18}F]FDG uptake can also be observed, sometimes preceding MRI-detectable midbrain tegmental atrophy (the "Hummingbird sign"). CBS is distinguished by asymmetric striatal hypometabolism, with concordant cortical asymmetry, usually affecting the frontoparietal regions[1, 6, 8, 10, 12, 28].

In amyotrophic lateral sclerosis (ALS), [^{18}F]FDG PET typically demonstrates hypometabolism involving the primary motor, premotor and supplementary motor cortices, with extension into the frontoparietal regions. Conversely, relative hypermetabolism is often observed in the medial temporal cortex, cerebellum, and brainstem. ALS exists in a continuum with frontotemporal dementia, as up to half of patients show subtle cognitive or behavioral impairment, while approximately 10-15% fulfil criteria for overt frontotemporal dementia[1, 6, 8]. Huntington's disease has a well-described, characteristic neuroimaging finding: severely reduced [^{18}F]FDG uptake in the bilateral striatum. Beyond this core finding, patients also exhibit widespread cortical hypometabolism as well as increased thalamic, occipital, and cerebellar metabolism. Wilson's disease has also shown a decreased striatal uptake, mainly in the caudate nucleus and in the lenticular nuclei, while the cortical glucose metabolism often remains normal [1, 2, 6, 8, 11].

Epilepsy

In the interictal phase, [^{18}F]FDG PET typically demonstrates hypometabolism in the seizure onset zone (SOZ) and propagation zones, which may extend across the entire irritative zone. A global reduction of grey matter metabolism relative to controls has also been reported, attributable to mechanisms including neuronal loss, reduced synaptic density, vascular changes, or post-ictal depression. In temporal lobe epilepsy (TLE), hypometabolism often extends beyond the presumed epileptogenic zone, consistent with the concept of epileptogenic and propagation networks. Prefrontal asymmetry correlates with mild cognitive impairment, whereas bitemporal hypometabolism is associated with memory deficits and increased risk of postoperative decline. In extratemporal lobe epilepsy (ETLE), focal hypometabolism is a strong predictor of postoperative seizure freedom. Although hypometabolism is the predominant finding, interictal hypermetabolic cortical or subcortical foci may occur, reflecting hypermetabolic cortical or subcortical foci may occur, reflecting pathological hyperactivity or activated inhibitory circuits.

In children and adolescents, where etiologies are diverse (tumors, birth-related lesions, malformations of cortical development), [^{18}F]FDG PET is especially valuable. Lesions typically present as hypometabolic, often exceeding the extent visible on MRI, and PET may reveal abnormalities in MRI-negative or equivocal cases – particularly in focal cortical dysplasia type II. It is essential for evaluating multilobar, drug-resistant foci, guiding complete resection and surgical outcomes, especially in hemispherectomy. In specific epilepsy syndromes, [^{18}F]FDG PET can localize the epileptogenic tuber in tuberous sclerosis complex (typically as hypometabolism exceeding MRI abnormalities), reveal predominantly hypometabolism changes in Sturge-Weber syndrome (with cortical hypermetabolism in young children signaling severe disease requiring early surgery), demonstrate heterogenous uptake patterns in Lennox-Gastaut syndrome where focal hypometabolism may guide surgical planning, assess contralateral hemispheric integrity and cognitive prognosis in hemimegalencephaly, and detect early metabolic abnormalities in Rasmussen encephalitis – both hypo- and hypermetabolism – thereby supporting diagnosis when MRI is inconclusive and excluding bilateral involvement. Pediatric interpretation is challenging given age-dependent normal uptake patterns, underscoring the importance of software-based quantification against age-matched controls. FDG PET usually reveals asymmetric hypometabolism, but the abnormality often exceeds the true ictal onset zone, making it more reliable for identifying laterality and lobar localization rather than the precise seizure focus[1, 6, 12, 14].

Neurooncology

[^{18}F]FDG PET is an established diagnostic tool in oncologic imaging due to its ability to evaluate lesions based on glucose metabolism activity. It provides valuable information in differentiating between common enhancing malignant brain tumors (e.g., high and low grade gliomas), metastatic brain tumors and primary central nervous system lymphoma (PCNSL). Semi-quantitative measures like Standardized Uptake Value (SUV) and Tumor-to-Background Ratios (TBR) are useful, while SUVmax is reported as the main interpreting tool, with corresponding values from highest to lowest, in order: PCNSL > metastatic brain tumors > high-grade gliomas > low-grade gliomas. However, its impact can be limited in brain imaging compared to amino-acid PET due to the high physiological uptake of [^{18}F]FDG in normal brain gray matter and variable uptake by inflammatory lesions. Delayed acquisitions (typically 3-5 hours post-injection) are often proposed to increase the tumor-to-healthy brain uptake ratio, which can be particularly beneficial for differentiating recurrence from post-treatment necrosis. Brain metastases arising from primary tumors with low [^{18}F]FDG uptake – such as mucinous adenocarcinoma, lobular breast carcinoma, and renal cell carcinoma – should generally not be evaluated with this tracer, although a focal hypometabolic area may occasionally indicate a large metastatic lesion[1, 6, 17, 29, 30].

Cerebral Infectious and Inflammatory Diseases

While the high physiological glucose uptake in normal brain gray matter can sometimes limit contrast between lesions and healthy tissue, particularly when compared to amino-acid PET in some conditions, [^{18}F]FDG PET/CT has demonstrated clinical utility across a spectrum of these disorders. In neurosarcoidosis, lesions typically display increased [^{18}F]FDG uptake, sometimes preceding or exceeding MRI abnormalities. In autoimmune encephalitis (AIE), distinct patterns of regional abnormalities have been described depending on the antibody subtype: medial temporal lobe and basal ganglia hypermetabolism with parietal–occipital hypometabolism is common, with anti-LGI1 encephalitis showing preferential medial temporal and basal ganglia involvement, while anti-NMDAR encephalitis often combines occipital hypometabolism with frontal or medial temporal hypermetabolism. Suppurative meningomyelitis may be identified as increased linear uptake within the spinal canal, which normalizes after treatment, whereas ventriculitis is characterized by intense periventricular hypermetabolism even when CT is inconclusive. In HIV-positive patients, PET aids differential diagnosis between primary CNS lymphoma, which shows high focal uptake, and cerebral toxoplasmosis, which typically demonstrates low uptake. In neuropsychiatric lupus (NPSLE), striatal hypermetabolism has been frequently observed, correlating with psychiatric and motor manifestations, although cortical findings are variable and sometimes non-specific. In Long-COVID, a reproducible pattern of hypometabolism has been reported at the group level, typically involving fronto-orbital olfactory regions, (para)limbic areas, the brainstem, and cerebellum. Regional changes correlate with clinical symptoms, with frontal hypometabolism linked to concentration and mood disturbances, medial temporal changes to memory impairment, and pontine abnormalities to paresthesias. Finally, in alveolar echinococcosis, [^{18}F]FDG PET/CT commonly demonstrates annular or irregular peripheral hypermetabolism surrounding the lesion. Uptake intensity reflects granulomatous inflammatory activity and microvascular proliferation and can therefore assist in assessing disease activity[1, 6, 19-22].

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration for publication elsewhere. This research received no external funding.

Authors' contribution

Conceptualization M.R.M, G.S.P., A.I.B and T.S.M.; methodology, G.S.P., L.E.M.,D.M.,T.S.M.; validation, D.M., O.C.C. and O.M.S.; data curation, D.M., A.M.R., G.I.; writing—original draft preparation, G.S.P, A.I.B.,L.E.M.; writing—review and editing, M.R.M., O.C.C., G.I.; supervision, A.M.R., D.M., O.M.S.; project administration, M.R.M.; All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted under the Declaration of Helsinki. The research was conducted under ethical guidelines and regulations, ensuring compliance with all necessary protocols.

Patient consent for publication

Not applicable

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ORIGINAL ARTICLE

Comparison of the Cytotoxic Effects of Lactobacillus casei Extract with Newcastle Disease Virus in Human Colorectal Cancer

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Abstract: Background and purpose: Colorectal cancer is one of the most prevalent cancers globally, representing a significant public health challenge. Treatment methods include surgery, chemotherapy, and targeted therapies, selected based on disease stage and patient status. Common cancer treatments, such as chemotherapy and radiation therapy, often induce considerable side effects, including fatigue, nausea, hair loss, and blood disorders, which can impact patients' quality of life. Consequently, researchers are focusing on developing novel drugs and targeted therapies aimed at reducing side effects while enhancing treatment efficacy. Innovative therapies, including bacterial and oncolytic viruses, can specifically target cancer cells while sparing healthy tissues. The present study aims to compare the cytotoxic effects of Lactobacillus casei extract with Newcastle disease virus on human colorectal cancer. Materials and methods: Human colorectal cancer cells were cultured and treated with various concentrations of Lactobacillus casei extract and Newcastle disease virus to determine the IC50. Cell viability and apoptosis rates were then assessed using MTT assay and acridine orange/propidium iodide staining. Statistical significance was set at $P<0.05$ for all evaluations. Results: The results demonstrated that both Lactobacillus casei extract and Newcastle disease virus significantly reduced cell viability and increased apoptosis in a concentration- and time-dependent manner. Caspase-8 and -9 activity measurements indicated that Newcastle disease virus and Lactobacillus casei extract activated both the mitochondrial and extrinsic apoptotic pathways. Conclusion: Based on the findings, it appears that bacterial and oncolytic viruses could be considered as complementary therapeutic options alongside chemotherapy and radiotherapy, following clinical trials.

Keywords: Colorectal cancer cells, Lactobacillus casei, Newcastle disease virus, probiotics, oncolytic virus

INTRODUCTION

Cancer is a major health problem and one of the leading causes of death in the world today. Cancer is the uncontrolled growth and multiplication of cells. Cells that become cancerous no longer perform their normal functions and usually do not respond to signals that prevent uncontrolled growth [1]. However, in many cases, cancer cells can counteract the proposed treatment strategies and sometimes even develop resistance to chemotherapy, leading to faster tumor growth. Therefore, in the last two decades, scientists have tried to choose their strategies as intelligently as possible for successful combat against cancer [2]. According to various studies, colorectal cancer is the third most common cancer worldwide. The walls of the colon and rectum are made up of several layers. Colorectal cancer starts in the innermost layer (mucosa) and can spread to other layers and, consequently, to blood or lymphatic vessels, leading to metastasis in other parts of the body [2]. In recent years, mortality from colorectal cancer has increased in Asia, and according to studies conducted in Iran, its prevalence is on the rise [3]. Treatment methods for colorectal cancer include surgery, radiotherapy, or chemotherapy, and the choice of treatment method depends on the phase of the disease. One of the most commonly used chemotherapy drugs in the treatment of patients with colorectal cancer is 5-fluorouracil (5FU) [4, 5]. Common side effects of chemotherapy drugs include drug resistance and reduced immune system function in the patient. As a result, identifying novel treatment methods aimed at combating drug resistance and

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strengthening the immune system has been the focus of a huge number of studies [5]. One of the novel therapeutic methods is the use of oncolytic viruses and bacteria. The use of oncolytic viruses is a new perspective in the treatment of human malignancies, including the use of engineered viruses or viruses with tissue affinity for specific transformed cells, which increase the destruction of tumor tissue or its cells and prevent damage to non-cancerous cells [5-7]. Among the escape pathways of tumor cells from the anti-tumor responses of the immune system is the acquisition of defects in cellular antiviral pathways, such as those mediated by interferons [6-8]. Oncolytic viruses can target and destroy cancer cells by utilizing this unique cellular activity of tumors. The treatment with oncolytic viruses relies on a two-part process of selectively infecting tumor cells and then inducing anti-tumor activity through the release of tumor antigens and the stimulation of the immune system [7-9]. Unlike chemotherapy and radiotherapy, oncolytic viruses are self-amplifying treatments, and their therapeutic outcome is determined by a three-way competition between tumor growth, virus proliferation, and immune activation [10]. A wide range of different viral species have been investigated as cancer therapeutic agents, including adenoviruses, herpes simplex virus type 1, poliovirus, measles virus, Newcastle disease virus, reoviruses, vesicular stomatitis virus, Zika virus, etc [11]. Among oncolytic viruses, Newcastle disease virus has emerged as a promising non-engineered oncolytic virus. Newcastle disease virus is an enveloped, single-stranded RNA virus with a negative sense, belonging to the Paramyxoviridae family, and it causes significant economic losses to various poultry industries worldwide each year [12,13].

Although Newcastle disease virus is an avian pathogen, its impact on human cancers has been widely reported because Newcastle disease virus is antigenically distinct from common human pathogens. Furthermore, it exhibits oncolytic potential through specific replication in tumor cells rather than normal cells [13]. A wide range of bacterial species play a role in most physiological and metabolic activities and intestinal function. Probiotics are live microbial dietary supplements that are beneficial for creating microbial balance and nutritional equilibrium in the human intestine [14, 15]. Bacterial species used as probiotics are lactic acid bacteria, primarily from the genera Lactobacillus and Bifidobacterium. Bifidobacteria are Gram-positive, anaerobic, non-motile bacteria that lack spore-forming ability and are catalase-negative. Their normal habitat is the colon of the human and animal gastrointestinal tract, and their numbers remain stable except during old age, when they decrease. However, factors such as diet, antibiotics, and stress can also lead to changes in their numbers [16].

Various studies have reported that probiotics play a role in suppressing primary neoplastic ulcers and cancerous tumors in mouse models [16]. The anticancer effects of probiotics are achieved by preventing the conversion of procarcinogens to carcinogens, binding and inactivating mitogenic compounds, reducing the growth of procarcinogenic bacteria, decreasing the absorption of mitogens, and enhancing the immune system's function [17]. Lactobacillus casei is one of the types of Lactobacillus that is rod-shaped, Gram-positive, and facultatively anaerobic, non-spore-forming, non-motile, and polymorphic. It is considered a safe probiotic bacterium. Although several beneficial effects have been attributed to these bacteria, their anticancer activity is the most important characteristic of these bacteria [16,18]. Apoptosis is programmed cell death that plays a key role in regulating cell numbers. In many cancers, a reduction in the ability to undergo apoptosis leads to alterations in the process of cell proliferation and disruption [19]. There is substantial evidence that probiotics can play a role in regulating cell proliferation and apoptosis [20]. Additionally, with the discovery of various therapeutic effects of probiotics, including anticancer effects, modulation of differentiation processes in tumor cells, production of short-chain fatty acids, and changes in the expression of tumor genes, probiotics have become a research focus for many researchers around the world [21]. Therefore, the aim of the present study is to compare the cytotoxic effects of Lactobacillus casei extract with Newcastle disease virus in human colorectal cancer.

MATERIALS AND METHODS

HT-29 cell culture

The HT-29 cancer cell line was purchased from the cell bank of the Pasteur Institute of Iran and transferred to T25 flasks containing DMEM culture medium and 10% FBS, and cultured in an incubator with 5% CO2 at a temperature of 37 0C.

Lactobacillus casei bacteria culture

Lactobacillus casei bacteria (ATCC:393) were purchased from the Applied Virology Research Center of Baqiyatallah University of Medical Sciences. After culturing it in a specific culture medium (MRS), its extract was prepared by heating (at 56 0C for 60 minutes) [22].

Virus

The Newcastle disease virus, Lasota strain, was obtained from the Applied Virology Research Center of Baqiyatallah University of Medical Sciences.

Study design

After culturing cancer cells and observing a density of over 80%, the cells were treated with different concentrations of Lactobacillus casei extract (concentrations of 0.5, 1, 2, 3, 4, 5, 6 µg/ml) and Newcastle disease virus (concentrations of 0.5, 1, 2, 4, 8, 9 MOIs) to

determine the IC50 concentration. Then, to compare the toxicity and simultaneous effects, the IC50 concentration of both therapeutic agents was used. The drug 5-fluorouracil (34 µM) was used as a positive control.

Determination of Cell Viability by MTT Assay

The MTT assay is a method for assessing biological toxicity based on the formation of formazan color through the reduction of MTT (dimethylthiazole 2,5-diphenyltetrazolium bromide) or other tetrazolium salts. The tetrazolium ring of the MTT salt is broken by the succinate tetrazolium reductase system, which is an enzyme of the mitochondrial respiratory cycle and is found only in living cells, resulting in the formation of the insoluble substance formazan. Formazan is insoluble in water and appears as purple crystals on the surface of living cells. By measuring the absorbance using a spectrophotometer at specific wavelengths, the number of viable cells can be determined. This test is conducted based on the ISO 10993-5 standard, and its purpose is to evaluate cell proliferation under in vitro conditions. The MTT reagent is a yellow tetrazolium salt that is reduced by metabolically active cells, part of which is converted by dehydrogenase enzymes to produce reduced forms of NADH and NADPH. After counting the cells, 100 µl of DMEM culture medium containing 10% FBS with the required number of cells was added to each well of a 96-well plate. The 96-well plate was then placed inside an incubator and incubated for 24 hours. After 24 hours, the cells grew and filled the bottom of the wells. Then, the supernatant was removed from the wells, and treatments from different groups were added to the wells and incubated. After the incubation period, 25 µl of MTT solution (5 mg/mL PBS) was added to each well and incubated for 4 hours. During this time, the tetrazolium bromide was reduced by viable cells, leading to the formation of insoluble purple formazan crystals, which became soluble upon the addition of 100 µl of DMSO after 30 minutes. Then, the absorbance of each well was measured at a wavelength of 570 nanometers using an ELISA reader.

Percentage of cell apoptosis

HT-29 cells were collected into sterile 1.5 ml microtubes after treatment with different groups and centrifuged for 10 minutes at 1400 rpm. The supernatant was then discarded, and the cell pellet was resuspended in 1 ml of culture medium. The samples were then stained with 10 microliters of acridine orange and incubated for 15 minutes at 37 0C in 5% CO2. After the incubation period, the samples were washed twice with PBS, and 10 µl of propidium iodide were added and incubated for 5 minutes at 37 0C in 5 % CO2. In the final step, the samples were centrifuged for 10 minutes at 1400 rpm after washing with PBS. The supernatant was then removed, and 50 µl of the cell pellet were taken and placed on a glass slide. After placing a coverslip, the samples were examined under a fluorescence microscope with a 40X objective lens. The green cells were identified as healthy cells, while the orange cells were apoptotic.

Statistical analysis

Data analysis was performed using SPSS version 23 and Tukey's test was employed. In all analyses, a P-value of <0.05 was considered statistically significant. Additionally, graphs were plotted using GraphPad Prism version 8.2.1, and the data were reported as Mean ± SEM.

RESULTS

Determination of IC50 of Newcastle oncolytic virus and Lactobacillus casei

Figures 1 and 2 show the inhibitory effect on the growth of cancer cells after treatment with Newcastle disease virus and Lactobacillus casei extract using the MTT assay. According to the graphs, both agents reduce the growth of colorectal cancer cells in a concentration-dependent manner. The IC50 for the Newcastle oncolytic virus is 3.358 MOI, and for Lactobacillus casei, it is 4.23 µg/ml (Figures 1 and 2).

Cell Viability Results from MTT Assay

According to Figure 3, the synergistic anti-proliferative effects of the simultaneous treatment of Lactobacillus casei and Newcastle disease virus on HT-29 cells were evaluated using the MTT assay. A comparison was made between the results of 5-fluorouracil and the negative control group. The combined treatment group exhibited significantly higher cytotoxic effects compared to the control groups (Figure 3).

Cell viability results from the apoptosis test

In Figure 4, the level of apoptosis resulting from the simultaneous treatment of Lactobacillus casei and Newcastle oncolytic virus was determined using fluorescent staining. The combined treatment group exhibited significantly higher apoptotic effects compared to the control groups (Figure 4).

Figure 1: The viability levels in the groups with the virus are shown. Based on the linear graph formula, the IC_{50} of the virus was calculated to be approximately 3.358

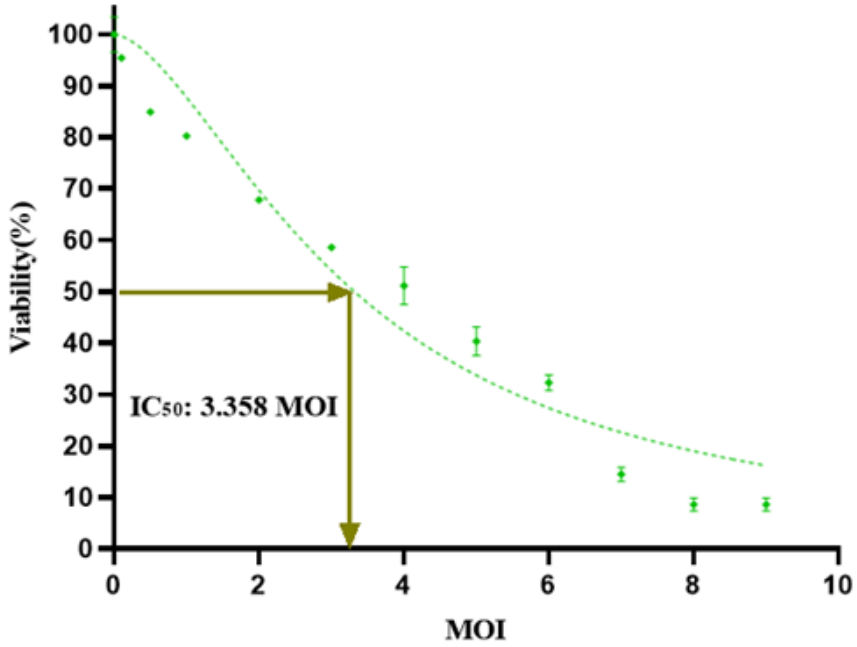


Figure 2: The viability levels in the groups treated with the bacteria are shown as mean ± standard deviation. Based on the linear Figure formula, the IC50 of the bacteria was calculated to be approximately 4.23 µg/ml.

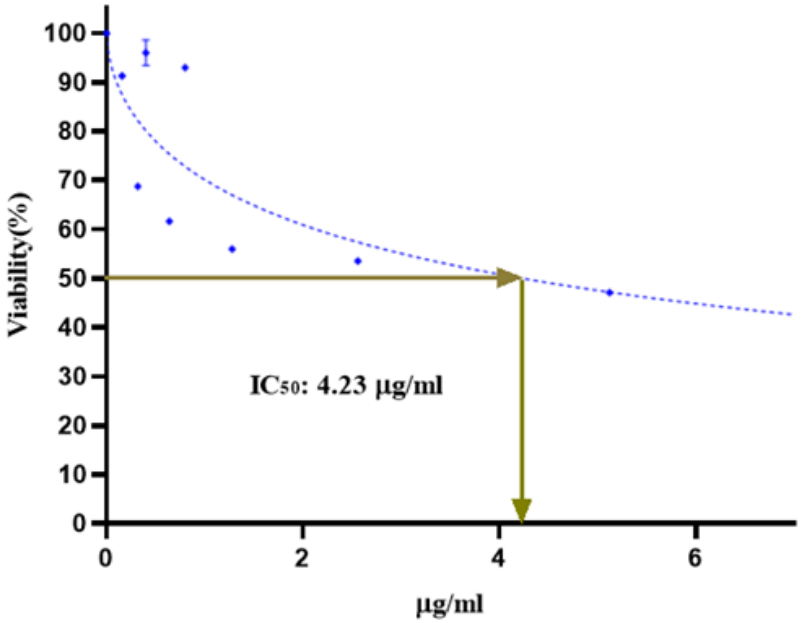


Figure 3: Viability in the treated groups combined with oncolytic bacteria and viruses as mean ± standard deviation (* indicates p < 0.05, ** indicates p < 0.01, *** indicates p < 0.001, **** indicates p < 0.0001).

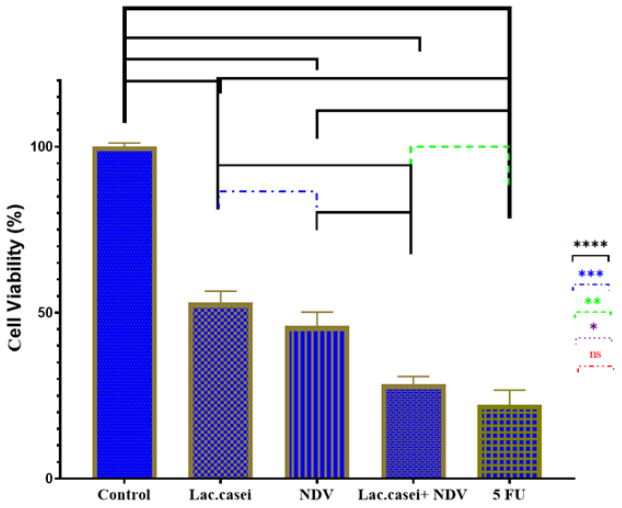
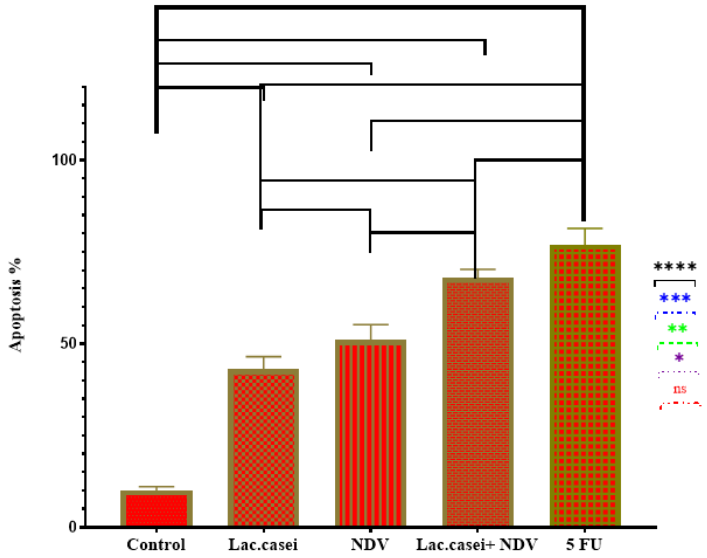


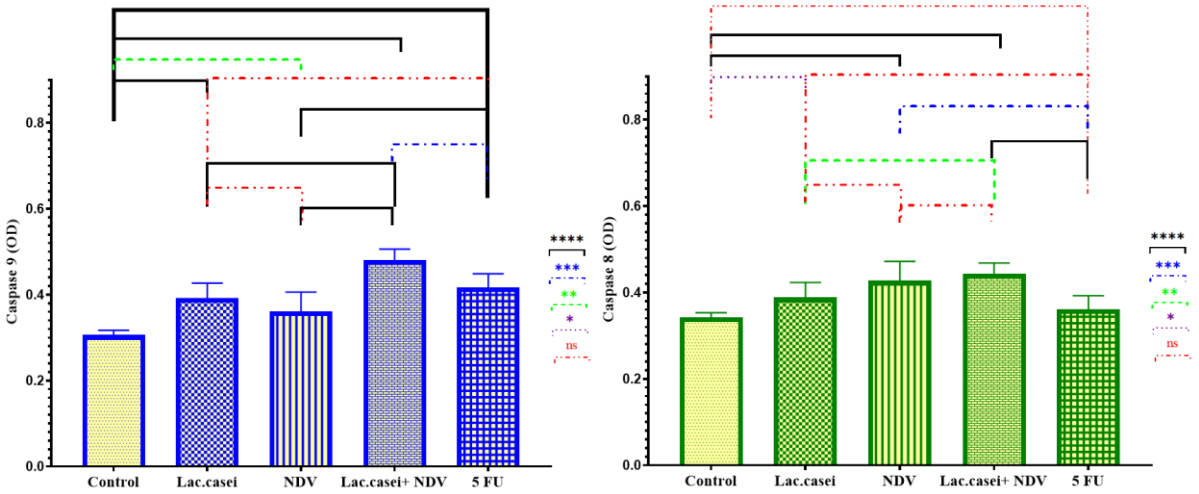
Figure 4: The percentage of apoptosis in the treated groups combined with oncolytic bacteria and viruses as mean ± standard deviation (* indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001, **** indicates p<0.0001).



Examination of caspase 9 and 8 production levels

In Figure 5, the levels of caspase 8 and 9 production after treatment with Lactobacillus casei and Newcastle oncolytic virus, both alone and in combination, are shown. The results indicated that the Newcastle oncolytic virus and Lactobacillus casei extract increased the activity of both caspase 8 and 9. In other words, the oncolytic virus and the bacterium activate both apoptotic pathways (Figure 5).

Figure 5: Figures show the levels of caspase 8 and 9 production in the treated groups combined with oncolytic bacteria and viruses as mean ± standard deviation (* indicates p<0.05, ** indicates p<0.01, *** indicates p<0.001, **** indicates p<0.0001).



DISCUSSION

Colorectal cancer is one of the most common malignancies of the digestive system, and diet plays a key role in its pathogenesis. There is abundant evidence that colorectal cancer is associated with an imbalance in the intestinal microflora [23]. Probiotics (such as Lactobacillus and Bifidobacterium) are live microorganisms that have numerous beneficial effects on health, and in addition to their positive gastrointestinal effects, they can help prevent colorectal cancer through various mechanisms [24]. There is no certainty in the treatment of cancer, and researchers are discovering new cancer treatment methods every day. For over a century, physicians have been interested in using viruses for cancer therapy, and in recent years, a small but growing number of patients have begun to benefit from this approach [25]. Some viruses tend to infect and destroy tumor cells. This group, known as oncolytic viruses, includes viruses that are found in nature as well as those that have been modified in the laboratory to effectively replicate in cancer cells without harming healthy cells [26]. So far, only one oncolytic virus, a genetically modified form of herpesvirus, has been approved by the Food and Drug Administration (FDA) for the treatment of melanoma, although a number of viruses are being evaluated as potential cancer therapies in clinical trials [27]. An increasing number of studies suggest that certain oncolytic viruses may work by stimulating an immune response in the body against cancer. When a virus infects a tumor cell, it replicates itself until the cell bursts. The dying cancer cell releases substances such as tumor antigens, which allow the cancer to be recognized by the immune system [28]. Based on the literature review conducted, the aim of the present study is to investigate the apoptosis induction pathway caused by Lactobacillus casei extract in combination with Newcastle disease virus in human colorectal cancer. The results of the current study indicated that the Lactobacillus casei extract and Newcastle disease virus led to an increase in the rate of apoptosis and a reduction in the proliferation of colorectal cancer cells. The results also showed that Newcastle disease virus and Lactobacillus casei extract induce apoptosis through both intrinsic and extrinsic pathways.

Kim et al. examined the effects of cellular components of ten different probiotics on eleven types of cancer cells. Their results indicated that probiotics had an inhibitory effect on cancer cells and attributed this effect to their peptidoglycans [29]. Lee et al. reported in their study that the cytoplasmic extracts of Lactobacillus casei and Bifidobacterium have a direct effect on inhibiting the growth of cancer cell lines. Since the uncontrolled proliferation of cancer cells is a major issue in cancer patients, any factor that can inhibit their proliferation could be beneficial for prevention and halting their progression. The best way to inhibit or suppress cell proliferation is to induce programmed cell death through apoptosis, as it will not cause inflammation in the body and cells adjacent to tumors, and as a result, it will be an immune factor for suppressing tumors [30]. The results of Baldwin et al.'s research also suggest that Lactobacillus acidophilus and Lactobacillus casei can enhance the induction of apoptosis in the LS513 carcinoma cell line and can be used as adjuvants in chemotherapy [31]. Other studies have shown that Bifidobacterium lactis induces apoptotic responses in genotoxic carcinogens shortly after the induction of carcinogens in the descending colon of rats [32]. Cell death by apoptosis is an important regulatory process for protection against oncogenes.

Additionally, numerous groups of scientists have reported that compounds derived from Lactobacillus acidophilus prevent the progression of colorectal cancer in animal models [33]. As a result, probiotics can be considered as a safe agent for combating cancer with no side effects. Probiotics enhance cytotoxic activity and are used as an adjunctive therapy alongside chemotherapy. Mehrabian et al. stated that Lactobacillus isolated from Tarkhina has a high anti-mutagenic and anti-cancer effect, which is indeed attributed to

the strengthening of the immune system by probiotics [34]. Dolati et al. showed that the extract of Bacillus coagulans has inhibitory effects on the MCF-7 breast cancer cell line in a concentration-dependent and time-dependent manner. Meanwhile, lower cytotoxic effects were observed in normal human foreskin fibroblast cells. The increase in the expression of BAX, caspase 3, and caspase 9 genes, along with the reduction of the anti-apoptotic gene BCL-2, confirmed the induction of apoptosis in cancer cells, supported by flow cytometry results [35]. Sivamaruthi et al. (2020) proved that the use of probiotics is beneficial in the management of colorectal cancer treatment [36]. Recently, several alternative therapeutic approaches have been explored to overcome drug resistance issues, with virotherapy emerging as a promising strategy. The idea of using viruses in cancer treatment was proposed in the early 1960s. Since then, several groups of DNA and RNA viruses with oncolytic properties have been identified, including the Newcastle disease virus.

The Newcastle disease virus was first discovered in 1927 in Newcastle upon Tyne and causes a highly contagious disease in birds and poultry [37]. The use of the Newcastle disease virus in cancer treatment was first reported by Cassel and Garret in 1965, and since then, interest in using the Newcastle disease virus as an anti-neoplastic therapy has steadily grown. The Newcastle disease virus, or avian paramyxovirus serotype 1, belongs to the Paramyxoviridae family and causes severe Newcastle disease in poultry and wild birds worldwide [38]. However, the Newcastle disease virus is non-pathogenic for mammals, making it a promising viral therapeutic agent for human malignancies. The oncolytic activity of the Newcastle disease virus has been studied since 1952, and the National Cancer Institute has listed the Newcastle disease virus among complementary and alternative therapies [39]. The interferon response prevents the replication of the Newcastle disease virus in healthy cells. However, the Newcastle disease virus induces oncolytic properties due to the uncontrolled division and high mobility of cancer cells. Several strains of the Newcastle disease virus have shown efficacy in in vitro, in vivo conditions, and in phases I and II of clinical trials [40]. Keshavarz et al. (2020) showed that treatment with Newcastle oncolytic virus significantly reduced TC1 cell proliferation and increased their apoptosis rate. They also showed that the apoptosis of TC1 cells induced by the oncolytic Newcastle disease virus is mediated by the production of reactive oxygen species. In summary, their results indicated that Newcastle oncolytic virus is a useful therapeutic candidate as a selective anti-tumor agent for the treatment of cervical cancer [41]. Al-Ziaydi et al. (2020) showed that the combined treatment of the oncolytic Newcastle disease virus with D-mannohaptulose resulted in greater inhibition of tumor cell proliferation compared to monotherapy with D-mannohaptulose. This suggests a new strategy for breast cancer treatment through the inhibition of glycolysis by reducing hexokinase levels [42].

In a study conducted in 2018 by Lin et al. in China, it was observed that the use of the oncolytic coxsackievirus resulted in a reduction in the growth of endometrial cancer (EC) cells [43]. In a study conducted in 2003 by Bell et al. at the American Center for Respiratory Disease Research, it was shown that oncolytic viruses have a cytotoxic effect on Ehrlich tumor cells and, by binding to these cells and entering them, cause cytopathic effects (CPE) and kill tumor cells [44]. In another study conducted in 2018 at the University of Illinois, USA, by Abdullahi et al., it was shown that oncolytic viruses are capable of replicating in Hepatocellular Carcinoma cell lines. They induce CPE that leads to the destruction of these tumor cells, while not affecting normal, non-cancerous human fibroblast cell lines [45]. In a study conducted in 2008 at Hebrew University in Jerusalem by Yaacov et al, the effects of attenuated oncolytic viruses on tumor cells of mouse and human lung were investigated in vitro. The study revealed that attenuated oncolytic viruses selectively induce CPE in tumor cells of both mouse and human lung compared to non-tumor lung cells, leading to the selective destruction of tumor cells [46]. In a study by Ahmad et al. (2020), the cytotoxic and anti-cancer effects of oncolytic viruses on bladder cancer cell lines were investigated. The study demonstrated that oncolytic viruses can induce apoptosis in bladder cancer, effectively eliminating these tumor cells [47]. Kazimirsky et al. (2016) reported that the use of mesenchymal stem cells infected with Newcastle virus enhances the anti-cancer effects of the Newcastle virus on glioblastoma. Additionally, these researchers noted that this increased anti-cancer effect is associated with an elevated secretion of TRAIL, which acts as a cytotoxic agent [48].

CONCLUSION

Based on the obtained results, it appears that the use of both therapeutic agents (probiotics and oncolytic viruses) leads to a reduction in cell proliferation and an increase in the percentage of apoptosis in cancer cells. Furthermore, the effectiveness of these two agents in combination therapy groups enhances each other's effects, suggesting that they have synergistic effects. Therefore, it can be concluded that the extract of Lactobacillus casei and the Newcastle disease virus have significant potential to be introduced as a new strategy for cancer treatment alongside chemotherapy and radiotherapy.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization, L.T., and H.E.; methodology, H.E.; validation, H.E., L.T., and M.D.; formal analysis, M.D.; investigation, M.E.; resources, S.K.A.; data curation, M.D.; writing—original draft preparation, M.E.; writing—review and editing, S.K.A.; supervision, H.E.; project administration, H.E. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

This study involved in vitro experiments using cellular models and did not include human participants, human data, or animal subjects. The research was conducted in accordance with all applicable international, national, and institutional guidelines for the care and use of laboratory materials.

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ARTICLE

Fighting against mental health stigma in military personnel – An analysis of the most important directions of research

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Abstract: Mental health stigma (MHS) among military personnel requires a complex approach, as it is influenced by ethical challenges and organizational norms distinct from those in civilian milieus. Stigmatization encompasses multiple dimensions -including social, self, anticipated, cultural, and structural stigma- that must also be examined within military settings. This article presents a conceptual analysis of key research directions in the field of MHS, based on a literature review conducted across three electronic databases (PubMed, Google Scholar, and Clarivate/Web of Science), from the inception of each database up to June 2025. The review focuses on active-duty service members and veterans, and identified six major domains involving MHS: (1) structural stigma within military contexts, (2) risk factors and consequences associated with MHS, (3) self-stigma among active-duty personnel and veterans, (4) the role of military healthcare providers in mitigating stigma, (5) military sexual trauma and its relationship to stigma, and (6) interventions aimed at decreasing MHS among military personnel. Although relevant primary and secondary studies were identified across these domains, significant research gaps remain, particularly in the last three areas. Addressing MHS in military populations is essential not only for improving quality of life, psychological well-being, and daily functioning, but also for maintaining combat readiness, unit cohesion, and peer acceptance.

Keywords: mental health stigma; barriers to treatment; quality of life; treatment adherence; post-deployment adjustment; veterans; self-stigma; structural stigma; anticipated stigma; social policies

INTRODUCTION

Stress in military personnel can arise from multiple sources, including training demands, deployment-related risks, combat exposure, and the challenges of reintegration into civilian life, as well as from extended family separations, frequent relocations, organizational pressures, exposure to non-combat trauma such as military sexual trauma or moral injury, concerns about stigma and barriers to care, and financial or resource-related difficulties [1]. Life-threatening situations, unpredictability and uncertainty of the professional schedule, moral injuries, witnessing death or severe traumas, facing harsh conditions, sleep deprivation, irregular meals, leadership challenges, high workload, cultural isolation when operating in foreign countries, but also psychological and emotional challenges, such as anxiety, survivor's guilt, or moral dilemmas may also represent significant stressors in this population. Retired military personnel have to deal with substantial post-deployment/reintegration stressors, such as adjustment

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to civilian life, employment challenges, loss of structure or identity, and veteran health issues.

It can be easily deduced that all of these difficult situations and stressors are creating a favorable context for the emergence of mental health conditions that require adequate assistance, in order to prevent a chronic trajectory, severe invalidations, or tragic complications. However, there are several barriers to accessing specialised services, and an estimated 66% of military personnel experiencing mental health problems do not seek help, although they could benefit from it [2]. Concerns about the stigmatisation of individuals accessing mental health services are among the most frequently reported reasons for avoiding psychiatric care in military settings [2]. This phenomenon is also largely present in the civilian population, with an estimated 50% of Americans having a mental illness failing to seek treatment as a result of stigma [3].

Mental health stigma (MHS) originates in a collection of negative stereotypes and involves prejudice and discrimination, thus interfering with the timely provision of the required care [4]. Delayed treatment may lead to severe consequences, such as increased morbidity, diminished well-being and quality of life, and a higher risk of unfavorable evolution [4]. The negative effects of stigma are not limited to the individual level, but encompass the patients' families (e.g., shame, isolation), healthcare professionals (e.g., burnout and demoralization), and society in its entirety (e.g., misallocation of resources for mental health services, decrease in the professional performance, or long-term increase in healthcare costs due to the onset of complications) [4].

According to Link & Phelan (2001), stigma has five components, i.e., labeling, stereotyping, separation, status loss, and discrimination [5]. Stigma is a socially constructed concept, but individuals may develop their own way to negatively perceive themselves, by introjection of cultural sterotypes, as reflected by the phenomenon of self-stigma. Regarding this last phenomenon, the model suggested by Corrigan (2006) includes the following stages: awareness of public stereotypes, agreement with the respective stereotypes at a personal level, application of the stereotypes to oneself, and negative consequences on the individual domain, such as reduced self-esteem [6,7].

When more closely analysed, public or social stigma refers to the perception of individuals by others, who may regard them as weak, unreliable, or unfit to perform military duties if they seek access to mental health services [1]. The information regarding mental disorders is usually gathered from mass media, which may detrimentally model the attitudes and judgments of individuals towards this type of pathology [1]. Mass media may enhance the level of stigmatization in this field by providing narrowly focused reports on dramatic cases of military personnel who kill themselves or harm others, therefore consolidating cultural stereotypes on psychiatric patients as being dangerous or, at least, unpredictable [1,8]. According to an analysis of mental health images in the printed media in three Central European countries, more than 50% of the retrieved articles contained negative statements reflecting stigma towards persons with psychiatric disorders [8].

In the case of military personnel, the presumed vulnerability attributed to those receiving psychiatric care stands in direct contradiction to the narrative of mental resilience and the endurance of hardship that, in the collective mindset, is strongly associated with this environment [2]. Furthermore, distinctive features of military peer culture frame mental illness as a potential threat to operational stability and team safety [2]. Unit leaders may, whether intentionally or unintentionally, promote the avoidance of psychiatric care, thereby reinforcing stigmatisation [2]. Stigmatizing conceptions may erroneously link the presence of a mental disorder in military personnel with incompetence, dangerous behaviors, disobedience, or lack of discipline [9]. Misconceptions about mental health that circulate within military environments can further discourage service members from engaging with psychologists and psychiatrists. Even in those individuals who are undergoing psychiatric treatment, stigma may lead to its premature discontinuation, and is endorsed by service members as a primary reason for drop-out [9,10].

Self-stigma is based on the internalisation of public stigma, thus leading individuals to consider themselves as less valuable due to mental health changes, even those symptoms placed in the minor register, such as anxiety, insomnia, or fatigue. The individuals tend to compare themselves with colleagues who are healthy and erroneously equate psychological disturbances with personal weakness or moral failure. A connected feature is the tendency to self-blame for their inability to maintain optimal mental functioning at all times [1,11,12]. As a consequence, self-esteem and self-efficacy are lower, and the intention to seek help may also be hindered by this misconception [11,12]. Examples of self-stigma misconceptions are "I am weak because I don't feel well", "I am a burden to my fellow soldiers", or "The diagnosis of PTSD (posttraumatic stress disorder) means I am crazy", which leads to poor effort invested in received treatment, poor self-esteem and self-efficacy, and denial of symptoms [11].

The latency for mental health services accessed by military personnel may vary from years to decades, according to several authors, due to internalised stigma [13]. Even after discharge from the service, ex-military personnel may have difficulties in motivating themselves to consult with a psychologist or psychiatrist due to the negative influence of self-stigmatisation [13].

The structured evaluation of this phenomenon can be conducted by the administration of the Self-Stigma of Mental Illness Scale (SSMIS), which has been developed by Corrigan et al. (2006) and includes references to a three-level model, i.e., stereotype agreement, self-occurrence, and self-esteem decrement [6]. Another instrument was created by Skopp et al. (2012), i.e., the Military Stigma Scale (MSS), which is a 26-item instrument, designed to measure both the public and the self-stigma, and the scale

demonstrated good internal consistency; soldiers who had been evaluated by a mental health service scored lower in self-stigma than those who had not [12].

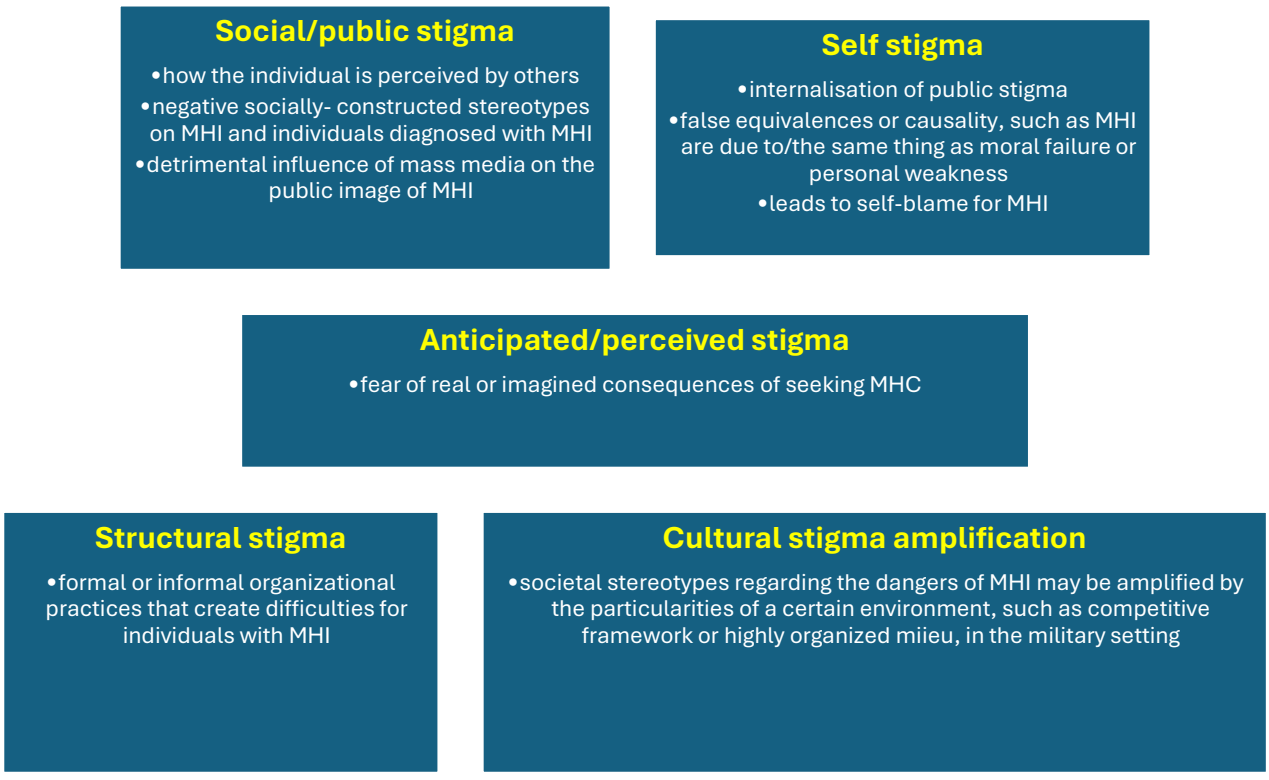
Perceived/anticipated stigma refers to the fear of real or imagined consequences of seeking mental health care, a phenomenon that has also been explored in the military environment. This phenomenon is related to different disadvantages that are anticipated, such as the loss of security clearance, missed career opportunities, delayed promotions, problems with the deployment eligibility or weapon handling clearance, etc. [14]. Military personnel may avoid mental health services for fear of not being registered in medical records and prefer informal, off-base support, sometimes of a doubtful quality, that delays the formal treatment [14,15]. According to a study that explored anticipated stigma in the US, UK, Australian, New Zealand, and Canadian militaries, in the re-deployment or immediate post-deployment period, similar patterns of reported stigma and barriers to care across the five nations were found [15].

Structural stigma is a concept that encompasses the formal and informal organizational practices that create difficulties for people with mental health problems, such as a lack of confidentiality, or command-level discretion in dealing with mental health documents, or unclear policy wording [16-18]. Otherwise put, structural stigma is the result of organizations and systems that deliberately or inadvertently produce and maintain social inequalities for individuals who experience mental health problems [16]. In a military environment, structural stigma is associated with the policies regarding mental health, which can be outdated and thus reinforce stigma, according to the US Department of Defense data [19].

Cultural stigma amplification is a phenomenon that emerges due to the interaction between military culture and broader societal stigma on mental health conditions. Societal stereotypes regarding the dangers of mental illnesses may be amplified in a highly organized, competitive environment, such as the military setting. A strong alignment with military values (duty, selfless service, honor, courage) correlated with stigma and influenced the readiness to access mental health services in military service personnel [9,20].

Taking into account the direct and indirect effects of stigma, with its various dimensions (Fig.1), on the general health of individuals, and the need to see the particularities of this phenomenon in a military setting, an exploration of the available data, followed by suggested directions of interventions, was considered opportune.

Figure 1: Stigma and its dimensions [1,2,8-20]
MHS= mental health stigma, MHI= mental health illness



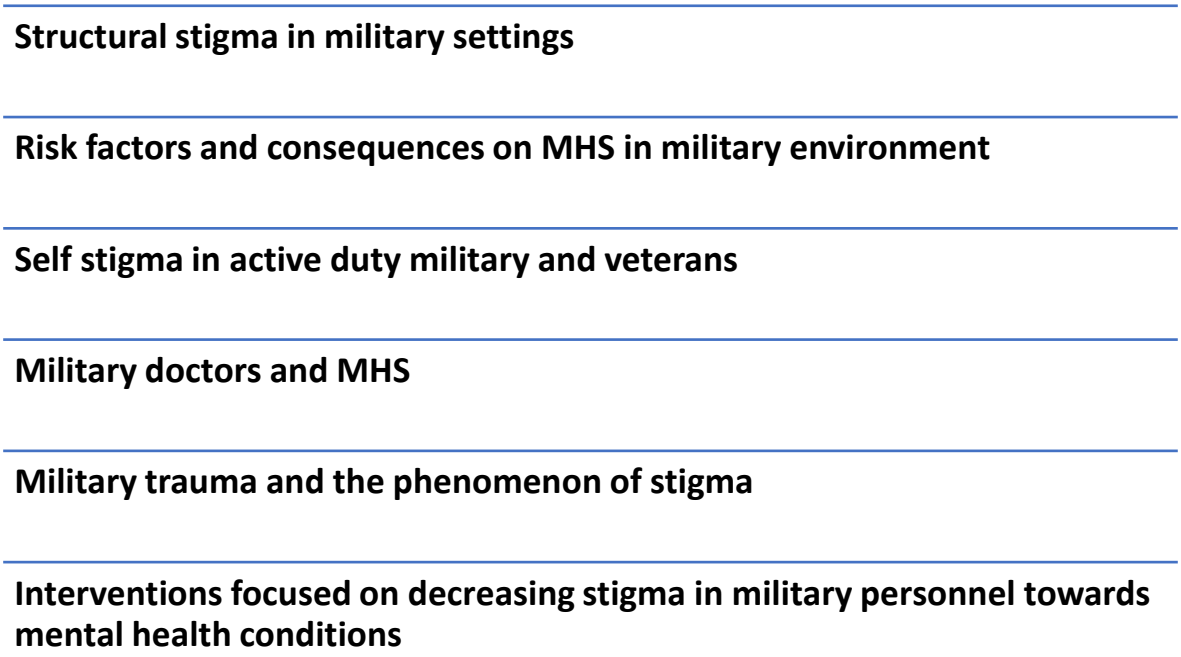
MATERIALS AND METHODS

This conceptual analysis is based on a literature search for primary and secondary reports focused on stigma related to mental health problems in military settings, which included three databases (PubMed, Google Scholar, and Clarivate/Web of Science), without lower temporal limitations for the publishing date (the upper limit was 01 June 2025) or for the language of published sources. The keywords used for this search were "stigma" OR "stigmatisation" AND "mental health" OR " psych*" OR individual diagnoses within the DSM-5 TR classification. The main directions of research in this field were further synthesized and compared with data regarding MHS reported in civilian studies.

RESULTS

The reports identified were distributed into six large categories: (1) structural stigma in military settings, (2) risk factors and consequences of MHS in military environment, (3) self stigma in active duty military and veterans, (4) military doctors and MHS, (5) military sexual trauma and the phenomenon of stigma, and (6) interventions focused on decreasing stigma in military personnel towards mental health conditions (Fig.2).

Figure 2: Directions of research in the field of stigma related to mental health conditions
MHS = mental health stigma



Structural stigma in military settings

According to a RAND (Research And Development) Corporation report,12% of the military policies in the US contained language that was pejorative or presented mental health diagnosis and treatment in a negative way [21]. Based on this RAND document, a lot of service members feared that seeking care would immediately lead to being reported to their commanders, raising concerns about the confidentiality of medical data in military settings [21]. A limitation of the career-impacting policies was recommended by the investigators in this project, in order to ensure such policies are evidence-based and not unnecessarily broad [21]. It was also recommended that mental health be integrated into overall fitness and readiness discussions as a means to mitigate structural stigma, and, in addition, higher-level leadership engagement in the promotion of mental health was suggested to reduce this type of stigma further and foster a supportive culture [21]. Expanding peer support and enhancing access to informal resources, as well as active monitoring and evaluation of mental health, were other potential solutions supported by the RAND report [21].

A study explored the attitudes of commanding and executive officers (N=138 participants) regarding US active duty members who received mental health and related services [22]. The responses to the survey were mainly neutral, and relatively few negative evaluations of service members who received specialised services were identified [22]. This study, focused on institutional culture and

military norms, showed that commanding officers' attitudes strongly influence whether the service members feel safe to seek mental health care, and that leadership endorsement or disapproval can either reinforce stigma or decrease it [22].

In a study of military personnel following deployment (N=2510), baseline leadership and cohesion were both significantly linked to stigma and barriers to care [23]. However, at follow-up (4–6 months later), only cohesion was significantly associated with awareness of and willingness to discuss mental health [23]. Shifts in perceived leadership and cohesion were related considerably to corresponding shifts in stigma and barriers to care [23]. Fear of being seen as weak and being treated differently by leaders was more frequently reported as a reason for stigma and a barrier to care [23]. In order to decrease these phenomena, effective leadership and cohesion building may be the best options, with increasing awareness and promotion of mental health discussions being helpful in the construction of supportive leader behavior [23].

A large-scale investigation of factors related to stigma toward psychiatric illness and mental health services among Japan Ground Self-Defense Force members (N=4754 participants) showed that age, psychiatric evaluations, leadership, and cohesiveness of the group were markedly associated with the two explored phenomena [24]. Therefore, demographic and Army culture factors need to be thoroughly assessed in military settings in order to develop adequate policies focused on the de-stigmatization of psychiatric services [24].

When analysed together, these studies support (1) the importance of addressing military policies as a vehicle of fighting against stigma related to mental health problems, via reformulation of core concepts and procedures in this field, but they also highlighted (2) the significant role of unit leadership in controlling the same phenomenon, through encouragement of unit cohesion and avoidance of negative evaluations of service member who accessed specialised health services.

Public and self-stigma in the military environment

A study of 97 military personnel found that self-stigma fully mediated the link between public stigma and both attitudes toward and intentions to seek behavioral health care [25]. These findings underscore the importance of shaping stigma-prevention policies to specifically target and reduce the self-stigma tied to seeking mental health services [25].

A review of the published studies on mental health service utilisation in military personnel and stigma (n=29 reports) showed that public stigma, self-stigma, and concerns about career consequences significantly reduce willingness to seek care, despite high levels of mental health need [26]. The review also highlighted the importance of targeted stigma-reduction interventions and policy changes to improve access to and utilization of mental health services in military populations, and emphasized patterns and inconsistencies across the literature regarding this topic [26].

According to a systematic review and meta-analysis (n=20 papers), the most endorsed stigma concerns in the military were "My unit leadership might treat me differently" (44.2%) and "I would be seen as weak" (42.9%) [2]. These results reflect the importance of the intricacy of social and internalised stigma, and the possible barrier to adequate mental health care raised by such phenomena.

In a study that investigated the influence of various stigma perceptions in therapy seeking and discontinuation among active-duty personnel (N=1324 participants), who were screened positive for a mental health problem, high scores on four stigma perceptions were recorded, i.e., perceived stigma to career, perceived stigma of differential treatment (i.e., the concern that others will treat them differently), self-stigma from seeking treatment (i.e., internalised negative beliefs about oneself for having sought help) and stigmatizing perceptions of soldiers who seek treatment (i.e., related to peers who are in need of treatment) [10]. When each of these perceptions was considered individually, all of them were associated with a reduced likelihood of seeking mental health treatment, but only three of them were related to the risk of treatment dropout, i.e., perceived stigma to career, perceived stigma of differential treatment, and self-stigma [10].

A study that explored the relationship between self and public stigma, on one side, and the attitudes/intentions towards seeking professional mental help in the military environment, on the other, included 442 students of the military academies in Greece, and showed that few participants reported willingness to access professional help, even in cases of suicidal ideation [27]. Many cadets valued independence and equated medical help-seeking to weakness; also, self-stigma and public stigma were connected with each other [27]. In a military environment, high self-esteem may consolidate the perspectives of self-reliance and stigma, decreasing the chances of accessing professional health services [27]. This study did not find any differences by gender or service branch regarding stigma or attitudes toward mental health services [27].

In conclusion, there is evidence that supports the interdependence of public and self-stigma associated with mental health problems in the military environment, which indicates the need to develop strategies focused on both dimensions. Also, these studies showed several factors that contribute to the perpetuation of self and public stigma, such as concerns about the negative impact of a psychiatric diagnosis on career, thus indicating the sensitive domains where interventions are needed.

Risk factors and consequences of mental health care stigma

A study that recruited 956 US National Guard military personnel confirmed the importance of exploring barriers to care and stigma in this population, because mild, moderate, and high stigma/barriers were highly present (30%, 20%, and 20%, respectively) [28]. The group with high stigma levels reported skepticism toward the mental health care system, strong career-related concerns, significant self-stigma, and major worries about leadership attitudes regarding mental disorders [28]. These individuals also exhibited higher rates of psychological distress, suicidal thoughts and behaviors, and mental health care utilization [28].

Another study found that both Canadian military personnel (N=1900 participants) and civilians (N=2960 participants) experience MHS and stigma related to physical diseases, with an association between stigma and poorer mental health outcomes, including psychological distress and suicidal ideation [29]. The authors of that study concluded that reducing stigma requires broad, systemic approaches that extend beyond the military context, and that elements of the military culture (such as the accent placed on toughness, strict fitness requirements) and the physical demands of the profession could explain a higher stigma in the military vs. civilian setting [29].

The relationship between stigmatisation associated with mental health conditions and help-seeking was investigated in a large study (N=1636 UK Armed Forces personnel) that evaluated the same participants immediately after deployment and six months later [30]. Stigmatising beliefs were associated with the reports of possible mental health disorder or harmful alcohol use after deployment, and the degree of stigma was related to changes in mental health symptoms severity [30]. Recovered cases experienced lower levels of stigmatization at a significant level, and new onset cases had significantly higher levels of the same parameter, when compared to those who never presented probable mental health problems [30]. Therefore, the stigma appears to be a dynamic phenomenon that fluctuates depending on the frequency and severity of psychopathological symptoms [30].

„Potential loss of personal military credibility and trust" (PL) and „negative perceptions of mental health services and barriers to help seeking" (NL) were the key components of the stigma/barriers to care phenomenon in a survey study that included 3405 UK military personnel during their deployment in Iraq and Afghanistan [31]. These components were associated with systematically assessed and subjective mental health, medical appointments and admission to hospital (for PL), and only with subjective and objective evaluations of mental health (NL) [31].

In a large survey-based study (N=23101 UK Armed Forces personnel deployed to Afghanistan and Iraq), stigma (including the fear of being treated differently by commanders and loss of trust among peers) was more important than the perceived barriers to care [32,33]. The barriers to reporting stigma were significantly greater during deployment than post-deployment, but anti-stigma campaigns may have resulted in a decrease in the time of this phenomenon post-deployment [32]. Male personnel, reporters of higher PTSD severity and greater combat exposure were significantly more frequently associated with stigma/barriers to care [33].

A study that enrolled Taiwanese military academy students (N=898) from six educational facilities evaluated the relationship between social support and depression [34]. The results of this study reflected the complex dynamics of social support and depression in military contexts, especially for females, who present even more elaborated relationships between the two variables [34]. The same cadets were evaluated three consecutive years, and the data showed that, over time, for female students, the depression does not erode their perception of social support as much as it does in male cadets [34]. The study showed that among cadets, if stigma is lower, they might feel safer acknowledging distress and benefiting from adequate support [34]. Also, when depression is present, and, as the study showed, it is associated with lower social support, cadets may be avoided, pitied, or treated differently, leading to less assistance, with male cadets being especially exposed to this treatment [34].

Iraq and Afghanistan veterans (N=305) presenting symptoms of depression, PTSD, or alcohol abuse received adequate treatment, especially if they were women (OR=4.82) and if they had more severe symptoms of PTSD and depression (OR=1.03 and 1.06, respectively) [35]. Interestingly, perceived barriers to care were not correlated in this study with adequate treatment utilisation [35]. Multiple explanations for this apparent contradiction are possible: barriers may affect timing, rather than eventual use, thus being a gradual phenomenon rather than a yes/no situation; when the level of distress is high, veterans may override barriers to care; there is a relatively small cohort and the methodology used (telephone survey data) has limited power to detect associations.

Members of US infantry units deployed to Iraq (N=2530) or Afghanistan (N=3671) were evaluated pre- and post-deployment, and the outcomes assessed were major depression, generalized anxiety, and PTSD symptoms [14]. Of those who had positive responses for a mental disorder, 23-40% were interested in seeking mental health specialists' help, which means a quite high proportion, between one quarter and a third of all cases [14]. Positive responses to a mental disorder were associated with more frequent concerns about possible stigmatization and other barriers to seeking mental health care, vs. those who did not acknowledge symptoms of mental disorders [14].

In a large UK military health study (N=821 participants), the most common barriers to care are related to the anticipated public stigma due to consulting mental health specialists, as well as to practical issues such as scheduling an appointment or having time off for treatment [36]. Interestingly, such barriers did not disappear after discharge from active duty, so that veterans added other obstacles to these, for example, a lack of information about mental health services and concerns about the civilian employers who would blame

them for their problems [36]. Individuals with mental health illnesses reported significantly more barriers to care than those without a precise diagnosis [36].

A qualitative study exploring the prevention of suicidal behavior among British Army personnel (N=21 service providers and 10 soldiers) showed that stigmatisation of mental illness in the Army may interfere with accessing mental health services in those with suicidal ideation [37]. Soldiers were trying to access support resources outside the Army and consulted commanding officers rather than healthcare professionals for solving their problems [37]. Helplines or independent sources of confidential advice and support were not mentioned by soldiers or service providers as relevant [37].

A review of 15 reports evaluated the mental health-related beliefs in active duty military personnel and veterans as barriers to service use, identified a lack of attention to the association between the two explored variables, a limited focus on personal beliefs about mental illness and mental health treatment, and the questionable methodology used in research focused on this topic [38].

A survey-based study of 4496 military personnel from the British Armed Forces identified a lack of trust in the healthcare system and perceptions of low-quality healthcare, but also a sense that organizational support for workplace and family life is absent [39]. Lack of confidentiality, fear of stigmatisation, and worries that the interaction with mental health specialists would endanger career prospects were highlighted by respondents, who admitted they would not honestly answer some items in the questionnaire [39]. Also, many respondents admitted they seek, when needed, medical help outside of the Armed Forces [39].

British soldiers who required a formal mental health assessment (N=317 participants) presented ≥2 predisposing factors, mainly family conflicts, relationship problems, and general military stress [40]. A significant proportion of this sample required mental health evaluation as a result of their wish to leave the Army, and admitted to self-harming ideology, with female soldiers being overrepresented [40]. Stigmatisation in this context was not related to social isolation, as the participants did not acknowledge feelings of isolation [40].

In a study investigating common reasons for psychiatric treatment dropout, 57 out of the 260 soldiers who had sought specialised help reported premature discontinuation of therapy [41]. Career-related stigma (concern that seeking treatment would harm one's military professional prospects) and differential-treatment stigma (fear of being treated differently by others) were both associated with an increased likelihood of dropping out of the mental health treatment in this study [41].

A study that explored the role of stigma and barriers to care in mental health seeking among British Army personnel (N=484 non-deployed participants) showed that 40% of the symptomatic personnel did not seek help, with more than 70% of alcohol misusers avoiding mental health services [42]. Also, more than 80% of probable mental health cases believed that for accessing specialised services, courage or strength is required [42]. Perceptions of possible negative career or social outcomes, along with one's current mental health status, can affect the decision to seek support [42].

In a survey study that consisted of structured telephone interviews with 1432 UK service personnel and veterans who reported recent mental ill health in the last three years, those presenting with criteria for probable common mental disorders and PTSD were significantly more likely to report concerns about perceived and internalized stigma and barriers to care compared to participants without a probable mental disorder [43]. Individuals with probable PTSD reported more stigma-related concerns and barriers to care vs. those with likely common mental disorders and alcohol misuse, although not at a statistically significant level [43].

All these studies create a framework for better understanding the factors that contribute to the perpetuation of stigmatisation related to mental health problems in military settings, and represent the directions of interventions for those interested in designing strategies to alleviate the weight of this stigma and its negative consequences. From the reviewed studies, the most relevant contributors to stigma are a skeptical approach toward the mental health care system, strong career-related concerns, worries about leadership attitudes toward mental illness, the accent placed on toughness and strict fitness requirements, potential loss of personal military credibility and trust of peers if psychiatric services were accessed, severe PTSD symptoms and greater combat exposure, lack of information about mental health services in veterans, and concerns of the same population about the civilian employers who would blame them for their mental problems. Regarding the consequences of stigma on individual health, the risk of early treatment discontinuation, unfavorable evolution of symptoms, and failure to access military medical resources were identified.

Military doctors and mental health stigmatisation

This topic is important due to the fact that military doctors support multiple sources of stress, having to face the need to ensure confidentiality of their patients, but also to help them in the most adequate ways, and to assist them in avoiding the risk of stigmatisation. A study that explored the attitudes towards mental health, self-stigma, psychological distress, and help-seeking among UK Armed Forces doctors (N=678 participants) vs. active duty and ex-military personnel (N=1448) showed that military doctors reported fewer mental disorder symptoms than comparison groups [44]. They also reported higher rates of stigmatizing beliefs, negative attitudes to mental healthcare, desire to self-manage, and tendency to self-stigmatisation, when compared to each of the control groups [44]. The potential negative effects and peer perceptions about receiving a mental disorder diagnosis were the main

topic of concern for military doctors [44]. Although alcohol use disorder and mental health problems were significantly reported by the study group, these participants were less likely to seek help than controls [44].

In conclusion, although the topic is interesting and certainly worthy of further exploration, the current data available in the literature is insufficient to formulate recommendations for this sub-population. However, based on limited data of low quality, the risk of stigmatisation is higher in military doctors than in control populations, suggesting a possible contribution of both social and internalised stigma.

Military sexual trauma and the phenomenon of stigma

The sensitive topic of military sexual trauma has been approached by several studies, mainly conducted in the US. The prevalence of this trauma and associated mental and physical health consequences varies largely depending on the method of assessment, definition of the phenomenon, and study sampling method [45]. A literature review found age, enlisted rank, hostile home life environment, and previous assault history as significant risk factors for military sexual trauma [45]. Increased rate of depression and alcohol abuse, significantly higher odds of meeting criteria for PTSD, but also an increased number of current physical symptoms, impaired health status, and more chronic health problems have all been associated with this type of trauma [45].

A survey-based study (N=22 telephone interviews) included servicewomen deployed overseas, and its results supported the existence of several important contributing factors to this phenomenon: deployment dynamics, military culture, and lack of consequence for perpetrators [46]. Stigma, concerns about confidentiality, and fear of negative reactions and blame from peers and supervisors can explain the low rate of reporting [46]. Also, barriers to care seeking were similar and referred to confidentiality concerns and stigma [46].

A large study, the 2019-2020 US National Health and Resilience in Veterans Study (N=4069 participants), concluded that female veterans reported substantially higher rates of military sexual trauma (44%); male veterans with this type of trauma had a three-fold increased odds of reporting later suicidal intent, and two- to three-fold higher odds of screening positive for current PTSD, depression, and lifetime PTSD; female veterans with sexual trauma had five fold greater odds for current PTSD, two fold greater odds for engaging in mental health treatment, and lower scores on psychosocial functioning, but higher scores on somatic symptoms [47]. An Independent Review Commission on Sexual Assault in the Military concluded, in 2021, that women and those with lower societal and institutional power, meaning lower rank, are more vulnerable to military sexual trauma [48]. The same Commission reported that sexual trauma survivors have, in many cases, significant and enduring consequences on individual mental and physical health [48]. Experiences of interpersonal betrayal in a military environment may be cumulated with perceptions of institutional betrayal, such as fear of reprisal or ostracism [48]. PTSD was the most frequently reported, and it may be associated with major depression, anxiety, eating disorders, substance use disorders, and increased risk of suicide [48]. From the physical health perspective, higher chronic disease burden and impaired reproductive health and sexual functioning have been observed [48].

Among veteran men who experienced military sexual trauma (N=20) but did not receive trauma-focused mental health care, the primary barriers to accessing adequate care were identified as stigma, limited knowledge, and gender-related factors [49]. Psychoeducation and outreach interventions have been suggested as potential interventions for this population [49].

A study that enrolled 911 women veterans living in the US revealed that military sexual trauma, but not exposure to combat, was correlated with lower infant birth weight, a slight decrease in the probability of having a full-term birth, and an increased likelihood of developing postpartum depression or anxiety (N=1752 unique pregnancies) [50]. Therefore, screening for military sexual trauma during pregnancy could be useful for configuring the prognosis of that pregnancy [50].

A retrospective review of disability reports and electronic medical records (N=322 active-duty women diagnosed and treated for PTSD) showed that military sexual trauma was the most frequent index trauma in the group of women requiring medical disability evaluation (OR=2.6) [51]. A significantly higher number of mental health visits for PTSD and more frequent chronic pain history were present in the study group than in the controls [51]. In this line of research, military sexual trauma significantly increases the risk of PTSD, and reporting both sexual traumas and PTSD in the military environment can be associated with public and self-stigma. The co-occurrence of military sexual trauma, chronic pain, and extensive mental health care in this population may represent higher challenges due to stronger internal barriers to seeking help in the specified environment.

In conclusion, the need to find adequate strategies for fighting stigma in active duty and veterans who have suffered sexual trauma can not be overemphasized, due to the negative impact of these events on professional life, mental health, and overall quality of life. The risk of PTSD is correlated in this population with self-stigma, but also with public stigma, complicating the design of interventions targeting this population.

Interventions focused on decreasing stigma in military personnel towards mental health conditions

Interventions aimed at reducing the stigma of mental health conditions need to incorporate both strategies for fighting societal stigma and self-stigma, due to the complex nature of these two phenomena and their interdependence [52]. For example, in a military setting, the stigma associated with PTSD could be mitigated by psychoeducation about the causes of and available treatment options for this

disorder [52]. Also, unit-level interventions that include contact with soldiers who have been successfully treated for PTSD, who may explain to others in that unit their experiences, in a supportive environment, may be helpful [52]. According to the framework of this method, fellow unit members could ask soldiers with PTSD questions about various aspects of the problem, which will lead to a better understanding of the mental health difficulties and of the mental health services' role [52]. Another method involves training the senior leaders in identifying signs of mental health problems and, thus, making them part of the psychoeducation programs [52].

General recommendations to decrease self-stigma in the military environment, related to mental health problems, are assurance of data anonymity, the use of non-stigmatizing language, and the enhancement of peer-to-peer and stigma-reduction programs development [53].

Offering regular mental health care evaluations as part of the normative, periodic controls may be a helpful de-stigmatising approach [1,14]. Psychoeducation of soldiers about their reactions to stress and assurance about confidentiality of provided data in the medical context could also be a beneficial measure in de-stigmatisation [11].

The empowerment approach is based on the idea that stigmatized individuals are not passive victims of prejudice and discrimination, but active social agents, who can identify positive roles attributed to their group (e.g., solidarity, creativity, adaptability), thus fostering resilience by acknowledging their belonging to a stigmatized group [54]. The stimulation of critical awareness is another technique of empowerment, focused on understanding how stigma operates at a social level and by teaching individuals on how to differentiate external prejudice from internalized stigma, therefore decreasing self-blaming [54]. Agency and choice are favoured within this approach, and this implies a shift from "What is happening to me?" to "What can I do with this situation?" [54]. Cultivation of personal strengths and constructing social support networks may also be helpful from this perspective [54].

Applied in a military setting, the empowerment method could involve reframing stigma as a source of strength by encouraging open discussion of mental health challenges and by reframing these individuals as resilient, not weak. For example, decorated veterans who sought care from mental health services are examples of responsibility and strength. This type of intervention would include framing therapy as a type of "mental health training" or a way to preserve operational readiness. Peer-led support groups may reinforce the idea that caring for each other includes physical safety and mental well-being, while the cultivation of personal strengths refers to the framing of psychological help as an extension of the soldiers' ethos, as the mind is in itself a powerful weapon that should be kept strong.

Psychoeducation refers to the presentation during the initial sessions of training of videos about myths regarding mental illness, contrasting with the scientific data about the pathogenesis and the recovery from such disorders [11]. Psychiatrists may be invited to participate in platoon meetings and answer questions about mental illness and available, efficient treatment [11]. In the same line of intervention, leaders discussing their ways of coping with PTSD after returning from a tour of duty with new recruits may be useful [11]. Formal media campaigns against stigma have been available in the US since 1999, and a National Mental Health Awareness Campaign was formed [11]. Public service announcements were used in this context to fight against stereotypes about mental illness and replace them with factual information [11]. It is expected that such interventions, applied since the earlier stages of military training, may be beneficial because they would prepare the soldiers before deployment or exposure to combat-related stress [11]. If they were informed by senior officers and by mental health professionals about the identification of symptoms and available evidence-based treatment and military resources, they could become less vulnerable to cultural stereotypes and stigmatisation, if confronted with such health problems [11].

Cognitive-behavioral therapies (CBT) against stigma represent an important therapeutic resource that has been explored for improving attitudes toward mental health treatment and decreasing stigma [55]. When applied in the military setting, for active duty soldiers with PTSD (N=162 participants), exposure therapy (ten sessions) led to significant improvements vs. waitlist in readiness to talk about mental health problems and concerns about social stigma regarding mental health problems [55]. The study concluded that a decrease in the severity of PTSD manifestations and favourable changes in perspectives towards mental health therapy independently predict later reductions in stigma [55].

Technology-based treatments in PTSD may be valuable in mitigating MHS in the military setting. The DE-STRESS (Delivery of Self Training and Education for Stressful Situations) model was constructed by the US Department of Defense and was based on a method that could be implemented in a primary care environment [56]. In order to detect early and approach the stress reactions in due time, Web-based training is provided, and computer-based interventions are made available for military personnel [56]. Each patient is monitored on a daily basis by a trained therapist, so that the recovery process can be kept on track, but the main benefit of this approach is the avoidance of any perceived stigma associated with usual consultations with a mental health specialist [56]. The DE-STRESS program starts with a confidential presentation of the basic concepts in therapy and stress management, and after that, they have daily awareness sessions and, as needed, supplementary sessions with a therapist [56]. This program includes training of diaphragmatic breathing, progressive muscle relaxation, and basic cognitive restructuring [56].

Creative art therapy has also been explored in cases of military personnel for a variety of indications. Creative Forces®: NEA Military Healing Arts Network is a program of the National Endowment for the Arts, developed in collaboration with the US Departments of

Defense and Veterans Affairs [57]. Its mission, as posted on the initiatives webpage, is to enhance the health, quality of life, and overall well-being of service members, veterans, and their families and caregivers who have been affected by trauma [57]. Creative art therapies are used in this program not only for clinical symptoms of PTSD and traumatic brain injury, but also to reduce stigma associated with these pathologies, isolation, and related psychological health problems in veterans [57].

A case analysis of a 47-year-old service member's trauma processing through art and narrative therapy demonstrated good results by expanding the understanding of treatment progress recorded in journal notes, stimulating imagery, and changing linguistic indices of trauma processing [58]. In this case, although a transient increase in the severity of PTSD symptoms was observed, improvements in coping strategies have been reported, and the patient returned to whole military duty following treatment [58].

Veterans diagnosed with PTSD (N=11) received individual art therapy and cognitive processing therapy (CPT), or CPT alone, and the results were positive in both groups, according to the PTSD Checklist-Military Version and Beck Depression Inventory-II scores [59]. Although no difference between the two interventions was observed when scores were analysed, the addition of art therapy may still be helpful in improving trauma processing by increasing access to emotion, healthy distancing, and enhanced trauma recall [59]. Although stigma was not assessed in this study, the impact of art therapy in combination with CPT in veterans with PTSD may contribute to decreasing the stigma of traditional psychotherapy used alone, making it more acceptable. Art therapy also offers a less threatening, indirect channel of communicating emotions and thus avoids the fear of being judged for showing vulnerability, an important aspect of perpetuating stigma in the military environment.

Interpersonal therapy was explored in multiple trials for PTSD, and in an open study that enrolled 50 US military service members, veterans and family members, this type of therapy was administered during 14 sessions [60]. Patients receiving interpersonal therapy showed a decrease in PTSD and depressive symptoms severity to a significant level [60]. In relation to MHS in military contexts, the collaborative, relationship-focused nature of interpersonal therapy may help normalize therapeutic engagement in a less stigmatized framework.

Family therapy could be introduced as a tool in the management of patients within a military setting, to decrease MHS [61]. The participation of veterans' families in the treatment of veterans with PTSD is desired by both patients and their caregivers, and the potential of improving the outcomes is essential [61]. A study based on qualitative interviews (N=31 providers at 10 US Veterans Health Administration facilities) confirmed that clinicians offered at least occasionally family-inclusive sessions and highlighted the negative impact of PTSD symptoms on the patients' familial relationships [61]. Therefore, by integrating trusted relatives into therapy, treatment becomes normalized and less threatening, helping to reduce both self-stigma and fear of external judgment, as noted by VHA clinicians who observed the positive impact of family participation on veterans' willingness to seek and sustain treatment [61].

The Families OverComing Under Stress (FOCUS) program provides resiliency training to enhance family psychological health in US military families impacted by combat- and deployment-associated stress [62]. Using a family narrative framework, FOCUS delivers a tailored intervention that integrates core components such as psychoeducation, emotional regulation strategies, goal setting and problem-solving skills, techniques for managing traumatic stress reminders, and the enhancement of family communication [63]. According to a secondary analysis of data in this program (N=488 unique families at baseline and 331 families pre- and post-intervention), a high level of satisfaction with this intervention was reported by families, and a positive impact on parent-child indicators was observed [63]. At baseline, the evaluations indicated higher psychological distress for service members, civilian parents, and children vs. community norms, but significant improvements were observed across all measures for all the categories of population included, i.e., Brief Symptom Inventory (BSI) for self-reports on psychological distress, McMaster Family Assessment Device (FAD) for family functioning, and Strengths and Difficulties Questionnaire (SDQ) for assessment of children mental health problems [62]. Another secondary analysis of the data in the FOCUS program (N=2615 unique families) reported that parental anxiety and depressive symptoms were significantly reduced postintervention and the positive effect was preserved at two subsequent follow-up assessments [64].

Therefore, the FOCUS program offers concrete evidence that addressing mental health proactively leads to better outcomes for the whole family, countering the stigma of treatment inefficacy or the lack of trust in the ability of a treatment to change the severity of psychological status. Also, because the intervention is focused on the family system, it avoids framing distress as a personal flaw, thus avoiding internal stigma; the focus of attention is shifted from individual stress to shared stressors and collective solutions [62].

Participants in a survey study (N=18 US military veterans and 13 family members) viewed engagement in therapy as a family-level decision undertaken with the expectation that it would enhance overall family life [65]. Veterans were often motivated to seek treatment in order to preserve their relationships with loved ones, with family members playing a central role by encouraging engagement in care [65]. In particular, relatives who understood PTSD as a treatable condition rather than a fixed aspect of personality conveyed more positive expectations about the effectiveness of therapy, while veterans embedded in social networks that included others with military or trauma-related experiences reported greater understanding and more supportive norms surrounding treatment [65]. Because PTSD profoundly affects the family system, relatives are frequently involved in the therapeutic process, and their early engagement -at a level aligned with both the patient's and family's preferences- may foster positive subjective norms that enhance veterans' perceptions of the value of treatment [65].

Social policies offer the possibility of accessing a large population using targeted interventions. Potential objectives for this type of intervention are encouraging early help-seeking treatment and sustained engagement, improving measurement and conceptual clarity on stigma types, focusing on broader barriers, including self-stigma and treatment attitudes, and exploring the potential role of social networks in helping individuals overcome stigma-related barriers to seeking care [2].

The previously mentioned FOCUS program demonstrates that prevention programs can and should be integrated into military systems, helping to normalize mental health support as part of standard family readiness services [62,64].

Fighting structural stigma in a military setting involves policy reforms with the strengthening of confidentiality and clear guidelines that avoid stigmatisation related to mental health problems [19]. Leadership training that openly supports mental health care and normalizes mental health as a component of overall health, encouraging cultural and educational interventions, can all be helpful in this domain. An analysis that explored the level of incorporated changes in the vulnerability factors related to structural stigma in the military environment, initially identified by the US Department of Defence, showed that in almost 59% of the 129 mental health policies with stigmatizing language that were reissued, language changes were implemented [9]. These results indicate that a collaborative effort at the institutional level could be very beneficial to identify and modify potentially stigmatizing language in official documents in the military setting [9]. Furthermore, it is expected that such changes could lead to a substantial reduction in problematic policies in military services and prevent the appearance of stigma language in newly initiated documents [9].

In 2011, the Department of Defense issued a command notification policy that established a presumption of confidentiality for service members who voluntarily pursue mental health care or substance use education [66]. The intent was to reduce stigma, with command notification required only under clearly defined circumstances -such as risk of harm to self or others, mission-critical concerns, inpatient admission, entry into substance use treatment, or a command-directed evaluation [66]. The policy seeks to safeguard individual privacy while ensuring operational readiness, outlining specific responsibilities for both healthcare providers and commanders in managing necessary disclosures [66].

Mental health should be acknowledged as an essential element of overall well-being, with the traditional binary view of service members as either “ready” or “unfit/ill” giving way to a continuum of readiness and broader access to diverse support personnel [67]. The US Army has addressed the issue by training leaders to promote a supportive culture and reduce stigma, expanding access to psychological health services beyond duty hours, and creating educational resources designed to challenge stigma [67]. Combat Operational Stress Control programs integrate mental health and substance use treatment providers into each unit’s fitness and preventive care services [67].

Policy modifications that could further reduce stigma in the military setting are related to the creation of an organizational framework allowing service members to be able to seek professional help during the duty day, or not to automatically equate seeking mental health support with losing their job or security clearances [52].

Military members and veterans who were confronted with destructive leadership had more reports of internalized MHS and a lower likelihood of accessing mental health services, according to a study that enrolled 232 participants [68]. Supportive leadership, on the contrary, was associated with a greater likelihood of seeking help from specialised services, and was indirectly related to lower stigma [68].

Overall, multiple interventions are available for decreasing the impact of stigma on the accessibility of mental health services, starting from the general, organizational recommendations, to the individual level (psychoeducation, psychotherapy), and up to the social policies. Although their effects on reducing stigma were not systematically assessed, there is hope that essential programs such as FOCUS will be replicated and their long-term consequences will be evaluated.

DISCUSSION

The stigma and barriers to care associated with mental health services in civilian society are extensively researched topics in the literature, with multiple warning signs being raised by researchers [4,69,70]. These phenomena have a significant impact on the patients' overall quality of life, functionality, evolution, prognosis, risk of complications, and life expectancy; therefore, increasing societal awareness about the need to fight against stigmatization-related negative consequences is essential. Aspects like early detection of stress disorders, depressive episodes, addictive disorders, or psychotic disorders, timely initiation of adequate treatment for such mental illnesses, as well as correct monitoring of the mental health in vulnerable populations, require addressing social, structural, and internalized stigma [71-75]. The approached phenomena in this article are by no means limited to psychiatric disorders, because organic pathologies may, as well, be connected to stigma, with AIDS, cancer, Down's syndrome, diabetes, obesity, intestinal disorders, epilepsy, and SARS-CoV-2 infection being among the most cited in the literature [76-78]. Monitoring the treatment effects also requires a continuous involvement of the patient in the therapeutic alliance, which can not be realized without the patient's distancing from the stigma associated with chronic treatments [79-81]. These considerations are equally valid for civilian and military populations, with some particularities related to the structured environment, professional models, and limitations to the individual liberties that are co-substantial with the military environment.

Ethical challenges related to mental health care in the active-duty personnel may be connected to the fear of stigmatization at multiple levels: confidentiality of data regarding mental health vs. command responsibility, the dual responsibility of mental health professional for their patients and for the institution, informed consent and mandatory health evaluations, etc. Public stigma, structural stigma, and self-stigma have intricated relationships in this specific environment that reduce help-seeking, delay treatment, and increase the risk of complications, thus reducing the combat readiness in active personnel. Fear of disclosure due to confidentiality limits, policies requiring command notification, and dual loyalty are points of intersection between medical ethics, military ethos, and MHS [36,52,82,83].

The reports reviewed in this article allow for delimitation of six domains where strategies for reducing MHS in the military environment may be applied. The first of these domains is represented by the need to carefully address the structural stigma in such settings, especially that related to the most frequently met pathologies, like PTSD, depression, substance use disorders, and suicidal tendencies [83]. Mental health problems are not isolated phenomena, since, for example, the reported rates of substance use disorders in veterans are over 15% for alcohol and more than 7% for other drugs, with unmarried individuals and veterans younger than 25 being at higher risk [83]. Deployment, combat, and challenges of reintegrating into civilian life are factors that contribute to the psychiatric disorders previously mentioned [83]. Active-duty service members often face a strong stigma around seeking mental health care, largely due to concerns that doing so could negatively impact their military careers, which delays the psychiatric evaluations and treatment initiation [83]. The discussion about adequately addressing structural stigma is by no means limited to the military environment, because negative health outcomes derived from organizational-based prejudice, discrimination, and marginalization may arise in any setting [84]. Educational approaches that reduce structural stigma have been suggested as potential solutions both in civilian and military populations. For example, structural competency has been advocated as a potential instrument that enhances health professionals' ability to recognize and respond to social and structural determinants that contribute to the maintenance of structural disparities [84].

The second domain of interest identified, based on the literature review, was expanding the understanding of risk factors and consequences of MHS in the military environment. The results of our analysis highlighted the differences between the military and civilian settings, with career-related worries and concerns about how mental illness is perceived by unit leadership and peers being among the most detrimental factors that perpetuate stigma in active-duty personnel. Difficulties in finding adequate information and doubts about the understanding of a psychiatric diagnosis (such as PTSD) by civilian employers are factors for stigmatisation in veterans. All of these factors are, in fact, negative prognosis factors for military personnel diagnosed with psychiatric disorders, due to delays in treatment, treatment discontinuation, and lack of a full engagement in one's treatment. As research in the general population demonstrated, stigmatization arising from misconceptions about mental illness was associated with illness duration, frequency of clinic visits, and diagnosis of psychotic disorders [85]. Disempowerment, reduced self-efficacy, increased psychiatric symptoms, and lower quality of life were consequences of stigma associated with mental illness in the general population [85].

Self-stigma in active duty military and veterans was the third dimension of analysis supported by this research. In the military, self-stigma is perpetuated by a culture that equates strength with the absence of psychological vulnerability, reinforced by leadership's promotion of the ideal soldier as someone free of mental or physical limitations. The solution of promoting personal empowerment as a way to challenge self-stigma has been suggested in civilian, as well as in military settings [86,26]. Other strategies were designed for mitigating the impact of self-stigma on personal health, starting from individual interventions to society-level policies [86].

The fourth domain of analysis was the impact of stigma related to mental health problems in military doctors, a subpopulation confronted with specific characteristics in this setting, based on more complex ethical challenges than in civilians. Stigma is not limited to the patients presenting psychiatric problems, but it extends to healthcare professionals, which complicates the delivery of adequate services [85]. Aspects like overestimation of coercion in mental health services, public ignorance about psychiatric disorders, and oversimplification of psychiatric difficulties all contribute to the extension of stigma on mental health professionals [85].

The fifth domain of interest for the research in the field of stigma is military sexual trauma and the stigmatization that stems from these types of events. In the civilian population, negative self-image, disclosure concerns, and concerns about public attitudes have been associated with stigma related to sexual violence [87]. In a study (N=453 Swedish young adults), 89% of those who reported a history of sexual abuse or intimate partner sexual violence also scored at least one item on a stigma scale [87]. Also, stigma in these cases was associated with more severe symptoms of generalized anxiety, depression, PTSD, greater need for treatment, and shame [87]. In military sexual trauma, there is a double-layered betrayal of trust, at the interpersonal and institutional level, complicating the relationships between social, structural, and self-stigma [55].

Finally, finding the most appropriate interventions focused on decreasing stigma in military personnel towards mental health conditions is an important area of research in the field of MHS. Although only a few therapies have been explicitly explored for decreasing stigma in the military, there is room for hope by looking at research conducted in the field of stigma in the civilian population, encompassing education, mental health literacy campaigns, contact with individuals who have already confronted mental problems, peer services, legislative and policy change, etc. [88,89]. However, specific strategies targeting the military personnel exist, and programs like FOCUS, or individual and group therapy focused on social aspects of the core psychiatric symptoms, as well as interventions for mitigating structural stigma, have already been implemented [19,59,62].

Limitations of the article

There are limitations that have to be listed, with the most important one being the lack of a systematic review on which the conclusions are based; therefore, it is not excluded that relevant sources for the objective of the article might have been missed. Secondly, there is a paucity of data regarding specific dimensions of the analysis, for example, the role of MHS in the activity of military doctors, or the targeted therapeutics for reducing stigma in military personnel. Thirdly, it is important to note that for other potentially relevant dimensions of stigmatisation in military personnel, such as the cultural modelling of stigma or particularities of MHS in ethnic minorities, data have not been identified by this search.

CONCLUSION

Exploring the domain of stigmatization related to mental health problems, with all its dimensions, i.e., social, self, structural, perceived, and cultural stigma, is a necessity in order to preserve the combat readiness, the military personnel morale, and the proper functioning in daily activities of the active-duty military. Among veterans, the interest in more research in the field of MHS is derived from the need to improve the prognosis of patients diagnosed with PTSD, major depression, and other psychiatric disorders that may be difficult to accept, as they contradict the model of strength promoted by the Army. The available data that was reviewed supports the need for better policies that meet both the necessities of the military institutions and the mental health requirements of the personnel, but also for large-scale programs dedicated to psychoeducation, leadership awareness of mental health issues, involvement of families in psychotherapy, offering regular psychiatric evaluations as a way to preserve the readiness for action, and applying the empowering strategies whenever is the case.

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Authors' contribution

Conceptualization, O.V., B.M.P., A.G.M., F.A.A, and O.M.S.; methodology, O.V., CA.C, and F.C.P.; software, O.V.; validation, O.V., C.A.C., D.G.V., F.C.P., O.M.S., F.A.A., and A.G.M.; formal analysis, O.V., A.G.M.; investigation, O.V., A.G.M., F.C.P., F.A.A., and B.M.P.; resources, O.V., O.M.S, and D.G.V.; data curation, O.V.; writing—original draft preparation, O.V.; writing—review and editing, O.V., A.G.M., B.M.P, D.G.V, F.C.P., and O.M.S.; visualization, O.V., C.A.C., F.A.A., and F.C.P.; supervision, O.V. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

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REVIEW

Minimally invasive evaluation of chronic maxillary sinusitis with CBCT

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Abstract: Background: Although CBCT was introduced in dentistry, it has a specific role in rhinology for assessing uncomplicated maxillary sinusitis. CBCT offers valuable information on anatomy and pathology with a low irradiation dose. Methods: We performed a systematic search on PubMed on the use of CBCT in detecting maxillary sinus pathology and the relation between dental lesions and maxillary sinusitis. Results: Specific findings, such as mucosal thickening, retention cysts, or antroliths, have been found to be associated with dental problems. These alterations can be incidental findings during the management plan for patients with dental problems, but can also be the reason that prompts the patient to perform the imaging investigation. Conclusions: The literature on the topic is quite comprehensive and clarifies percentages and the correct use of CBCT. As a minimally invasive procedure, CBCT finds its utility in assessing patients with dental problems, as they are more prone to accepting this fast, pain-free, and non-claustrophobic method. There are several limitations, such as the not-so-large target area and the less-than-average, limited pictures. However, CBCT remains a valuable tool that can be used for patients with suspected sinus problems that require dental treatment to ensure there are no future sinus complications.

Keywords: CBCT (Cone Beam Computed Tomography), maxillary sinusitis, mucosal thickening, dental pathology

INTRODUCTION

CBCT (Cone Beam Computed Tomography) is a radiographic imaging technique used for medical assessment of the hard tissue structures of the face. Although its main use is for dental pathology, it has a specific role in rhinology for the evaluation of chronic sinonasal pathology, mainly in the maxillary sinus. A wide range of chronic sinus lesions may be detected on the CBCT: mucosal thickening, fluid or air-fluid levels, retention cysts, pseudocysts, polyps, tumors, foreign bodies within the maxillary sinus, and bone pathology (like fibrous dysplasia) [1]. Anatomic variation of the maxillary sinus can also be assessed on the CBCT, providing valuable details prior to surgery.

In most cases, the pathology described on the CBCT within the maxillary sinus is incidental, but thorough information can be obtained due to the 3D acquisition of the images. The most frequent maxillary lesions are mucosal thickening (polypoid/non-polypoid) and retention cysts [2, 3, 4]. The entire volume of the maxillary sinus is described, including the natural ostium, accessory ostia (if present), the ostiomeatal complex, the floor and roof of the maxillary sinus, and the relation with the roots of the teeth. The relation between dental (periapical lesions, root contact with the floor of the maxillary sinus, periodontal bone loss) and sinus pathology can be determined on the CBCT. The root contact with the sinus was the only dental pathology associated with lesions within the maxillary sinus [3]. Odontogenic maxillary sinusitis is the most common pathology diagnosed with CBCT; it can be related to specific tooth injuries, especially the upper molars and the first and second premolars, which are in close vicinity to the floor of the sinus [1]. Periapical lesions and periodontal pathology can determine alteration of the respiratory epithelium within the maxillary sinus, but maxillary sinus lesions can appear in the absence of dental pathology [5, 6, 7]. The relation between the sinus lesions and dental lesions has to be assessed from a clinical, endoscopic, and imaging point of view. When maxillary sinus pathology is described on the CBCT, the ENT specialist has to evaluate the predisposing factors of

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obstruction within the nasal fossa (nasal septum deviation, septal spurs, concha bullosa, inferior turbinate hypertrophy, polyps in the nasal fossa or middle meatus). The best way to obtain thorough information is nasal endoscopy, either rigid or flexible.

The incidence of maxillary sinus pathology findings on CBCT is around 50% [1, 5], but there are studies showing 76% incidental sinus pathology findings [6].

Although CT (computed tomography) is the gold standard for imagistic assessment of the paranasal sinuses, and in complicated cases, CT associated with MRI is necessary to assess the site of the disease, the extent of the lesions, and the orbital and cerebral involvement. CBCT has certain benefits for defining uncomplicated sinusitis. One of the advantages of CBCT is the low dose of radiation compared to classic CT [1]. Although there are other low-dose imaging acquisition techniques available, like extremity CBCT and clinical multidetector computed tomography (MDCT), CBCT proved its superiority when addressing maxillary sinus pathology [8]. Another advantage of CBCT is the quality of the images obtained – a 3D assessment of the entire maxillary sinus cavity.

The relation between periodontal disease and mucosal thickening of the maxillary sinus can be investigated with CBCT. There is a direct and significant correlation between the severity of alveolar bone loss and mucosal thickening: the more severe the alveolar bone loss, the thicker the mucosa within the maxillary sinus [9,10]. It must be noted that a thickening of the mucosa less than 2 mm is considered normal [10,11]. The distance between the root apex and the floor of the maxillary sinus is another factor that influences mucosal thickening: the greater the distance, the lower the mucosal thickening [10]. The periodontal disease is considered among the most common causative factors of odontogenic sinusitis [10].

In particular situations, dental implants may contribute to odontogenic sinusitis, especially in cases of migration of the implant to the sinus when maxillary ostium obstruction develops. If alveolar bone resorption is present, then maxillary sinus lifting or bone grafting is recommended [12]. The bone architecture and dimensions prior to implantation are assessed with CBCT. Low bone mass identified on imagistic acquisitions should be taken into consideration when planning implant treatments, especially in patients with endocrine and metabolic disease (osteoporosis, postmenopausal state, diabetes mellitus, Cushing's disease) [13, 14, 15].

Another use of CBCT is the possibility to distinguish odontogenic from non-odontogenic sinusitis, taking into account the dimension of the mucosal thickening (over 2 mm), the location of the sinus pathology (floor of the sinus/ entire sinus), the relation between sinus teeth and floor of the sinus, and the presence/absence of periodontal pathology. Texture analysis using specific contrast and correlation parameters of the CBCT acquisition images can enhance the differentiation between odontogenic and non-odontogenic sinusitis, offering a more precise diagnosis and allowing a better management plan [11].

Anatomic variations of the maxillary sinus can be described on CBCT: from intrasinus septa to accessory ostium and hyper/hypo pneumatization of the maxillary sinus. The presence of an accessory ostium is a favorable factor of chronic maxillary rhinosinusitis due to alteration of mucociliary clearance, and it has to be assessed preoperatively either by CT or CBCT [16,17]. During functional endoscopic sinus surgery, the accessory ostium should be eliminated to restore the clearance of the sinus. Septation within the maxillary sinus can contribute to non-odontogenic maxillary sinusitis and should be addressed surgically if the situation requires [18].

MATERIALS AND METHODS

We performed a systematic search on PubMed on the use of CBCT in detecting maxillary sinus pathology and the relation between dental lesions and maxillary sinusitis. An interrogation was made on specific terms: “cone-beam computed tomography” , “odontogenic sinusitis”, “maxillary sinusitis”, “anatomic variations”, “endoscopic sinus surgery”, “dental lesions”. We included: original comparative studies relevant to CBCT in rhinosinusitis, and studies relevant to the relation between dental and sinus pathology. We excluded papers/studies with non-sinonasal applications of CBCT.

RESULTS

The available literature and studies indicate that CBCT has become a reliable tool in the evaluation of sinonasal pathology. It can be used in cases that are suspected of acute or chronic sinus pathology, or it can reveal incidental findings of chronic asymptomatic conditions. Due to the fact that this type of investigation is routinely used in patients with dental problems, conditions of the maxillary sinus are most often found. However, its use encompasses all sinus pathology, and there is a large variety of alterations that will be revealed.

A thickening of the sinus membrane is one of the most often encountered alterations, and it can be discovered in any sinus, but again, it is more often associated with the maxillary sinus in patients with endodontic conditions. The average thickness in a normal healthy maxillary sinus is about 1.18–1.21 mm [19], while in patients with associated apical conditions, the thickness was about 2.56–2.74 mm [19-22]. Another study emphasized the connection between apical periodontitis and membrane thickening in the maxillary sinus, this condition becoming a rule in patients with severe apical periodontitis, with a percentage as high as 100% [20]. Further studies are consistent with these findings, revealing a likelihood of membrane thickening three times more often in patients with periapical lesions than in healthy patients [22]. A very interesting aspect is the fact that membrane thickening appeared more often, even in

patients that did not have contact between the periapical lesions and the sinus floor, and the presence of root canal treatments did not alter these percentages [21].

Another condition that was associated with membrane thickening on CBCT was periodontal bone loss; in patients with a severe condition, the risk was 4.6 times higher than in those with mild bone loss [23]. Vertical intrabone pockets were also present in association with this imagistic finding, thus showing another risk factor that we have to keep in mind. A very interesting result from the literature showed that in 4 months from extraction, the thickened membrane will reverse to normal.

Mucous retention cysts are also more often related to the maxillary sinus, with a percentage as high as 28.6% [24, 25]. The symptoms, if present, will vary according to the size of the cyst, and the exact location may differ as well, with up to 53.6% in the sinus walls [24, 25]. Due to the fact that CBCT is routinely used in patients with dental problems, these findings may influence the course of treatment. The studies also revealed that patients with periapical lesions, endodontal treatment, or significant bone loss [26] are prone to this pathology.

Antroliths are calcified masses of the maxillary sinus. They can have various shapes and sizes, with a reported maximum of 91 mm [27]. Although the reflex is to remove the antrolith, the studies revealed that its presence does not increase the risk of membrane perforation during dental implant procedures [28].

The reviewed literature also emphasized the role of CBCT in diagnosing intramaxillary foreign bodies. The nature of these foreign bodies is varied, ranging from tooth fragments to implants or complete teeth [29]. Of course, one of the most often encountered foreign bodies is root filling material that reached the maxillary sinus via a perforated root [30]. The studies emphasized a very important aspect, and that is that most patients who developed this condition did not have a CBCT prior to surgery [30]. Screws that are used in dental practice could also migrate into the maxillary sinus, especially if the sinus membrane is thin. Due to its high resolution in assessing bone and structures of similar consistency, CBCT is a valuable tool in evaluating these patients.

DISCUSSION

There is a wide range of problems that may affect the maxillary sinus. In patients requiring dental treatments, we have to thoroughly evaluate the local problems in order to avoid complications. The cases of dental implant failure are often associated with undiagnosed sinonasal problems that will lead to complications and secondary implant problems.

The high cost of such complications and the morbidity of the patient justify the routine use of imaging investigations in order to exclude any state that might lead to such complications. CBCT represents another tool to serve the same purpose, and that of ensuring a complete evaluation of our patients.

However, there are certain advantages of the technology that make it stand out. Aspects such as low exposure to radiation, availability, and cost-efficiency are just some of the advantages provided by this technology. An overweight or claustrophobic patient can also safely undergo the investigation.

Another aspect that must be taken into account is the legal problems that might surface in case of complications. The scan results not only help us provide the best standard of care for our patients with minimum complications, but also provide a reliable evaluation that can be reviewed at any moment.

CONCLUSION

Experience and the available literature indicate that the proper assessment of patients requiring more extensive dental treatment should include an imagistic evaluation prior to treatment initiation. This aspect is even more important for patients requiring dental implants, as they are prone to sinus infection and implant failure if proper drainage is not ensured. CBCT has proven its value in assessing these patients, providing high-quality images with a low-dose exposure to radiation. It is suitable for claustrophobic patients; it is a fast and reliable diagnostic tool.

Its limitations, such as the not-so-large target area and the less-than-average, limited pictures when compared to conventional CT scans, do not alter the accuracy in diagnosing maxillary sinus problems. As shown by the numerous articles describing its use and advantages, this method has become a standard of care, especially for patients undergoing significant dental treatments, allowing an evaluation of the site requiring intervention and revealing any silent conditions that could translate into future complications.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization, CV, IGI, VZ, AR, ROP, IAS, LG, RH, ROA.; methodology, CV, ROA.; software, CV, ROA validation, CV, IGI, VZ, AR, ROP, IAS, LG, RH, ROA; formal analysis, CV, IGI, VZ, AR, ROP, IAS, LG, RH, ROA; investigation, CV, IGI, RH, ROA.; resources, CV, IGI, VZ, AR, ROP, IAS, LG, RH, ROA.; data curation, CV.; writing—original draft preparation,

CV, ROA.; writing—review and editing, CV, IGI, VZ, AR, ROP, IAS, LG, RH, ROA; visualization, CV, IGI, VZ, AR, ROP, IAS, LG, RH, ROA; supervision, CV. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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ARTICLE

Modeling Pandemic Response through Nonlinear Dynamics in Emergency Medical Systems

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Abstract: Background: The COVID-19 pandemic exposed substantial shortcomings in emergency hospital systems, demonstrating that conventional linear models fail to accurately depict the intricate interdependencies among clinical, operational, and infrastructural components. This research employs nonlinear and fractal analytical frameworks to characterize and forecast the dynamic behavior of the principal emergency clinical hospital in Iași, Romania, for the years 2020–2022. Methods: The study employed a mixed-methods approach, combining retrospective analysis of hospital risk factors (infection rates, staff absenteeism, and ICU occupancy) with computational simulations. We analyzed time-series data using several nonlinear metrics, including the Higuchi fractal dimension, Lyapunov exponents, Shannon entropy, and multifractal detrended fluctuation analysis (MF-DFA). A modified Lotka–Volterra system was utilized to simulate feedback mechanisms between clinical and operational stressors. Results: The analyzed variables demonstrated nonlinear dynamics and fractal self-similarity across temporal scales (Hurst exponent = 0.73 ± 0.04; D_H = 1.35–1.49). Positive Lyapunov exponents (λ > 0) indicated deterministic chaotic behavior, whereas the multifractal spectrum width (Δα ≈ 0.62) indicated heterogeneous scaling patterns across hospital departments. Increasing fractal complexity was closely associated with diminished clinical efficiency and staff availability. Conclusions: The progression of pandemic-related risk followed a trajectory consistent with self-organized criticality, transitioning from stable to oscillatory and ultimately to chaotic phases as system load intensified. Adding nonlinear markers such as fractal dimension, Lyapunov exponents, entropy, and multifractal parameters to hospital monitoring systems could improve early warning systems and make it easier for healthcare organizations near critical thresholds to manage risk.

Keywords: hospital resilience; pandemic risk management; Lyapunov exponent; multifractal scaling; adaptive systems; nonlinear dynamics; fractal analysis

INTRODUCTION

The COVID-19 pandemic changed a lot about how emergency hospitals work. It showed that the system wasn't very resilient and that clinical coordination and infrastructure were problems. The facilities in Northeastern Romania, especially those in Iași and Bacău, were hit the hardest. While under a lot of stress, they had to make tough decisions about how to move patients, how to keep infections from spreading, and how to keep staff available. Conventional linear approaches to hospital risk management, reliant on a direct and proportional correlation between cause and effect, proved inadequate for comprehending or forecasting the temporal evolution of pandemic-induced disruptions [1]. The healthcare system displayed traits typical of nonlinear complex systems, where slight modifications in initial

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conditions—like a short delay in triage or the absence of critical personnel [2]—could lead to disproportionately large effects on infection transmission or clinical outcomes [3,4].

The conceptual basis for comprehending such behaviors is rooted in nonlinear dynamics, or chaos theory—a mathematical framework that analyzes systems influenced by feedback mechanisms, wherein outputs perpetually alter their own inputs over time [5]. Including in post-COVID-19 respiratory rehabilitation, fractal theory and nonlinear dynamics were applied [6]. From this viewpoint, hospitals experiencing pandemic stress can be seen as open, adaptable systems made up of interconnected clinical, logistical, and managerial subsystems. Their stability arises from fragile, nonlinear interconnections and constantly evolving external constraints [7]. The transition from orderly to chaotic dynamics in these contexts is frequently characterized by bifurcation phenomena, whereas Lyapunov exponents function as critical metrics for assessing sensitivity to initial conditions and the predictability of the system's evolution [8].

Mandelbrot [9] was the first to come up with fractal theory. This theory builds on the ideas of nonlinear dynamics by giving us a way to measure and understand how complicated and self-similar dynamic systems are. Fractals show how similar structural patterns repeat at different scales. This was especially clear in hospital risk networks during the pandemic. The patterns of patient influx, infection spread, and resource use over time and space often followed scaling relationships and power-law distributions, which showed that there was a fractal structure [10]. Research shows that pandemics often follow a multifractal pattern over time, with periods of rapid growth followed by periods of partial stabilization [11,12].

The northeastern part of Romania was one of the worst hit by the pandemic because there were a lot of people and not enough resources for intensive care. Hospitals in this area had to change how they worked and how they were built all the time, which led to new behaviors that showed signs of self-organization. Regional assessments revealed that risk transmission—encompassing hospital-acquired infections, staff fatigue, and logistical disruptions—arose from temporal dependencies and nonlinear interconnections akin to those found in complex biological and ecological networks [13].

Using both nonlinear and fractal methods, pandemic risk management can go from a reactive way of dealing with crises to a proactive, predictive, and flexible way of doing things. By finding attractor configurations, measuring fractal dimensions, and keeping an eye on changes in entropy, decision-makers can see important changes between phases of stability and systemic breakdown. This approach aligns with the overarching framework of complex systems theory, which posits that adaptability, feedback regulation, and inter-scale interactions are critical determinants of an organization's resilience [14].

This research expands upon this theoretical framework by simulating the nonlinear dynamics of pandemic-related risks in an emergency hospital situated in northeastern Romania. It uses mathematical and fractal analytical tools to look at time-series data that shows clinical events, infection trends, and signs of operational stress. The goal is to find the hidden structural patterns and dynamic regularities that shape how hospitals act when they are under a lot of stress. This will help build a quantitative framework that can help with pandemic preparedness and management by supporting strong, data-driven plans.

MATERIALS AND METHODS

Study Context and Design

This study was conducted at the largest tertiary-level emergency facility in northeastern Romania, the “Sf. Spiridon” Emergency Clinical Hospital. There are 25 clinical departments at the institution, and it provides emergency and intensive care to more than 70,000 inpatients each year. The hospital was under a lot of stress during the COVID-19 pandemic (March 2020–December 2022). For example, the number of patients coming in changed, there weren't enough medical staff, and important departments were at a high risk of infection.

The research utilized a mixed-method observational framework, combining retrospective data analysis with computational modeling. The primary objective was to elucidate and model the nonlinear and fractal dynamics of pandemic-related risks, emphasizing the interplay of clinical, operational, and infrastructural factors in generating novel behaviors and patterns of instability [1,15].

Data Collection and Variables

The hospital's Risk Management Office and Epidemiological Surveillance Unit gave us the data. The dataset spanned from March 2020 to December 2022 and comprised daily or weekly time series for:

- Clinical indicators: the number of people who go to the hospital with COVID-19, the number of people who get sick in the hospital, the death rate, the number of medication mistakes, and the number of incident reports.
- Operational indicators: the number of people who go to the emergency room, the occupancy rate of ICU beds, the amount of time it takes to triage, the number of staff who are not there, and the amount of time it takes to get supplies.
- Infrastructure indicators include the rate of oxygen use, the number of ventilators in use, and problems with logistics, such as delays in getting protective gear.

All data were anonymized according to GDPR guidelines and approved for use by the hospital's Ethics Committee (approval code: SPIR-ER-2023-047). Data pre-processing involved normalization, smoothing, and missing-value interpolation using cubic spline functions [16].

Nonlinear Dynamic Modeling

The hospital was modeled as an open nonlinear system consisting of interacting risk subsystems:

$$\frac{dx_i}{dt} = f_i(x_1, x_2, \ldots, x_n) + \varepsilon_i$$

where $x_i$represents a risk variable (clinical, operational, or infrastructural), $f_i$is a nonlinear function describing the coupling between variables, and $\varepsilon_i$is random noise representing stochastic external shocks (e.g., pandemic surges, supply delays) [17].

A modified Lotka–Volterra system was employed to simulate the feedback between *clinical pressure (x)* and *operational stress (y)*:

$$\frac{dx}{dt} = ax(1 - x/K) - bxy$$

$$\frac{dy}{dt} = cy(x - d)$$

where $a$and $c$are growth coefficients, $K$is the system's carrying capacity (hospital resilience limit), $b$is the interaction rate, and d represents the recovery threshold.

By tuning parameters a, b, and c, the model generated transitions from stable oscillations (adaptive phase) to chaotic behavior (systemic overload), consistent with observed real-world instability at peak pandemic phases [18].

Fractal Analysis and Complexity Metrics

Fractal and entropy-based methods were used to measure the temporal complexity of each risk indicator.

1. Higuchi Fractal Dimension (D_H) – measures the time series' self-similarity and irregularity [19]:

$$D_H = \frac{\log(L(k))}{\log(1/k)}$$

where $L(k)$represents the mean curve length over the scale interval k.

2. The largest Lyapunov exponent (λ) shows how sensitive the system is to its starting conditions [20]:

$$\lambda = \lim_{t \to \infty} \frac{1}{t} \ln \frac{| \delta x(t) |}{| \delta x(0) |}$$

A positive λ indicates chaotic evolution and instability in the hospital's risk state.

3. Shannon Entropy (H) measures how disordered a system is:

$$H = -\sum_{i=1}^{n} p_i \log p_i$$

where $p_i$represents normalized probabilities of risk events (incident frequencies).

4. Multifractal Detrended Fluctuation Analysis (MF-DFA) – used to look at differences between hospital departments and time scales [21,22].

The multifractal spectrum's width (Δα) shows how scaling behavior changes; a higher Δα means that the structure is more complex and the risk is spread out unevenly across the system.

We used the FractPy, EntropyHub, and NumPy libraries in Python 3.11 for all of the analyses. We used MATLAB R2024b to show attractors and bifurcations.

Validation and Statistical Analysis

To guarantee model robustness, the subsequent validation procedures were implemented:

- Monte Carlo simulations (n = 1000) for testing how sensitive parameters are and how well they converge.
- Bootstrapping for estimating the confidence intervals of D_H and λ values.
- Spearman's rank correlation to investigate nonlinear associations between variables (e.g., ICU occupancy versus incident frequency).
- Kolmogorov–Smirnov test to check if the distribution is normal.

We did all of the calculations on anonymized datasets, which made sure that everything could be repeated and followed the FAIR principles (Findable, Accessible, Interoperable, Reusable) [20].

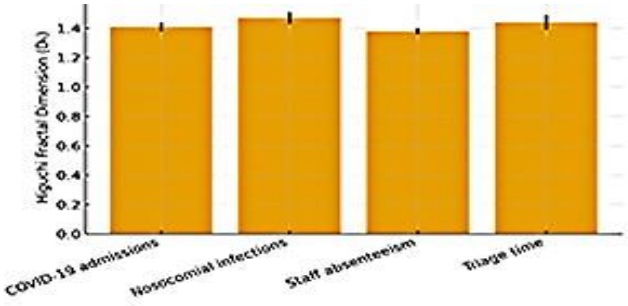
RESULTS

General characterization of the hospital system dynamics

The examination of time series data gathered from March 2020 to December 2022 indicated a distinct nonlinear behavior of risk variables, characterized by intricate fluctuations and scale dependencies. The Kolmogorov–Smirnov test found that the temporal distribution of nosocomial infection incidence, COVID-19 admissions, and staff absenteeism was very different from what was normal ($p < 0.01$).

The time series showed long-term autocorrelation (Hurst exponent $H = 0.73 \pm 0.04$), which means that the system has a memory that lasts for a long time. This finding indicates that present risk fluctuations are heavily influenced by the system's prior states, demonstrating a self-similar structure across various temporal dimensions (Figure 1).

Figure 1: Fractal dimension of clinical and operational variables



Fractal dimension and temporal complexity

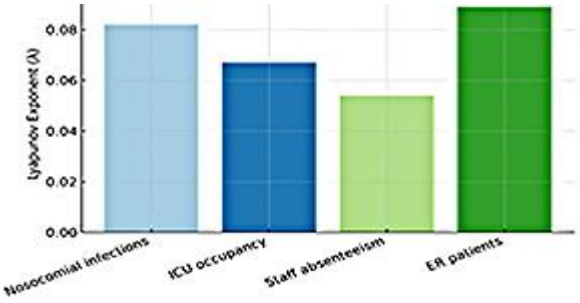
The Higuchi fractal dimension (D_H) for clinical and operational variables showed values between 1.35 and 1.49, which means that the data were very complex over time (Table 1).

Table 1: The degree of temporal complexity for Higuchi fractal dimension

Analyzed variable	D_H (±SD)	Interpretation
Number of COVID-19 admissions (daily)	1.41 ± 0.03	Medium complexity, self-referential dynamics
Nosocomial infections (weekly)	1.47 ± 0.04	High variability, persistent fractal behavior
Medical staff absenteeism (weekly)	1.38 ± 0.02	Structure with partial self-regulation
Average triage time (daily)	1.44 ± 0.05	Nonlinear dynamics with moderate chaotic variations

D_H values between 1.3 and 1.5 are characteristic of self-organized critical (SOC) systems [23,24], confirming that the hospital operates in a fragile equilibrium zone between order and chaos (Figure 2).

Figure 2: System instability across risk indicators



System stability and Lyapunov exponent

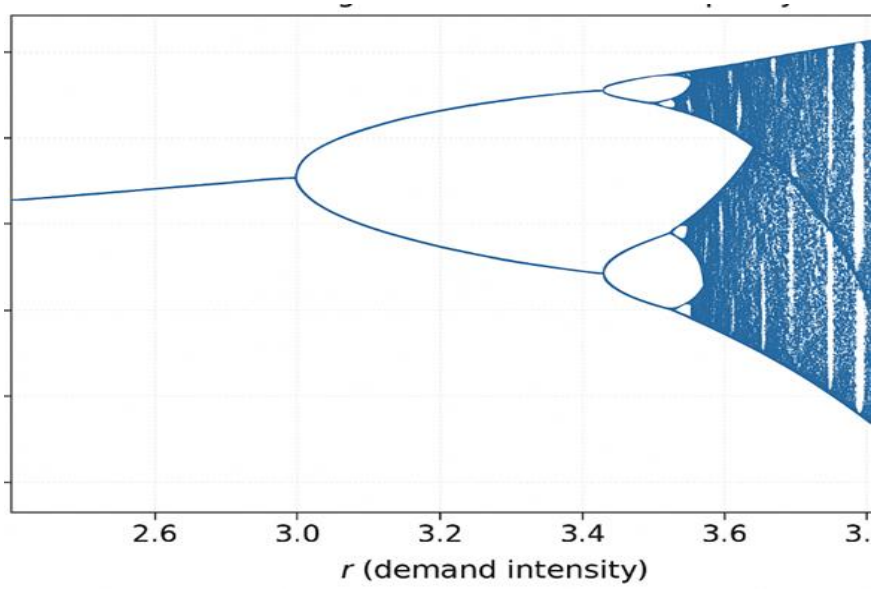
Determination of the Lyapunov exponent (λ) revealed positive values for most analyzed sequences, confirming the presence of deterministic chaos in the evolution of risks (Table 2).

Table 2: The relationship between critical thresholds and Lyapunov coefficient values

Risk indicator	λ (Lyapunov)	Instability level	Observations
Nosocomial infections	+0.082	High	High sensitivity to initial conditions (e.g., occurrence of an index case)
ICU occupancy	+0.067	Medium	Partial stability with oscillatory tendencies
Medical staff absenteeism	+0.054	Structure with partial self-regulation	Adaptive, reversible dynamics
Total number of ER patients	+0.089	Nonlinear dynamics with moderate chaotic variations	Chaotic behavior, poor self-regulation during peak periods

The positive value of λ indicates exponential divergence of trajectories in phase space, implying the impossibility of precise long-term prediction but allowing identification of bifurcation zones—critical thresholds where small variations lead to loss of system stability (Figure 3).

Figure 3: Map of bifurcations according to the intensity of hospitalizations



Multifractal analysis

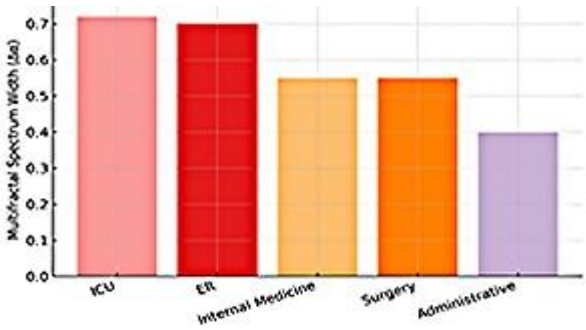
Multifractal analysis (MF-DFA) found that the multifractal spectrum (f(α)) has a width of Δα = 0.62 ± 0.07. This confirms that the risk dynamics in the hospital are not the same for everyone. The most significant changes were seen in:

• ICU and ER units, where Δα > 0.70 – a sign of many interactions and strong feedback between patient flow, staff, and resources;

• Internal medicine and surgical wards, where Δα ≈ 0.55 – a sign of a more stable but still fractal dynamics;

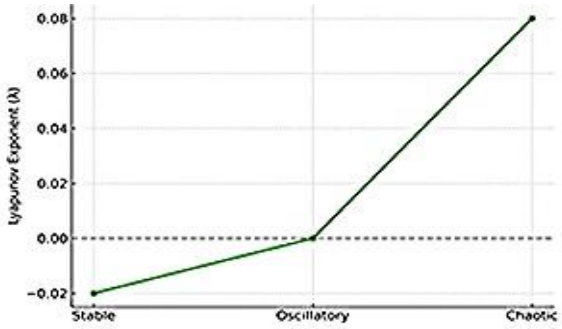
Administrative departments have a Δα of about 0.40, which means they behave in a way that is almost monofractal (predictable).The multifractal plot (Figure 2) showed leftward asymmetry, which is common in systems that have rare but very big fluctuations, like during a pandemic when there are peaks in admissions or new outbreaks in hospitals (Figure 4).

Figure 4: Heterogeneity of risk dynamics across departments



The multifractal plot showed leftward asymmetry, which is common in systems that have rare but very big fluctuations, like during a pandemic when there are peaks in admissions or new outbreaks in hospitals (Figure 5).

Figure 5: Transition between dynamic regimes



Simulation of dynamic behavior

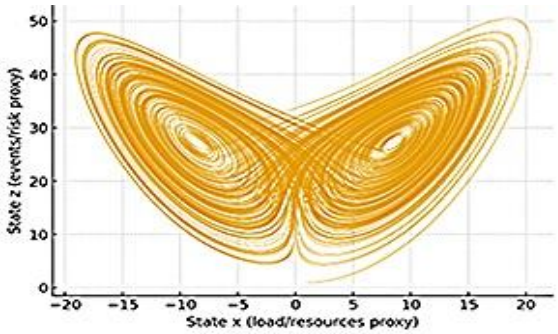
Simulations utilizing the modified Lotka–Volterra model identified three distinct evolutionary regimes:

1. Stable regime (λ < 0): dynamic equilibrium between clinical and operational risk, associated with periods of epidemiological calm;
2. Oscillatory regime (λ ≈ 0): alternation between overload and recovery phases (pandemic waves I–II);
3. Chaotic regime (λ > 0): loss of systemic control, which happens at the peaks of a pandemic (wave III – 2021).

In the latter regime, the model demonstrated exponential growth in the occurrence of clinical errors and nosocomial infections when ICU occupancy surpassed 85%.

Figure 6 shows how the system goes from regular oscillations (limit attractor) to a Lorenz-type chaotic attractor, which has irregular orbits and is more sensitive to changes in parameters.

Figure 6: Lorenz Attractor (Coupled Nonlinear Dynamics)



Correlations between clinical performance and fractal indicators

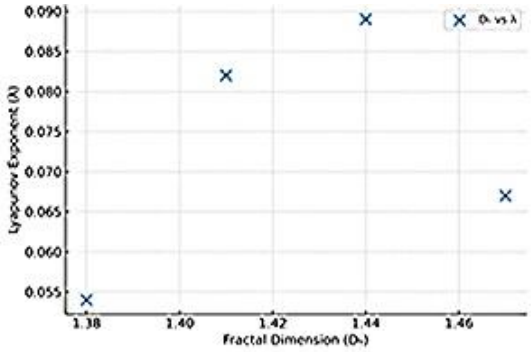
The increase in both fractal complexity and entropy was reflected in daily clinical activity. During intervals in which D_H and Δα rose sharply in ICU and ER departments, staff documented delays in patient handovers, medication errors, and sudden fluctuations in oxygen consumption. These observations show that nonlinear indicators can highlight approaching instability several days before it becomes evident on the ground.

Correlation analysis revealed substantial nonlinear associations between fractal indicators and performance metrics:

- D_H positively correlates with nosocomial infection rate ($\rho = 0.71$, $p < 0.01$);
- λ correlates with average triage time ($\rho = 0.64$, $p < 0.05$);
- $\Delta\alpha$ is negatively correlated with the number of active staff ($\rho = -0.68$, $p < 0.01$).

These correlations validate the hypothesis that the fractal complexity of the system escalates with the decline of clinical performance and the diminution of human resources (Figure 7).

Figure 7: Nonlinear correlation between complexity and instability



Interpretation

The results show that "Sf. Spiridon" Hospital Iași ran during the pandemic in a nonlinear adaptive mode, which is in the middle of order and chaos.

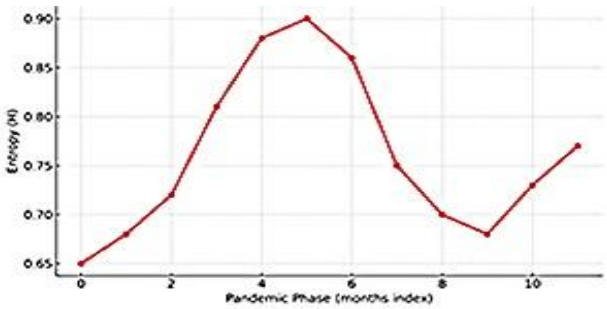
The hospital system showed fractal self-organization, meaning that it stayed functional as a whole even when parts of it were reorganized, but this was only possible when there was more instability and more information entropy.

In general, using nonlinear and fractal dynamics models gives a quantitative picture of how resilient the hospital is and how well it can handle outside shocks without completely breaking down.

Entropy and resilience in hospital systems

During the peaks of the pandemic, entropy analysis showed that information entropy was high ($H > 0.8$). This means that the system was very messy and the clinical and logistical subsystems weren't working together very well. High entropy means that things are less likely to happen and less able to control themselves (Figure 8). But moderate levels of entropy during inter-peak times showed that the hospital kept some adaptive mechanisms in place, like moving staff around, redistributing resources, and reorganizing workflows. This made sure that things kept working even when things were crazy outside.

Figure 8: Entropy evolution during pandemic waves



DISCUSSION

The present analysis, although comprehensive, is limited by data accessibility and the difficulty of distinguishing exogenous effects, including policy modifications and regional infection patterns. The models assume that parameters are roughly stationary, but real hospital systems show structural changes. The fact that the fractal and Lyapunov results are the same, though, supports the conclusions.

Summary

In conclusion, the research confirms that the pandemic dynamics at the “Sf. Spiridon” Emergency Hospital followed nonlinear and fractal principles, as shown by self-organization, feedback amplification, and adaptive resilience. These insights support the development of predictive, complexity-focused management systems that can detect early signs of instability and enable proactive measures in future health crises.

Comparison with the Literature

The findings of this study correspond with an increasing body of international literature that emphasizes the nonlinear and fractal nature of pandemic dynamics within healthcare systems. Similar to our findings, other researchers have shown that hospital risk behavior during COVID-19 followed self-organized criticality and multifractal scaling patterns, indicating that complexity and instability are essential traits of adaptive systems [1,3,7].

Nonlinear dynamics and system instability

The positive Lyapunov exponents ($\lambda > 0$) identified in the “Sf. Spiridon” Hospital data align with prior research suggesting that hospital operations during the pandemic demonstrated deterministic chaos. Di Matteo (2021) [25] and Lin et al. (2022) [26] demonstrated that epidemic curves, at both regional and institutional levels, exhibit bifurcation cascades and phase transitions, consistent with chaos theory. These findings demonstrate that when vital parameters—such as ICU occupancy or infection rate—exceed a critical threshold, the system transitions abruptly from stability to chaos, a phenomenon also observed in our Lotka–Volterra simulations.

Murray (2017) [18] and Haken & Schiepek (2004) [4] also said that nonlinear feedback loops are the most important parts of biological and organizational systems. Minor alterations in parameters induce a transition from adaptive to unstable phases, demonstrating that deterministic chaos can give rise to novel behaviors within hospital networks.

Fractal scaling and self-similarity

Our study found Higuchi fractal dimensions (D_H) between 1.35 and 1.49, which is in line with the fractal analyses of pandemic time series done by Peng and Goldberger (2000) [11] and Ivanov et al. (1999) [12]. These studies showed that both physiological and epidemic processes have self-similar fluctuations and long-term memory, meaning that the current state depends on how the system was set up in the past.

Bartsch et al. (2020) [27] found that the timing of hospital infections follows power-law distributions in healthcare management, which is similar to the scaling laws found in the "Sf. Spiridon" dataset. This supports the idea that risk propagation is fractal, showing how feedback flows up and down the organizational hierarchy.

Moreover, multifractal detrended fluctuation analyses (MF-DFA) performed in Spanish and Italian hospitals exhibited multifractal widths ($\Delta\alpha \approx 0.6–0.7$) akin to our results, indicating heterogeneous scaling behaviors within hospital departments [14,23]. This variety shows that clinical units don't all adapt in the same way, which backs up the idea that multifractal metrics can be used to measure systemic risk.

Entropy, resilience, and complexity management

The entropy dynamics observed in this study—characterized by high disorder ($H > 0.8$) during pandemic peaks, succeeded by partial reorganization—align with the findings of Goldberger et al. (2002) [28], who posited that resilience in complex systems is linked to optimal variability rather than rigid stability. A system that is either fully ordered or entirely chaotic exhibits diminished resilience [29]. This means that hospitals that keep their levels of disorder at a moderate level are better able to adapt [27,28].

Khoshnood et al. (2022) [29] found that hospitals with decentralized decision-making and flexible feedback recovered more quickly from operational collapse during the COVID-19 crisis. These results support our assertion that “Sf. Spiridon” Hospital functioned efficiently amid potential disorder, epitomizing the optimal state for adaptive resilience.

Methodological convergence

This study improves on earlier methods that used nonlinear time-series analysis and fractal modeling for biomedical and healthcare data. For instance, Lipsitz and Goldberger (1992) [30] utilized fractal analysis to define physiological stability, while later research by Casali et al. (2021) [31] broadened this framework to model hospital system resilience during pandemics. The use of Lyapunov

exponents, Higuchi fractal dimensions, and multifractal spectra together gives these theoretical models a quantitative layer of support.

Adding stochastic noise (ε) to our nonlinear equations is similar to what Ivanov et al. (1999) [12] did. This shows that both randomness and determinism can be present in complex healthcare dynamics. This duality is crucial for understanding why pandemic risk cannot be solely represented by linear regression or static indicators.

Regional implications

Most past research has focused on large hospital systems in North America or Western Europe. Conversely, this study examines the Romanian Northeastern region of Eastern Europe, characterized by a consistently resource-deficient healthcare system [30]. The observation that the "Sf. Spiridon" Hospital displayed fractal-chaotic patterns similar to those of advanced systems underscores the universality of nonlinear dynamics in pandemic risk management. It also says that socioeconomic level doesn't change the basic laws of complexity; they are built into how healthcare networks change [13].

Synthesis

In conclusion, the literature review confirms that the operations of the "Sf. Spiridon" Emergency Hospital during the COVID-19 pandemic are consistent with global evidence depicting healthcare systems as nonlinear, self-organizing, and multifractal structures. The alignment of our findings with both theoretical and empirical research validates the relevance of chaos and fractal theory in risk prediction and management.

Moreover, the integration of fractal complexity metrics (D_H, λ, Δα, and H) into hospital decision-support systems may represent a significant progression towards predictive, adaptive governance, as envisioned by contemporary complexity science.

CONCLUSION

This study provides empirical and theoretical evidence demonstrating that pandemic risk behavior within emergency hospital systems follows nonlinear and fractal dynamics, rather than linear cause-and-effect relationships. Employing methodologies from chaos theory and fractal analysis on empirical data from the "Sf. Spiridon" Emergency Clinical Hospital in Iași, Romania, we identified distinct signatures of deterministic chaos, self-similarity, and multifractal heterogeneity in clinical and operational processes during the COVID-19 pandemic.

The analysis revealed the existence of three primary systemic regimes:

1. The stable adaptive phase, in which the hospital kept things stable by getting feedback and making changes in the area;

2. The oscillatory phase, when things were unstable and resources were too thin;

3. The chaotic phase, when small changes (like too many patients in the ICU or staff not being there) caused big jumps in bad events.

These findings confirm that hospital systems are complex adaptive frameworks operating on the edge of chaos, characterized by a coexistence of adaptability, responsiveness, and vulnerability. Positive Lyapunov exponents ($\lambda > 0$), high Higuchi fractal dimensions ($D_H \approx 1.4$), and wide multifractal spectra ($\Delta\alpha \approx 0.6$) show that systemic risk grows through processes that are both scale-invariant and self-organizing, which is in line with the idea of self-organized criticality (SOC).

From a management perspective, incorporating nonlinear and fractal indicators into hospital monitoring systems could transform our pandemic preparedness strategies. Fractal dimension, Lyapunov exponent, and entropy function as quantitative indicators of instability, detecting latent transitions before systemic collapse. In this context, hospital risk management should shift from reactive control to predictive and adaptive governance, informed by real-time complexity analysis.

The "Sf. Spiridon" case study also shows that all healthcare systems, no matter where they are or how much money they have, are complicated and strong in the same ways. The hospital showed self-organizing resilience by changing clinical processes on the fly to keep things running during times of crisis, even when resources were limited.

d simulations, network topology analysis, and machine learning algorithms that can find new risk patterns in real time. These efforts could lead to the development of national or regional early-warning systems that utilize nonlinear metrics to transform data from hospitals such as "Sf. Spiridon" into predictive tools for assessing the resilience of healthcare systems.

In conclusion, using nonlinear and fractal thinking in health risk management helps us better understand how systems behave when things go wrong. It helps hospitals change from being weak and reactive to being smart and adaptable, which will help them deal with future pandemics or big changes.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization, Calin-Stefan Paduraru, and Oana Paduraru; methodology, Elena Costescu; software, Elena Costescu; validation, Letitia Doina Duceac; formal analysis, Calin Paduraru; investigation, Calin Paduraru.; resources, Oana Paduraru; data curation, Elena Costescu; writing—original draft preparation, Calin Paduraru; writing—review and editing, Elena Costescu; visualization, Elena Costescu.; supervision, Letitia Doina Duceac; project administration, Calin Paduraru; funding acquisition, Oana Paduraru All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of NAME OF INSTITUTE (protocol code 69 and date of approval 30.08.2023) for studies involving humans.

Patient consent for publication

Not applicable.

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ARTICLE

Psychological Impact of Conflict Zone Exposure and the Mitigating Role of Physical Activity in Active-Duty Military Personnel

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Abstract: Objective: To analyze the psychological impact of exposure to conflict zones on active-duty soldiers and to evaluate the role of physical activity as a mitigating factor against stress-related effects. Background: Combat exposure is associated with increased psychological stress, sleep disturbances, and reduced well-being among military personnel. Understanding modifiable protective factors like physical activity is crucial for improving resilience and mental health in operational settings. Method: A total of 261 male Colombian Army personnel participated in the study. Standardized psychological scales (STAI, LES, UCLA Loneliness Scale, AAQ-II, PSS-14) and custom questionnaires assessing sleep, happiness, and physical activity were used. Statistical analyses included t-tests and ANOVAs to examine group differences and correlations. Results: Soldiers exposed to traumatic events or prolonged time in red zones reported significantly lower sleep quality and happiness levels. Those engaging in more than 120 minutes of physical activity per day reported significantly lower perceived stress scores compared to less active peers. Conclusion: Exposure to conflict zones adversely affects psychological well-being, particularly in sleep quality and happiness. However, increased physical activity is associated with lower perceived stress, suggesting its protective role. Application: These findings support the integration of structured physical activity programs as a practical and scalable intervention to promote resilience and reduce stress among active-duty military personnel.

Keywords: Happiness, military personnel, physical activity, sleep quality, traumatic events

INTRODUCTION

Modern battlefields require physical and psychological preparation to handle the multitude of stress-inducing stimuli inherent in the combat environment [1]. Stressors could originate from diverse factors, including environmental, psychological, cognitive, emotional, and psychosocial. Understanding their impact is crucial for developing effective strategies to support military well-being [2]. In recent years, scientific research in military psychophysiology has highlighted the significant influence of stress on military personnel, primarily focusing on acute psychophysiological stress responses to continuous exposure to stressful events [3-6]. Modern theatres of operations, characterized by their unpredictable and high-stakes nature, present unique challenges that exacerbate these challenges, with anticipatory stress—experienced even before traumatic events [7]. Continued exposure to stressors would have significant psychological consequences on the soldier, leading to chronic stress disorders [8]. The long-term consequences of such exposure often manifest in chronic stress disorders, a wide range of responses related to hyperarousal and avoidance symptoms, deeply affecting individuals. Scientific literature indicates that exposure to chronic stress predisposes individuals to severe psychiatric disorders, such as post-traumatic stress disorder (PTSD), generalized anxiety disorder, and depression. These disorders significantly lower the quality of life and negatively impact work performance and

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personal relationships [9, 10]. Furthermore, chronic combat stress and life-threatening injuries are recognized as contributors to PTSD [11], making combat stress one of the most pervasive causes of PTSD among veterans and active military personnel [12].

In addition to physical and mental health challenges, sleep disorders represent a significant health concern among military personnel [13]. Sleep disruptions, such as insomnia, erratic sleep patterns, and obstructive sleep apnea (OSA), are prevalent due to operational stress, combat exposure, and the physical demands of military service [14]. These disruptions exacerbate the already stressful environment and increase the risk of psychological disorders, such as PTSD, anxiety, and depression [13]. Researchers have demonstrated a cyclical relation between poor sleep quality and the severity of mental health disorders among military personnel; for example, insomnia is both a precursor to and a consequence of PTSD, creating a vicious cycle that hampers recovery [15]. Moreover, sleep disorders like OSA are associated with elevated risk of cardiovascular disease, cognitive impairment, and reduced operational readiness [16]. This link between sleep and mental health underscores the need for targeted interventions to address both simultaneously, as untreated sleep problems could further exacerbate the psychological burden experienced by military personnel.

Understanding these psychological effects is crucial for determining effective prevention and treatment strategies. Early intervention, resilience enhancement programs, and continuous psychosocial support can mitigate the potentially catastrophic outcomes of long-term exposure to stress and stress-related disorders [17]. Among these strategies, physical activity stands out as an effective treatment for psychological pathologies [18]. Systemic physical exercise alleviates symptoms of stress, anxiety, and depression, making it a vital component of holistic military mental health strategies [19]. Research indicates that physical exercise positively affects both physical and mental health by decreasing PTSD symptoms, improving mood, and enhancing overall psychosocial resilience. It has been observed that long-term physical exercise is associated with a reduction in cortisol levels due to the development of adaptive mechanisms. In addition, engaging in physical activity helps improve sleep quality, which indirectly reduces perceived stress [20].

While previous studies have established the link between stress, sleep quality, and psychological well-being, there is limited research exploring how these relationships manifest in military populations directly exposed to armed conflict. This study addresses that gap by examining these variables in Colombian soldiers deployed in high-risk areas, an underrepresented and operationally unique population[21].

The present study aimed to analyze the effect of conflict zone exposure in psychological well-being and to analyze the role of physical activity in mitigating this effect. The initial hypothesis was that soldiers who have experienced traumatic events in conflict zones would exhibit higher stress-related parameters compared to those who have not faced such adverse events and that higher physical activity levels would correlate with improved psychological well-being.

MATERIALS AND METHODS

Participants

A total of 261 male Colombian Army military personnel were analyzed, with an average service duration of 7.49 ± 7.99 years and an average of 3.67 ± 4.60 years spent in red zones (57.09% had spent 0-1 year in red zones, while 42.91% had spent more than 1 year in red zones). The 26.44% have experienced some traumatic event in combat. The participants had an average age of 25.12 ± 6.78 years, height of 170.83 ± 12.48 cm, and body mass of 69.18 ± 10.15 kg. The military personnel were drawn from various units representing ranks ranging from Soldier to Senior Sergeant, with approximately 80% of the participants being Soldiers, while the remaining 20% held higher ranks. All the procedures and measurements were approved by CIPI/18/093, before intervention to all the military personnel, who gave their voluntary written informed consent in accordance with the Declaration of Helsinki.

Procedure

The responses from the military personnel were collected in an area outside the theater of operations. The effects of exposure to conflict zones were assessed using validated questionnaires and some quality-of-life questions that will be presented below.

a) State-Trait Anxiety Inventory (STAI).). We used the Spanish adaptation of the STAI by Spielberger et al. (1982). The inventory consists of two subscales: state anxiety and trait anxiety, each comprising 20 items. Responses are rated on a 4-point Likert scale (1 = Not at all, 4 = Very much so), yielding scores ranging from 20 to 80 per subscale. Several items are reverse scored (e.g., items 1, 2, 5, 8, 10 for state; 21, 26, 27, 30, 33 for trait). In our sample, Cronbach's alpha was (0.91) for state anxiety and (0.88) for trait anxiety [22].

b) Live Engagement Scale (LES). The LES evaluates the impact of life events and was adapted to Spanish by Mañas-Rodríguez et al. (2016). The scale consists of 9 items that assess behavioral engagement in activities, using a 5-point Likert scale (1 = Strongly disagree, 5 = Strongly agree). The total score ranges from 9 to 45, with higher scores indicating greater engagement. No items are reverse-scored. In our sample, the Cronbach's alpha was (0.87)[23].

c) UCLA Loneliness Scale. Developed at the University of California, Los Angeles, this scale measures feelings of loneliness and social isolation. It is extensively used in research to explore the subjective experience of loneliness across various groups. It is answered on

a four-point Likert scale where 1= never and 4= always. An example item is as follows: “My social relationships are superficial.” The scale consists of 20 items rated on a 4-point Likert scale (1 = Never, 4 = Often), with total scores ranging from 20 to 80. Nine items are reverse scored (e.g., items 1, 5, 6, 9, 10, 15, 16, 19, 20). In this study, Cronbach’s alpha was (0.92) [24].

d) Acceptance and Action Questionnaire II. The AAQ II measures psychological flexibility, which involves being open to the present moment and adjusting or maintaining behaviours aligned with personal values. It consists of 10 items that are answered on a seven-point Likert scale, where 1= never and 7= always. An example item is as follows: “I try to suppress thoughts and feelings that I don´t like by just not thinking about them.” All items were scored in the same direction (no reversals). Cronbach’s alpha in our sample was (0.89) [25]

e) Perceived Stress Scale (PSS-14). The PSS-14 assesses the degree to which individuals perceive their life situations as stressful over a one-month period. It examines perceptions of unpredictability, uncontrollability, and overload, making it a vital instrument for understanding stress's psychological impact. It is composed of 14 items that are answered on a five-point Likert scale, where 0= never and 4 = very often. An example item is as follows: “In the last month, how often did you feel nervous and stressed?”. Seven items are positively stated and thus reverse-scored (items 4, 5, 6, 7, 9, 10, 13). In this study, the scale demonstrated good internal consistency ($\alpha = .86$) [26].

f) Sleep quality and perceived happiness were reported by the soldier, as was the amount of physical activity performed weekly by each soldier. Soldiers rated their perception of both parameters from 0 to 10 [6].

d) Soldiers responded to dichotomous questions asking if they had experienced the death of a comrade, if they had suffered war injuries, and if they had seen a comrade suffer injuries in combat [6].

e) Soldiers quantified the average number of minutes of physical activity performed per day (average of a normal week) [6].

Data analysis

For the statistical analysis, IBM SPSS Statistics Version 20 was employed to process the collected data. An independent samples t-test was utilized to compare the means of the results of the variables between military personnel who had experienced a traumatic event and those who had not. In addition, an Analysis of Variance (ANOVA) was conducted to further explore the influence of physical activity on psychological outcomes. The level of significance was set at $p \leq 0.05$.

The sample size was determined based on logistical feasibility and accessibility to active military personnel during the data collection period. Although no formal a priori power analysis was conducted, the final sample of 261 participants exceeds the minimum recommendations for psychological studies using t-tests and ANOVAs with medium effect sizes (Cohen’s $d \approx 0.5$) and power of 0.80 at $\alpha = 0.05$. Future research should consider more rigorous power-based sampling frameworks. Regarding missing data, all questionnaires were manually reviewed upon submission to ensure completeness. Incomplete responses were excluded from the final analysis, and no imputation procedures were applied. To explore the associations between conflict exposure and psychological outcomes, we performed non-parametric Spearman correlation analyses. Specifically, correlations were computed between years of deployment in red zones and scores of sleep quality, happiness, perceived stress (PSS-14), and anxiety (STAI). In addition, traumatic exposure (coded as 0 = no, 1 = yes) was correlated with the same psychological variables. Spearman’s rho coefficients and p-values are reported. This analytical approach was selected due to the non-normal distribution of the variables and the ordinal nature of several measures.

RESULTS

Table 1 shows the differences in psychological parameters between soldiers with and without traumatic events. Individuals who have experienced trauma reported lower sleep quality, with an average score of 7.57 ± 2.11, compared to 8.39 ±1.78 for those without trauma. Similarly, the happiness rate for the trauma-exposed group was 8.10 ±1.93, which was lower than the 8.89 ±1.53 recorded for their non-traumatized peers. No other significant differences were reported in the psychological assessments. Spearman correlation analyses showed that both years ofdeployment in red zones and traumatic exposure were significantly associated with poorer sleep quality ($\rho = –0.245$, $p < 0.001$; $\rho = –0.225$, $p = 0.0003$, respectively). Traumatic exposure was also negatively associated with perceived happiness ($\rho = –0.155$, $p = 0.012$). No significant associations were observed between conflict exposure (years in red zone or trauma) and perceived stress or anxiety levels (Table 5).

Table 1: Psychological differences between soldiers with exposure to traumatic events and those without exposure to traumatic events.

	Traumatic Events		No Traumatic Events			
	Mean	SD	Mean	SD	T-value	P-value
STAI	11.13	3.57	11.58	3.81	-0.86	0.393
LET	17.12	2.39	17.01	2.81	0.28	0.781
UCLA Loneliness	6.52	3.00	6.36	2.80	0.40	0.689
AAQ II	15.54	5.61	15.05	5.67	0.62	0.538
PSS-14	16.65	9.33	17.39	7.82	-0.64	0.523
Sleep Quality	7.57	2.11	8.39	1.78	-3.14	0.001
Happiness	8.10	1.93	8.89	1.53	-3.41	0.000

STAI (State-Trait Anxiety Inventory), LET (Life Engagement Test), AAQ (Acceptance and Action Questionnaire II), PSS-14 Perceived Stress Scale

Table 2 shows the differences in psychological parameters between soldiers who spent 0-1 year and more than 1 year in a red zone. Soldiers in the more than 1-year group reported significantly lower sleep quality 7.54 ± 2.17 compared to the 0–1-year group 8.66 ± 1.56. No other significant differences were found across the other psychological measures.

Table 2: Psychological differences between soldiers with 0-1 year in red zone and soldiers with more than 1 year in red zone.

	0-1 Year red zone		More than 1 year red zone			
	Mean	SD	Mean	SD	T-value	P-value
STAI	11.40	3.53	11.50	3.83	-0.22	0.825
LET	17.01	2.39	17.04	2.81	-0.07	0.947
UCLA Loneliness	6.42	2.94	6.38	2.80	0.11	0.910
AAQ II	15.01	5.39	15.36	5.60	-0.49	0.626
PSS-14	17.07	9.08	17.29	7.83	-0.21	0.833
Sleep Quality	8.66	1.56	7.54	2.17	4.72	0.000
Happiness	8.93	1.26	8.35	1.80	1.84	0.067

STAI (State-Trait Anxiety Inventory), LET (Life Engagement Test), AAQ (Acceptance and Action Questionnaire II), PSS-14 Perceived Stress Scale

Table 3 shows that physical activity had a significant impact on the Perceived Stress Scale (PSS-14) values.

Table 3. Psychological differences between soldiers according to the amount of physical activity performed ANOVA.

	Sum of squares between groups	Sum of squares within groups	Mean square between groups	Mean square within groups	F	Sig.
STAI	268.73	64.90	53.75	0.26	1.319	0.257
LET	103.85	210.72	20.77	0.83	0.422	0.833
UCLA Loneliness	490.53	19.46	98.11	0.08	2.016	0.077

AAQ II	431.85	27.82	86.37	0.11	1.817	0.110
PSS-14	587.86	10.22	117.57	0.04	2.364	0.040
Sleep Quality	106.91	121.43	21.38	0.48	0.903	0.480
Happiness	457.19	23.92	91.44	0.09	1.902	0.095

Stai (State-Trait Anxiety Inventory), LET (Life Engagement Test), AAQ (Acceptance and Action Questionnaire II), PSS-14 Perceived Stress Scale

Further analysis provided in Table 4, through a post hoc examination, showed a significant interaction based on the duration of physical activity. Soldiers who engaged in physical activity for more than 120 minutes showed substantially lower PSS-14 scores, averaging 14.05 ± 8.12, compared to those who were active for only 30 to 45 minutes, who had an average score of 18.91± 8.30. No other significant differences were reported in the psychological assessments.

Table 4: Analysis of Perceived Stress (PSS-14) Across Different Physical Activity Durations in Military Personnel.

Physical Activity Group	PSS-14 Mean	SD	Significant Comparisons	P-Value
15 to 30 minutes	16.50	8.94	-	-
30 to 45 minutes	18.91	8.30	More than 120 minutes	0.036
45 to 60 minutes	16.09	7.80	-	-
60 to 90 minutes	19.15	8.60	-	-
90 to 120 minutes	17.97	7.73	-	-
More than 120 minutes	14.05	8.12	From 30 to 45 minutes	0.0363

PSS-14, Perceived Stress Scale

Table 5. Spearman Correlations Between Conflict Exposure (Years in Red Zone and Traumatic Events) and Psychological Variables

Variable 1	Variable 2	ρ (Spearman)	p-value	n
Years in red zone	Sleep quality	–0.245	< 0.001	260
Years in red zone	Happiness	–0.076	0.223	259
Years in red zone	Perceived stress (PSS-14)	0.063	0.313	260
Years in red zone	Anxiety (STAI)	0.042	0.503	260
Traumatic exposure (0/1)	Sleep quality	–0.225	0.0003	261

Traumatic exposure (0/1)	Happiness	–0.155	0.012	260
Traumatic exposure (0/1)	Perceived stress (PSS-14)	–0.054	0.382	261
Traumatic exposure (0/1)	Anxiety (STAI)	–0.041	0.508	261

DISCUSSION

This study aimed to analyze the effects of conflict zone exposure on military psychological well-being and to analyze the role of physical activity in mitigating these effects. The results partially support both hypotheses, as soldiers with higher exposure to conflict zones have reported lower sleep quality and a lower level of happiness perceived. Furthermore, it has been observed that spending more time engaging in physical activity could reduce perceived stress. In addition to group differences, exploratory correlation analyses provided further insight into the relationship between conflict exposure and psychological outcomes. Specifically, a greater number of years deployed in red zones showed a significant negative association with sleep quality ($\rho = -0.245$, $p < 0.001$), indicating that prolonged exposure may progressively deteriorate restorative sleep. Traumatic exposure was also negatively correlated with both sleep quality ($\rho = -0.225$, $p = 0.0003$) and perceived happiness ($\rho = -0.155$, $p = 0.012$), supporting the notion that adverse operational experiences have cumulative psychosocial consequences. No significant correlations were found with perceived stress or anxiety, reinforcing the idea that these constructs may be more strongly influenced by training-related resilience mechanisms rather than direct exposure.

One of the aspects highlighted in the scientific literature regarding the effects of experiencing traumatic events in conflict zones is the association with disturbances in sleep quality. Regarding sleep quality, the data revealed that soldiers with a history of trauma showed worse sleep quality compared to those without trauma exposure due to a probable dysregulation of the sympathetic nervous system [27]. This finding aligns with previous studies indicating that individuals exposed to traumatic events often report sleep disturbances. For instance, Coelho and Costa [28] found that war veterans exhibited heightened sympathetic nervous system activation, reflected in higher catecholamine levels, which contribute to poor sleep quality. Similarly, studies on Malvinas and Vietnam war veterans highlighted the prevalence of symptoms such as insomnia, nightmares, and difficulty falling asleep [29, 30]. These disorders may be due to cumulative stress associated with exposure to combat zones, which exacerbates sleep problems even in the absence of traumatic events. Comparable findings have been observed in other professional groups working in highly demanding and stressful conditions, such as healthcare workers [31] and police officers [32], where cumulative stress negatively affects sleep quality. Like the findings on sleep quality, soldiers with traumatic experiences reported lower perception of happiness. A longer experience in combat zones and accompanied by traumatic moments has a psychosocial impact on the soldier, reducing the quality of life and happiness [33]. Previous researchers with Peruvian reservists exposed to conflict showed that low happiness levels were predominant in 49% of participants, with PTSD symptoms reported in 67% [34]. Along the same lines, veteran soldiers deployed in long-term conflict zones such as the Iraq or Afghanistan wars showed a decrease in perception of happiness, or quality of life, due to the traumatic situations experienced in conflict zones [35].

While soldiers with experience in conflict zones showed diminished perceptions of happiness and sleep quality, their evaluations of stress and anxiety revealed no significant differences. State anxiety levels, as measured by the STAI, were low across the sample and consistent across both groups, suggesting a balanced commitment to life despite exposure to traumatic experiences. Similarly, perceived stress, as measured by the PSS-14, showed no significant differences between groups, with both reporting moderate levels of stress within the normative range. These findings suggest that, while traumatic experiences may significantly impact specific domains such as sleep quality and happiness, their effect on perceived stress and anxiety may be less pronounced among military personnel. This pattern was further confirmed in the correlation analyses, which showed no significant association between either years in red zones or traumatic exposure with stress (PSS-14) or anxiety (STAI). This suggests that, while sleep and emotional well-being appear to be sensitive to cumulative operational exposure, perceived stress and anxiety may be more strongly buffered by military training, habituation, and unit cohesion. This resilience can likely be attributed to the psychological preparation inherent in military training, which equips soldiers to manage stress effectively through exposure to simulated high-pressure scenarios and resilience-building strategies [36, 37]. Previous studies have highlighted the role of psychological training in enhancing coping mechanisms and emotional regulation, contributing to the ability of military personnel to maintain moderate stress levels and low anxiety even in challenging circumstances [38]. This preparation is particularly evident in professional soldiers, who, because of their training and experience, may be less inclined to report feelings of stress or anxiety. These findings are consistent with our correlation analyses, which demonstrated that both traumatic exposure and longer periods in red zones were moderately associated with poorer

sleep quality. The additional negative correlation between traumatic events and happiness reinforces previous observations that repeated exposure to threatening environments progressively diminishes subjective well-being.

This preparation of professional soldiers is reflected in their high psychological flexibility and low levels of perceived loneliness. Psychological flexibility, as measured by the AAQ-II, was notably high in both groups compared to non-clinical populations, indicating their ability to adapt to changing circumstances and manage difficult emotions effectively. This adaptability is likely fostered by military training, which emphasizes problem-solving, emotional regulation, and resilience. Similarly, loneliness levels, assessed through the UCLA Loneliness Scale, were remarkably low across both groups, significantly below the normative average for the general population. This finding highlights the strong camaraderie and social support inherent in military environments, which act as protective factors against isolation and stress. Previous studies support this, showing that cohesive military units provide both emotional and practical support, fostering resilience and enabling soldiers to cope better with adversity [39, 40].

Regarding the well-being and mental health of military personnel, it has been shown that physical activity has a significant impact on reducing perceived stress among the participants in this study. Soldiers who engaged in physical activity for more than 120 minutes reported notably lower stress levels compared to those who exercised for only 30–45 minutes. This finding highlights the role of regular physical activity as a protective factor against stress, aligning with previous research showing that physical activity decreases stress, anxiety, and depression [41]. Furthermore, physical activity is known to improve mood, boost self-confidence, enhance self-esteem, and alleviate sleep disorders, contributing to overall mental well-being [42]. The observed reduction in perceived stress among soldiers who engage in increased physical activity is consistent with that observed in previous studies [43]. In addition, it has been shown that higher levels of exercise during periods such as university examinations mitigated the psychophysiological effects of stress, supporting the notion that prolonged physical activity acts as a buffer against stress [44]. It would be interesting to analyze the effects of operative training on psychological well-being.

This study contributes to the literature by highlighting how established associations between stress, sleep, and emotional well-being play out in a real-world, high-risk context. Unlike general civilian samples, this population faces chronic exposure to violence and operational demands, which may shape their psychological resilience and influence the way stress-related symptoms are experienced and reported [45].

Practical applications

Understanding the impact of traumatic events on active-duty military personnel is highly valuable for preventing potential consequences. To improve the psychological indicators evaluated in soldiers, it is essential to design a comprehensive psychosocial intervention that addresses the impact of trauma, chronic stress, and prolonged service conditions in conflict zones.

The psychological well-being of active-duty military personnel is significantly affected by exposure to trauma, chronic stress, and prolonged service in conflict zones, necessitating comprehensive psychosocial interventions. Improving sleep quality through Cognitive Behavioral Therapy for Insomnia (CBT-I), relaxation techniques such as diaphragmatic breathing and mindfulness, and structured physical activity programs can mitigate stress and enhance resilience. Additionally, fostering emotional intelligence and promoting recreational activities can contribute to stress regulation and increased perceived happiness levels. Access to psychological support, including exposure therapies and Eye Movement Desensitization and Reprocessing (EMDR), is essential for addressing trauma-related symptoms, particularly those associated with PTSD, and improving sleep parameters. Institutional commitment, including leadership awareness, rotation policies, and expanded mental health resources, is crucial to the success of these interventions, ultimately strengthening soldiers' resilience and coping mechanisms in high-stress environments.

Limitations and future research directions

This study has contributed to the evidence base, but not without its limitations. The cross-sectional design limits inferences about causality. Additionally, the focus on this specific sample of military personnel in Colombia limits the generalizability of the findings. Future research could focus on conducting longitudinal studies to evaluate the long-term effects of traumatic events, including the role of physical activity. Additionally, physical training and adaptations should include specific interventions that consider the military unit's situation and operational context, which might lead to better results. Future studies should explore the role of other factors, such as social support and institutional policies, in mitigating the adverse effects associated with trauma and chronic stress.

CONCLUSION

Soldiers with greater exposure to combat zones reported lower perceptions of sleep quality and happiness. However, engaging in physical exercise is associated with reduced stress, potentially serving as a protective factor against stress-related disorders.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

This research received no external funding.

Authors' contribution

Conceptualization, Clemente-Suárez, and Curiel-Regueros; methodology Clemente-Suárez, and Curiel-Regueros; formal analysis, Curiel-Regueros; investigation, Clemente-Suárez, and Curiel-Regueros; resources, Clemente-Suárez; data curation, Clemente-Suárez, and Curiel-Regueros; writing—original draft preparation, Curiel-Regueros and Sánchez-Conde; writing—review and editing, Curiel-Regueros, Martínez-González, and Sánchez-Conde; visualization Martínez-González and Sánchez-Conde; supervision, Clemente-Suárez. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Universidad Europea de Madrid (CIPI/18/093)

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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ORIGINAL ARTICLE

Quality of Care and Post-COVID Disability in Romania: A Patient-Reported, Hospital-Wide Study

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Abstract: Background: COVID-19, declared a Public Health Emergency of International Concern, affected hospital operations by increasing the number of patients presenting to hospitals, the necessity to control infections, and the shortage of staff. Through our study, we evaluated the quality and quantity of care and how these changes affected patient experience and outcomes, and we identified actionable methods in order to prepare for the future. Methods: We analyzed data between 2020 and the first half of 2023 from a Romanian tertiary military hospital using patient-reported experience surveys and operational indicators (readmissions, postoperative complications). Associations were assessed using Pearson and Spearman correlation coefficients. We then benchmarked against an ideal surge-ready hospital using a 0-1 Composite Risk Index (CRI) that integrates occupancy, adverse-event density, flow reliability, and readmissions. Results: Overall satisfaction was strongly influenced by satisfaction with medical care ($p < 0.001$). Higher overall satisfaction was associated with fewer readmissions. Benchmarking showed the highest risk in the ICU, intermediate in Surgery and Internal Medicine, moderate in the ED, and the lowest in the Ambulatory. Satisfaction was highest in the initial period of the COVID-19 pandemic, dropped in 2022, and showed partial recovery at the end of this period. Conclusions: Quality of care is a critical measure of hospital performance, especially in the context of the COVID-19 pandemic. Patient feedback revealed areas of good practice and also the limits of the system, influenced by the burden of multisystem disease and limited resources. Post-COVID-19 disability outcomes are strongly influenced by the quality and continuity of care. Systematic use of patient-reported outcomes, standardized evaluation, and adaptive rehabilitation is essential to preserve the quality of care and reduce long-term functional impairment.

Keywords: quality of care; COVID-19 pandemic; post COVID-19 disability; patient satisfaction; burden of disease

INTRODUCTION

Quality of care (QoC) became a major challenge during the COVID-19 pandemic, especially once the World Health Organization classified it as a Public Health Emergency of International Concern (PHEIC)[1], creating disruptions in healthcare systems around the world. By definition, a PHEIC indicates a situation that poses a threat to public health, exceeds the borders of a single country, requiring global mobilization to prevent the spread and to provide assistance to affected countries. The declaration also helps in mobilizing international resources and preparing for a response[2].

During a PHEIC, like the COVID-19 pandemic, healthcare systems can become overwhelmed by large numbers of patients, especially when a large number of individuals need urgent medical care at the same time[3]. This can lead to shortages

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in hospital beds, medical equipment, and staff, ultimately affecting the quality of care provided (QoC). As COVID-19 affects multiple organ systems and represents a disruption of the daily care across all specialties, QoC is best analyzed across the entire hospital, rather than by department.

The COVID-19 pandemic has persistently affected healthcare services and the way hospitals delivered daily care changed due to overwhelmed healthcare systems [4], which led to changes in modes of care delivery [5], reorganization of hospital operations[6], staff shortages and burnout [7], delayed care and treatment[8] and supply chain disruptions[9], elements that would affect QoC.

Quality of healthcare (QoC) is an abstract concept, which makes it difficult to measure directly. There is no universal definition of healthcare quality, as different institutions and individuals may interpret it in various ways [10].

According to the WHO, the definition of QoC highlights the importance of healthcare services achieving positive health outcomes, addressing patients' needs and preferences, and being delivered in a safe and equitable way. It also emphasizes the efficiency of resource use, reducing delays, and ensuring that services are accessible to everyone, regardless of their background or situation. In addition to defining quality of care as effective and safe, the WHO also emphasizes the importance of the patient's perspective, defining it as people-centered[11]. The Institute of Medicine (IOM) defines healthcare quality as safe, effective, timely, patient-centered, efficient, and equitable[12]. Even though QoC is a theoretical idea, IOM defined the terms that compose the concept and provided a framework for measuring the items[13]. These attributes of QoC form the base of the measurable key performance indicators (KPI), widely used nowadays for evaluation of the healthcare performance. These indicators include patient access, inpatient and outpatient utilization, operating room utilization, ER utilization, generic utilization, patient safety, infection control, documentation, and patient satisfaction indicators reflecting patient-centeredness[14].

Starting from the QoC definition provided by literature, the main aim of our study is to evaluate QoC during the COVID-19 pandemic (March 2020 to May 2023)[15], in a military, emergency, and university hospital. A complementary objective is to benchmark "Dr. Carol Davila" Central Military Emergency University Hospital against an ideal, surge-ready hospital model, using a structured comparison (e.g., Composite Risk Index, flow reliability, triage capabilities) to identify system-level gaps that most influence patient-facing outcomes

The secondary aim is to translate these findings, including the comparison between ideal and actual performance, into a pragmatic preparedness blueprint for future health emergencies, by refining clinical and operational protocols, shortening response times, targeting workforce training and surge staffing, and prioritizing investments (e.g., digital triage, discharge reliability, ambulatory capacity) that are most likely to improve both QoC and resilience.

MATERIALS AND METHODS

The patient collection center was the "Dr. Carol Davila" Central Military Emergency University Hospital in Bucharest from 2020 to the first semester of 2023.

Inclusion criteria: adults (>18 years) hospitalized in any medical department of the "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest, receiving any type of care.

Exclusion criteria: patients who were unconscious or lacked decision-making capacity. According to the American Medical Association, Code of Medical Ethics Opinion 2.1.2: Decisions for Adult Patients Who Lack Capacity, 2016, decision-making capacity is the ability of a patient to understand relevant information, appreciate the medical consequences of their situation and choices, reason about treatment options, and communicate a consistent choice.

Data collection included information about first impression when entering the unit (cleanliness, discipline, luxury, quietness, austerity, disorder, lack of cleanliness), emotional impact when entering the unit (demoralized, no effect, uplifted), the modality of admission (ER, family doctor, specialist, ambulance, other), the recurrence of admission (first admission or a re-admission), about patient experience (reception with kindness, accompaniment to investigations, assistance during admission, understanding of illness, treatment, and associated risks, provision of personal medication, occurrence of post-operative complications, on-site opening of medication in patient’s presence, perception of pressure or coercion related to care, perceived necessity to reward staff). Data were also collected on service ratings, including staff attitude at reception, staff attitude during stay, medical care by doctor, nursing care, care by aides, post-op and ICU care, quality of meals, room facility conditions, sanitary conditions (bathrooms, toilets), overall cleanliness and data about information and safety (information about rights and responsibilities, knowing the staff who cared for them, information about treatment risks and side effects, about the use of protective equipment by the staff, and if they were informed about fall risks). Communication with the staff, overall satisfaction (general satisfaction, willingness to return, and recommendation of the hospital), and socio-demographic data were also collected.

Data collection instrument: “Patient Satisfaction Questionnaire- Continuous Hospitalization” approved by the quality officer in the "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest. The questionnaire was divided into two sections, the

first included the patient's perspective about the quality of the services (structured in 13 questions, with one or multiple answers), and the second part collected socio-demographic data.

Data analysis: Descriptive statistics were used to describe the study population and response distributions.

Patients were questioned at the end of the hospitalization process, after all types of continuous care. Participants received a written questionnaire in Romanian. The questionnaires were anonymous. They were subsequently placed by patients, relatives, or medical staff in a designated box, located in each medical ward, and were collected at the end of each month by designated staff.

The indicators used in analyzing quality of care from the patient's perspective were the first impression of the patient characterized by descriptive words, the patient's opinion about the services, using a grading from 1-5 (1 meaning very poor and 5 meaning very good), and overall satisfaction of the patient, ranging from very dissatisfied to very satisfied. Pearson correlation analysis was employed to assess the relationship between pairs of variables, utilizing the covariance approach. This method is considered one of the most reliable for evaluating associations between variables of interest.

A significance threshold of 0.01 was applied to all Pearson correlation tests. The strength of correlations was categorized as follows: strong ($r > 0.700$), moderate ($r = 0.300$-0.700), and weak ($r < 0.300$). We benchmarked "Dr. Carol Davila" Central Military Emergency University Hospital against an ideal, surge-ready hospital model to identify system-level gaps that most influence patient experience and safety during pandemics.

Using fractal theory and nonlinear dynamical systems, we modeled patient safety and hospital workflow as a complex adaptive system. To compare the mathematical model of an ideal hospital with the real situation at the "Dr. Carol Davila" Central Military Emergency University Hospital, we extracted relevant information from documents. Data analysis was conducted using IBM SPSS Statistics, version 25.0.

RESULTS

Demographic, General, and Specific Data Regarding Quality of Care from the Patient's Perspective

The study participants consisted of 10349 patients hospitalized in continuous care, spanning from 2020 through the first half of 2023, of whom 5143 were males (49,70%), and 5206 were females (50.30%). Ages ranged from 18 to 93 years, with a mean of 50,83 years. Patients came from 62.23% urban and 37.76% rural areas; 32,17% of them had higher education, while 67,83% had lower and middle education.

A marked decrease in annual COVID-19 admissions was observed at the Central Military Emergency University Hospital "Dr. Carol Davila" from 2020 to 2024. In 2020 and 2021, the hospital managed over 1,700 COVID-19 cases annually, reflecting the peak of the pandemic and the hospital's critical role in care delivery. Admissions dropped to around 1,450 in 2022, coinciding with expanded vaccination and improved public health measures. By 2023 and 2024, annual admissions fell to fewer than 400 and 200 cases (Figure 2).

Figure 1: "Patient satisfaction questionnaire- continuous hospitalization" used in "Dr. Carol Davila" Central Military Emergency University Hospital

PATIENT SATISFACTION QUESTIONNAIRE – CONTINUOUS HOSPITALIZATION

1. When you first entered the unit, what impression did you have? Choose three words that best describe the reception area:

Cleanliness	Discipline	Crowded
Luxury	Quietness	Austerity
Disorder	Lack of cleanliness	Other: _____

Please number 1, 2, and 3 in order of importance.

2. Did the reception environment affect your emotional state?
☐ It demoralized me ☐ No effect ☐ It lifted my spirits

3. How were you admitted?
☐ *Emergency Room* ☐ *Family Doctor* ☐ *Specialist Referral* ☐ *Ambulance* ☐ *Other:*__

4. Is this your first admission or a re-admission?
☐ *First Admission* ☐ *Re-admission*

5. During this admission, can you say:

P1. You were welcomed with kindness	☐ *Yes* ☐ *No*
P2. You were accompanied to investigations	☐ *Yes* ☐ *No*
P3. You were assisted at admission	☐ *Yes* ☐ *No*
P4. You understood your illness, treatment, and risks	☐ *Yes* ☐ *No*
P5. You brought medication from home	☐ *Yes* ☐ *No*
P6. You had post-operative complications	☐ *Yes* ☐ *No*
P7. Medications were opened in front of you	☐ *Yes* ☐ *No*
P8. You felt pressured or conditioned regarding care	☐ *Yes* ☐ *No*
P9. You felt the need to reward staff to receive attention	☐ *Yes* ☐ *No*

6. Please rate the following services (1 = very poor, 5 = very good, 9 = not applicable):

Service	*1*	*2*	*3*	*4*	*5*	*9*
Staff attitude at reception						
Staff attitude during your stay						
Medical care by the doctor						
Nursing care						
Care by nurse aides						
Post-op and ICU care						
Quality of meals						
Room and facility conditions						
Sanitary conditions (bathrooms, toilets)						
Overall cleanliness						

7. Were you informed about your rights and responsibilities as a patient?
Do you believe they were respected?
☐ *Always* ☐ *Sometimes* ☐ *Never (please specify):* _____

8. Do you know the staff who took care of you?
☐ *Yes* ☐ *No*

9. Were you informed about the risks and side effects of the treatments prescribed?
☐ *Yes* ☐ *No* ☐ *I was not informed*

10. Did the staff wear protective equipment during procedures, making you feel safe?
☐ *Yes* ☐ *No*

11. Were you informed upon admission about fall/slip risks in the hospital?
☐ *Yes* ☐ *No*

12. How do you rate communication with the healthcare team?
☐ *Unsatisfactory* ☐ *Fair* ☐ *Good* ☐ *Very Good*

13. Overall satisfaction:

13.1 How satisfied were you?
☐ *Very dissatisfied* ☐ *Dissatisfied* ☐ *Neutral* ☐ *Satisfied* ☐ *Very satisfied*

13.2 Would you return to this hospital if needed?
☐ *Definitely not* ☐ *Probably not* ☐ *Maybe* ☐ *Probably yes* ☐ *Definitely yes*

13.3 Would you recommend this hospital to others?
☐ *Definitely not* ☐ *Probably not* ☐ *Maybe* ☐ *Probably yes* ☐ *Definitely yes*

SOCIO-DEMOGRAPHIC DATA
Gender: ☐ *Male* ☐ *Female*
Age group: ☐ *<20* ☐ *20–29* ☐ *30–39* ☐ *40–49* ☐ *50–59* ☐ *60–69* ☐ *70+*
Residence: ☐ *Urban* ☐ *Rural*
Education: ☐ *Primary* ☐ *Secondary* ☐ *High School* ☐ *University*
Marital Status: ☐ *Married* ☐ *Single* ☐ *Partnership* ☐ *Widowed* ☐ *Divorced*
Department admitted to: _____

Figure 2: Trend in COVID-19 Patient Admissions by Year.

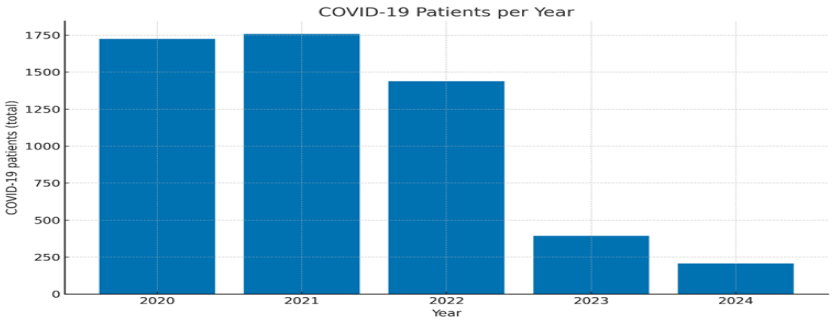
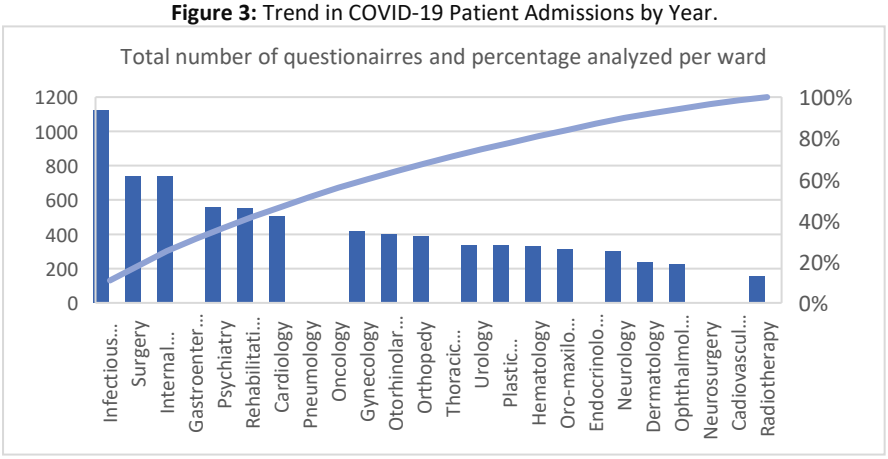


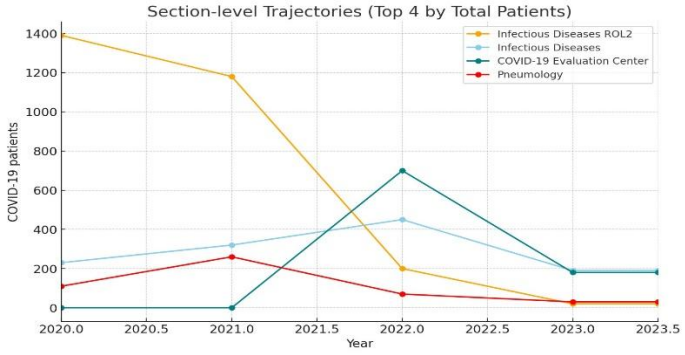
Figure 3: Trend in COVID-19 Patient Admissions by Year.



Most patients received continuous care in the Infectious Diseases ward, significantly more than in any other department t, and the ones who completed the least the Satisfaction Questionnaire were hospitalized in the Radiotherapy ward. Along with Infectious diseases, Surgery, Internal medicine, Gastroenterology, Psychiatry and Rehabilitation were characterized by a high percentage of completed questionnaires (Figure 3). Regarding the distribution per semester, most questionnaires were completed in the Infectious diseases ward between 2020 and 2022. In the first semester of 2023, Gastroenterology was the compartment with the most analyzed patients.

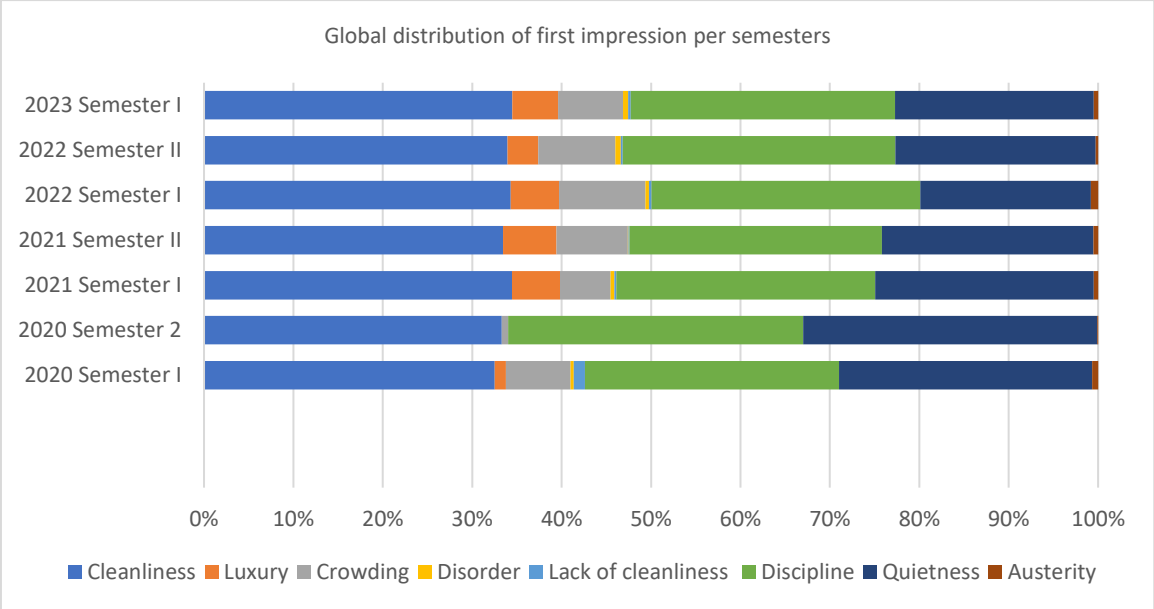
The yearly number of COVID-19 patients treated in the top 8 hospital sections at Emergency Military Hospital “Dr. Carol Davila” with the highest total case volumes during 2020-2024 were Infectious diseases ROL2, Infectious diseases, COVID-19 Evaluation Center and Pneumology. The “Infectious diseases ROL 2” were managed the majority of cases in the early pandemic, peaking at nearly 1,400 patients in 2020 and remaining the main COVID-19 section in 2021. However, admissions plummeted after 2021, reflecting both the centralization and then the redistribution of care as the pandemic evolved. The standard Infectious Diseases section also saw a big caseload, with a moderate peak in 2022, after which admissions gradually decreased. The “COVID-19 Evaluation center” only appears from 2022 onward, suggesting a new role for triage and ambulatory assessment as inpatient burdens decreased and outpatient management increased. All departments saw a substantial drop in admissions after 2022, consistent with overall trends of fewer severe COVID-19 cases requiring hospitalization (Figure 4).

Figure 4: Trajectory of COVID-19 Patient Volumes by Hospital Section (2020-2023)



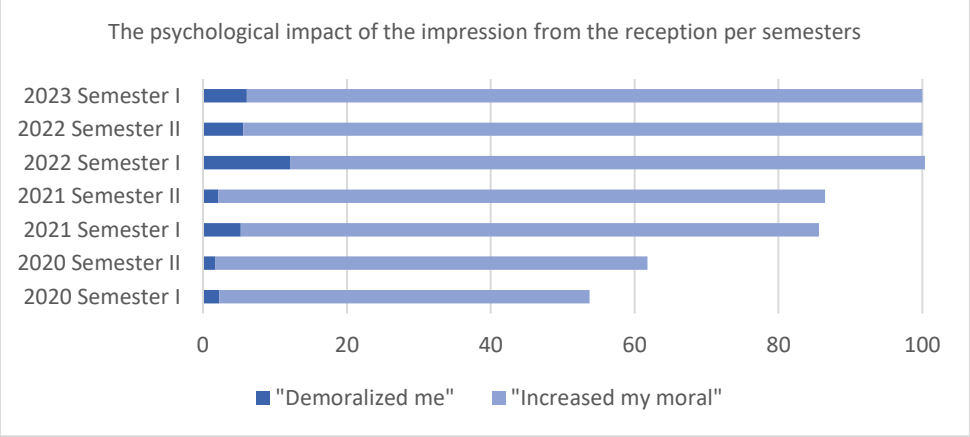
First impression of the patients about QoC was constant during the COVID-19 pandemic, most of them characterizing the reception area as clean, quiet and disciplined (Figure 5). Lack of cleanliness or disorder was reported by very few patients. After cleanliness, discipline and quietness, a small percentage of people mentioned that the reception area was crowded (6.73%). This can be observed starting with the second year of COVID-19 pandemics, first year being reported as less crowded. In the first year of the COVID-19 pandemic the compartment that reported the most crowding was Pneumology, followed by Gynecology, remaining years being followed by Infectious diseases with high percentage.

Figure 5: Trajectory of COVID-19 Patient Volumes by Hospital Section (2020-2023)



As a result of the appreciation of the reception conditions, 78.98% of people said their morale was boosted and only a small percentage of 5.03% were demoralized. For the remaining 15.98%, the reception conditions had no effect on perception (Figure 6). Patients were more indifferent to reception details in the first year of the COVID-19 pandemic. The impact increased the closer we got to the end of the pandemic.

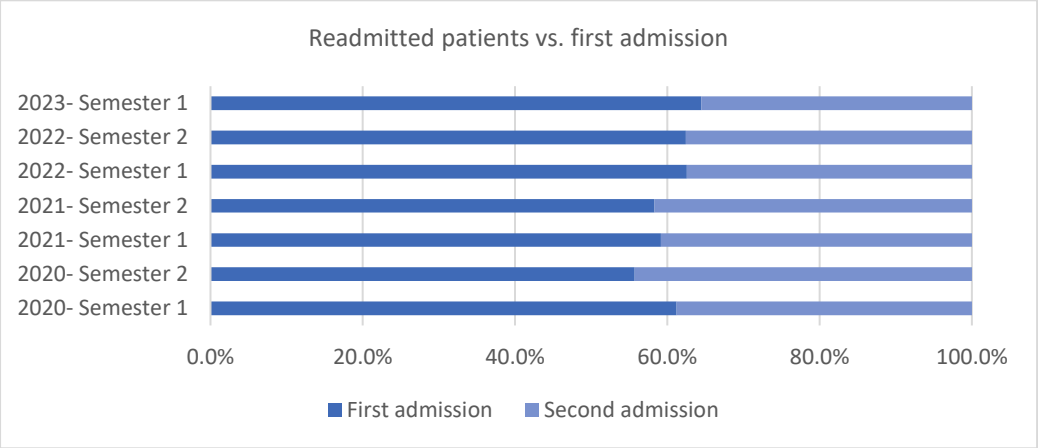
Figure 6: The psychological impact of the first impression from the reception, per semesters



The majority of patients presented to the hospital with a referral from their general practitioner (56.69%), followed by the percentage of patients who presented from the emergency room. It is noted that in the first year of the pandemic the percentage of patients presenting to the emergency room was lower than in subsequent years of the pandemic.

Most patients were at their first hospital admission (60.54%), but still a significant percentage had recurrent admissions (39.45%). There is a trend towards a decrease in recurrent hospitalizations as we approach the end of the pandemic (Figure 7).

Figure 7: Percentage of readmitted patients versus first admission, during the COVID-19 pandemic

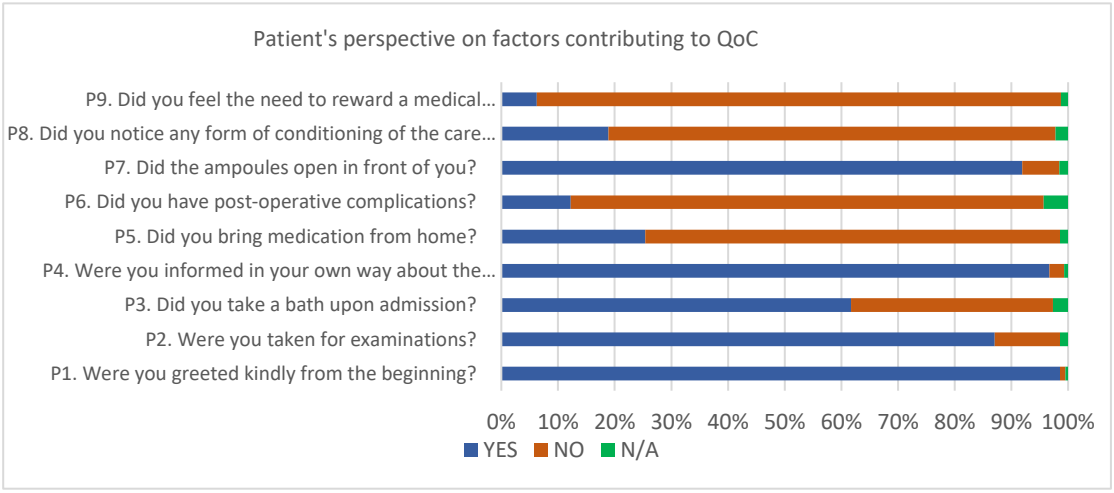


Regarding patient's perspective about specific items included in QoC (e.g. like greeting, accompanying investigations, taking a bath upon admission, being informed in an understandable way about their condition, bringing medication from home, having post-operative complications, opening the medicine vials in front of them, about noticing any form of conditioning or feeling the need to reward medical acts)overall, patients reported a positive experience.

A percentage of 98.54% of patients felt kindly greeted, and also a very high percentage of them, 96.67%, were informed in an understandable way about their condition. During the COVID-19 pandemic, only 61.67% of people admitted to all medical wards took a shower upon admission, with a slight increase in the first semester of the second year of the pandemic (68.04%), and slightly decreasing towards the end of the pandemic, respectively 53.46% in the 3rd semester of 2022. Regarding medication availability during this period, 25.41% of patients had their personal medication, but the majority of patients received it from the hospital (73.16%) (Figure 8).

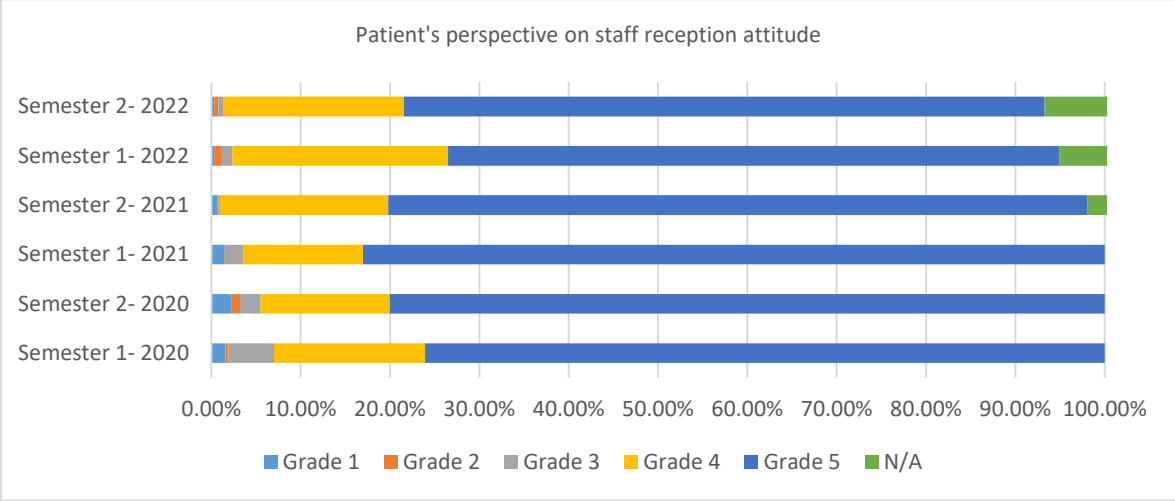
Patient's perspective about the services experienced during hospitalization between 2020 and first semester of 2023 was evaluated through these items: staff attitude at reception, staff attitude during their stay, medical care given by the doctor, nursing care, care given by nurse aides, post-op and ICU care, quality of meals, room and facility conditions, sanitary conditions (bathrooms, toilets) and overall cleanliness. The answers were rated on a scale of 1 to 5, where 1 means "very poor" and 5 means "very good". The majority of services were rated as "good" or "very good".

Figure 8: Patient's perspective on factors contributing to QoC, during the COVID-19 pandemic



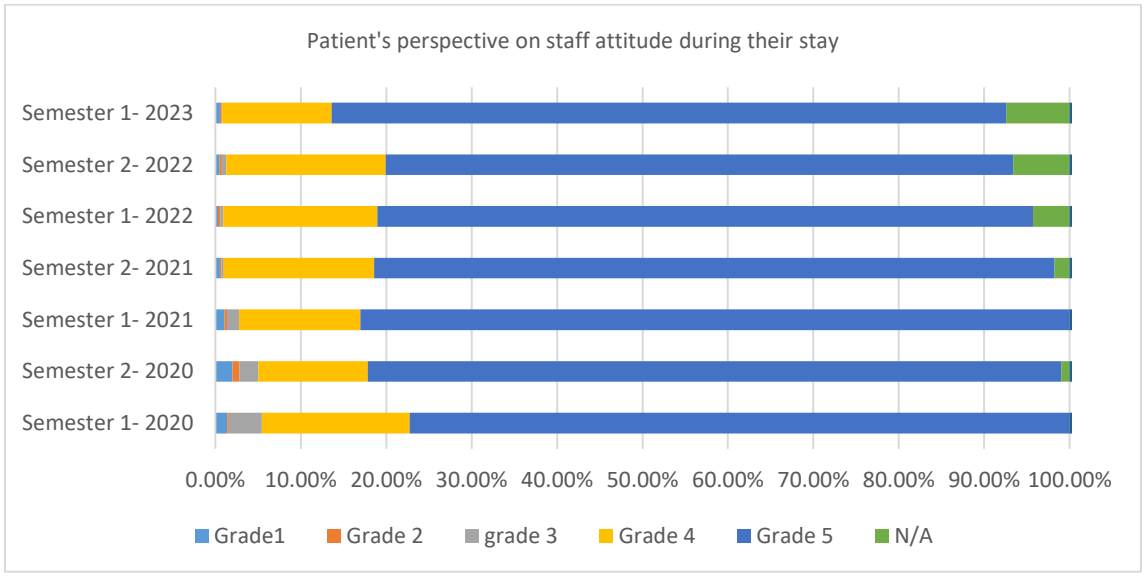
The attitude of the medical staff and the care provided were very good (answers 4+5) for patients in a proportion of over 94.26%, while a minority of 1.55% qualified staff at the reception as "very poor" or "poor".

Figure 9: Patient's perspective on staff reception attitude during the COVID-19 pandemic



Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Figure 10: Patient's perspective on staff reception attitude during the COVID-19 pandemic

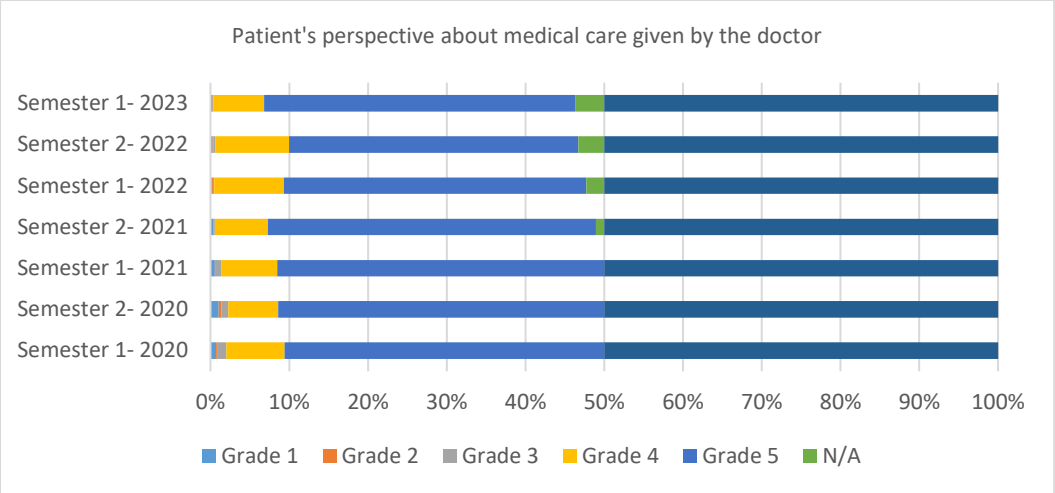


Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Later, during hospitalization, patients' opinions about the attitude of the medical staff remained favorable, 87% of them characterized it as good and very good (Figure 10).

Regarding the care provided by doctors, nurses and auxiliary care staff, it was assessed as "good" and "very good", in very high percentages: doctors - 94.84%, nurses - 94.93%, and nurse aids - 94.00% (Figure 11, Figure 12, Figure 13).

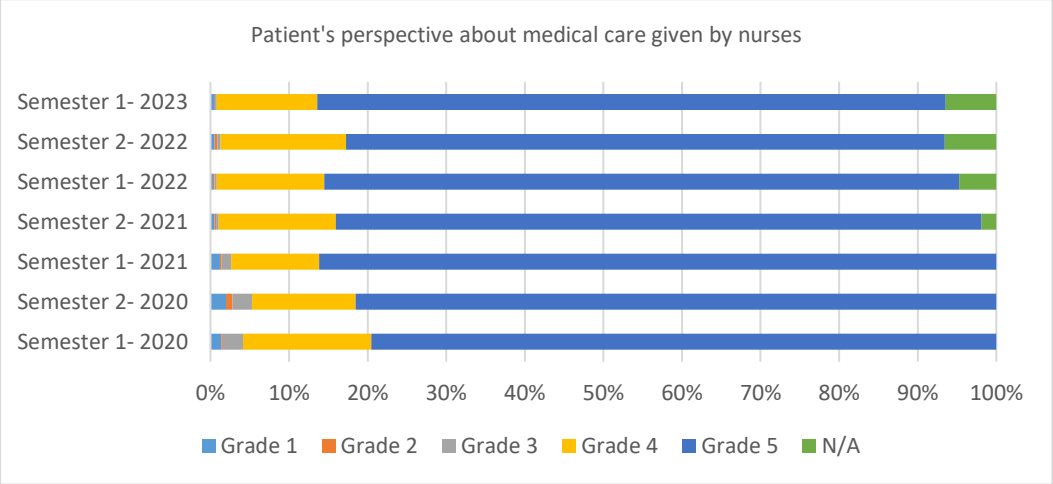
Figure 11: Patient's perspective about medical care given by the doctor during the COVID-19 pandemic



Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

It can also be observed that the highest percentage of "very good" ratings regarding the care provided by doctors is found in 2021 (semester 1 + semester 2) (Figure 11). The highest scores for care provided by doctors: Surgery I and II, Internal Medicine I, with >95% ratings of “Very good” and “Good”.

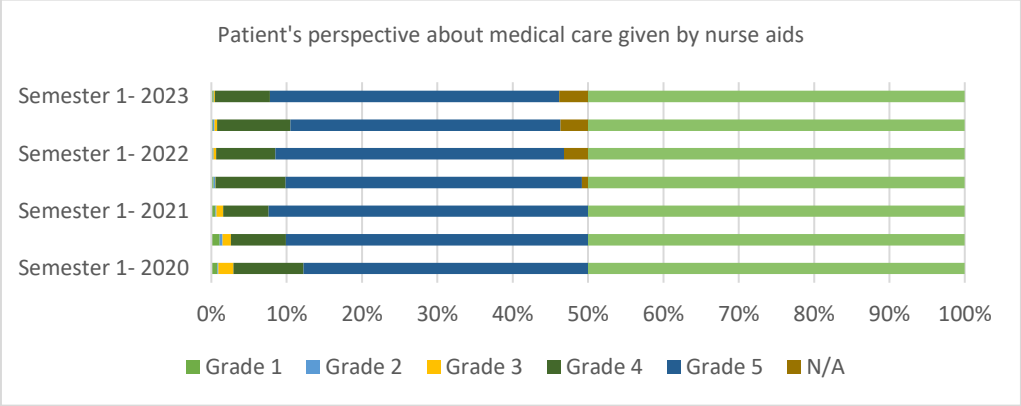
Figure 12: Patient's perspective about medical care given by nurses during the COVID-19 pandemic



Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Also, medical care given by nurses was appreciated most during 2021 (Figure 12). Care provided by nurses: was consistently above 94% for most departments.

Figure 13: Patient's perspective about medical care given by nurse aids during the COVID-19 pandemic

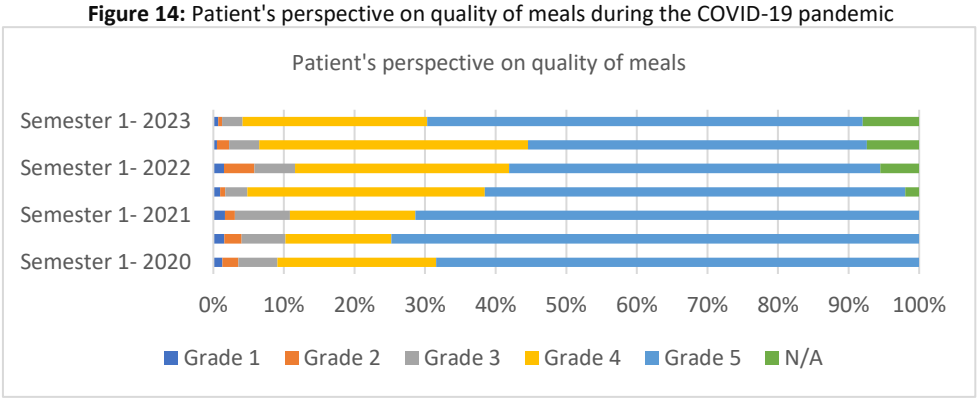


Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Regarding the care provided by nurse aids, the highest percentage of "very good" ratings is found in the 2nd semester of 2020 and the 1st semester of 2021.

Comparing with others QoC indicators from the patient's perspective, the quality of meals was slightly lower than the others, but still with a high percentage of "good" and "very good" qualifiers- 88.56% (Figure 14).

Figure 14: Patient's perspective on quality of meals during the COVID-19 pandemic

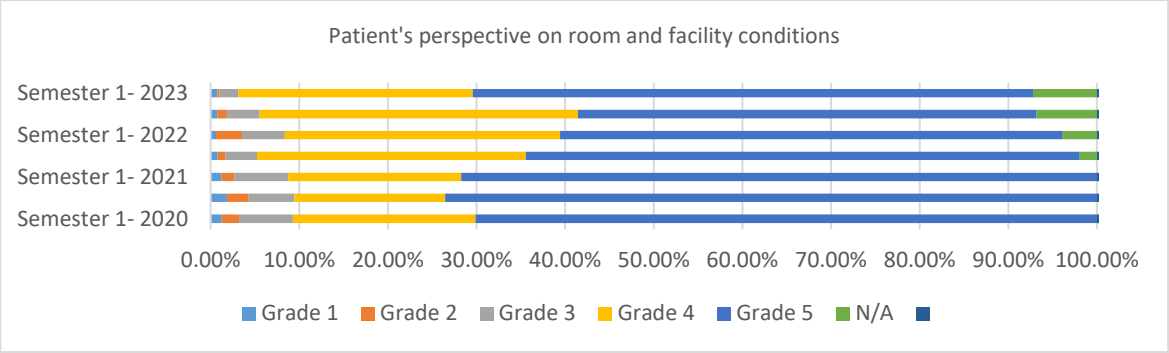


Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

It is also observed that in the first 3 quarters of the COVID-19 pandemic, patients' opinion of the quality of meals offered during hospitalization was better than in the second half of the pandemic interval.

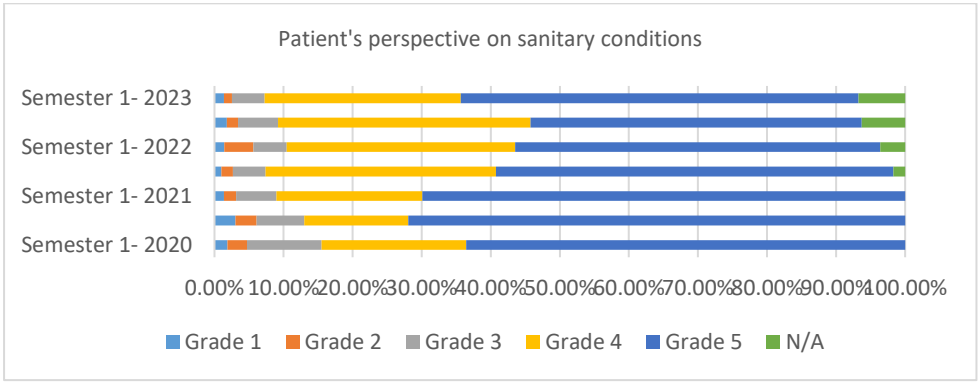
During the COVID-19 pandemic room and facility conditions were characterized by 64.22% of hospitalized patients as being "very good", and also "good" by 25.84%, giving the overall impression that in general, they were pleased with the accommodation conditions. (Figure 15).

Figure 15: Patient's perspective on room and facility conditions during the COVID-19 pandemic



Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Figure 16: Patient's perspective on sanitary conditions during COVID-19 conditions



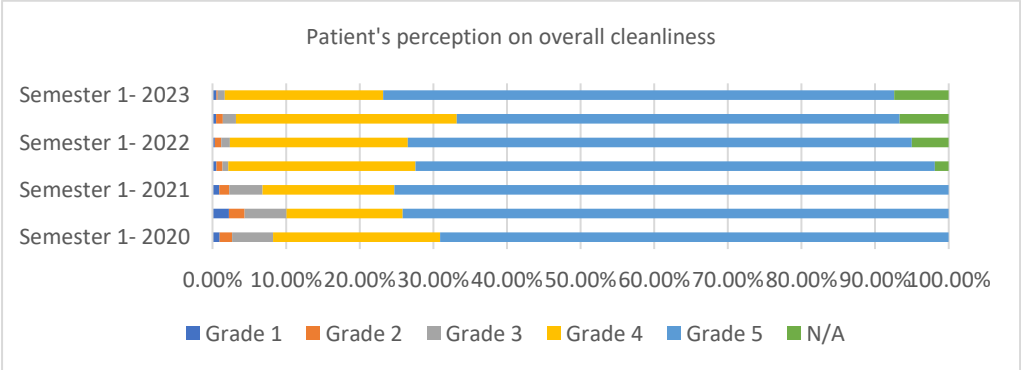
Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Regarding sanitary conditions, only 60.19% of patients reported very good conditions, while 26.95% referred to them as being "good". Overall, bathroom and toilet conditions were among the least appreciated qualifiers, even though, in total, the percentages of the 2 qualifiers (grade 4 + grade 5) that positively characterize these conditions are 87% (Figure 16).

The best perception of the sanitary conditions was in the second semester of 2020, and the worst perception was towards the end of the COVID-19 pandemic, in the second semester of 2022. (Figure 16).

Overall cleanliness was appreciated in proportion of 92% of the patients, while just 2% was not satisfied with the level of hygiene (Figure 17).

Figure 17: Patient's perception of overall cleanliness during the COVID-19 pandemic



Grade 1 = Very poor, Grade 2 = Poor, Grade 3 = Neutral, Grade 4 = Good, Grade 5 = Very good

Regarding the distribution per semester, most patients who characterized hygiene as being “very good” were hospitalized between the second semester of 2020 and the first semester of 2021.

Regarding question number 7, the majority of patients believed that they were informed about their rights and that they were respected. A discrete decrease in perspective toward the end of the COVID-19 pandemic can be noticed (Figure 18).

Figure 18: Patient's perspective on information and respect for rights during the COVID-19 pandemic

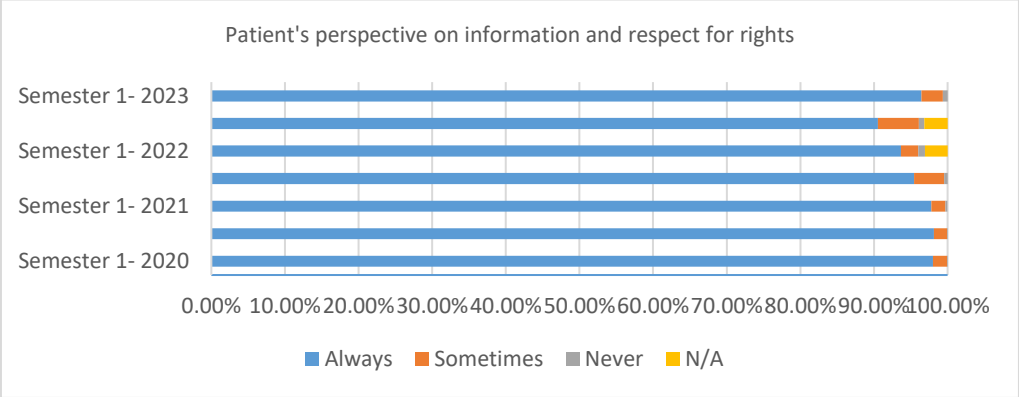
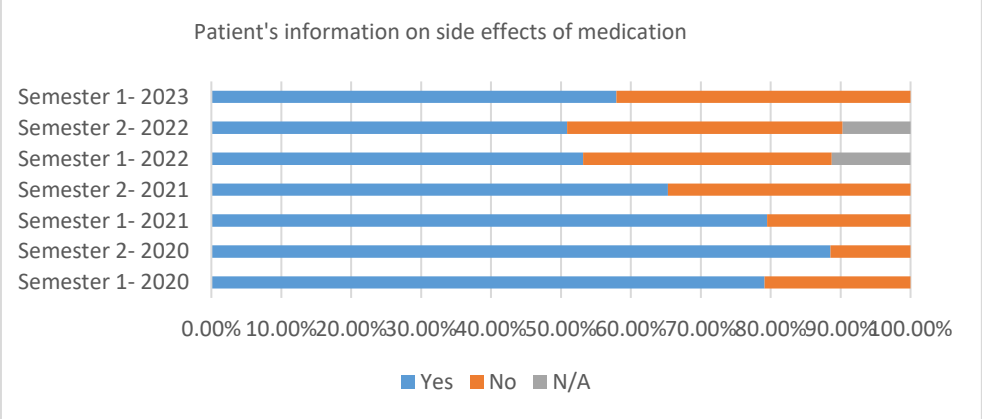


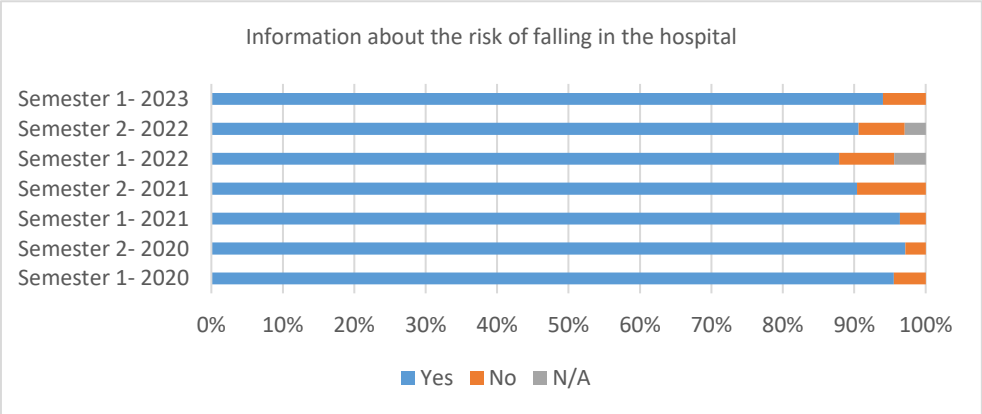
Figure 19: Patient's information on side effects of medication during the COVID-19 pandemic



Most patients were informed about the side effects of the medication, but the percentage is significantly increased in the first part of the COVID-19 pandemic (Figure 19).

Also, the majority of patients, 93.13%, was informed about the risk of falling into the hospital (Figure 20).

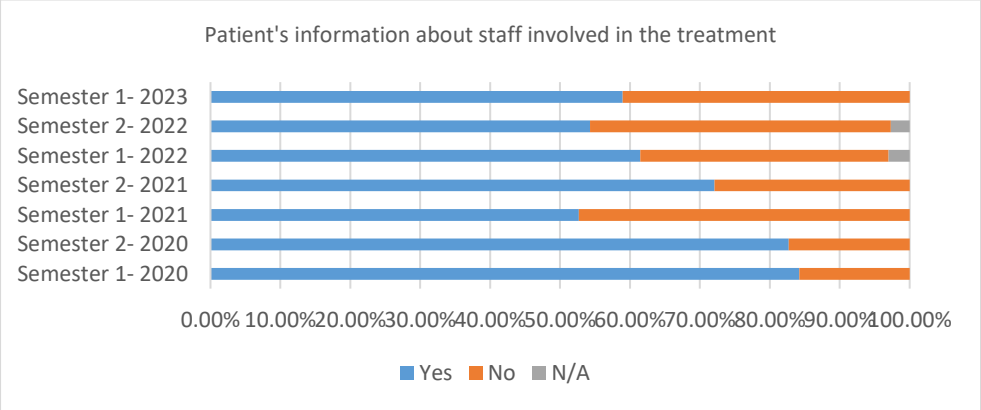
Figure 20: Information about the risk of falling in the hospital during the COVID-19 pandemic



The highest percentage of uniformed patients was in the second semester of 2021, in the middle of the COVID-19 pandemic (9.6%) (Figure 18).

A percentage of 66.63% of patients reported knowing about the identity and/or professional status of the medical personnel involved in the treatment administered (Figure 21).

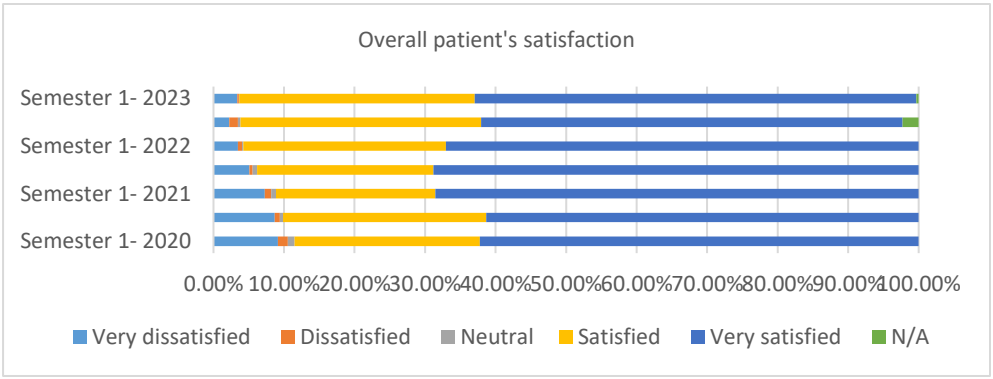
Figure 21: Patient's information about staff involved in the treatment during the COVID-19 pandemic



Given the specific items analyzed, patients were asked about overall satisfaction, and the opportunity to return (if needed) and about recommending the hospital services to others (if needed).

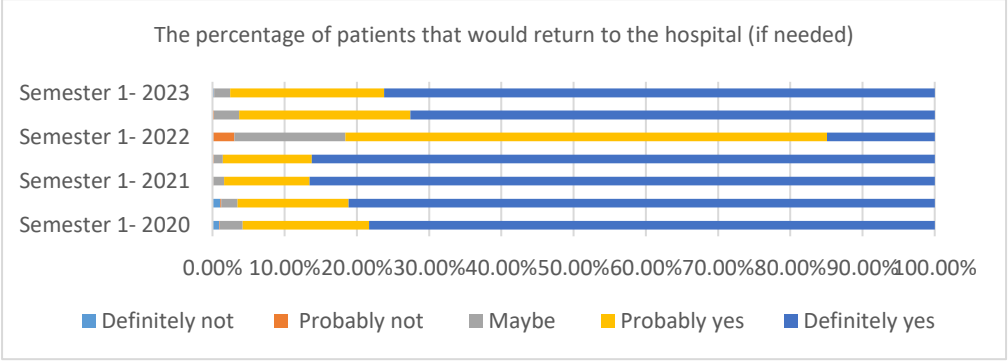
Overall, 92.76% of hospitalized patients during the COVID-19 pandemic reported being satisfied with their experience, with 64.34% "very satisfied" and 28.42% "satisfied" (Figure 22).

Figure 22: Overall patient satisfaction during the COVID-19 pandemic



Patient's satisfaction was lower in the first year of the pandemic but increased over time. Regarding willingness to return, 70.87% of patients stated they would "definitely return" if needed (Figure 21). Similarly, 60.23% indicated they would "definitely recommend" the hospital to others requiring medical care (Figure 23).

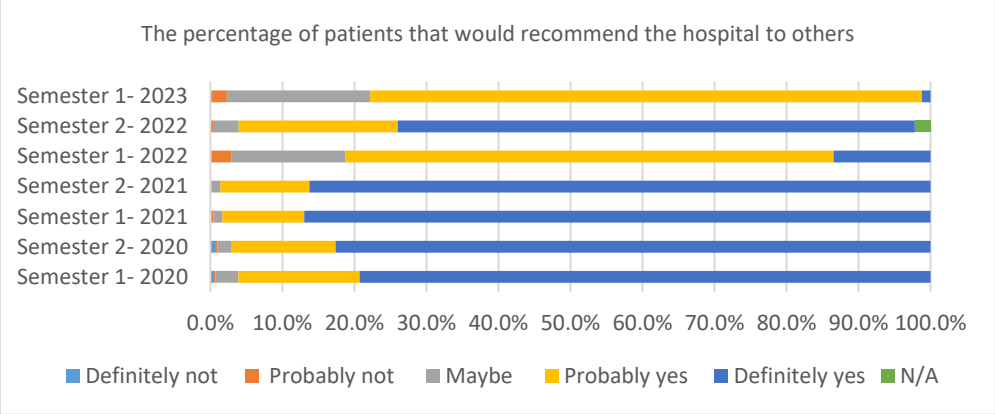
Figure 23: The percentage of patients who would return to the hospital (if needed), during the COVID-19 pandemic



Notably, in the first semester of 2022, confidence declined, with more patients responding “probably return” or “probably recommend” compared to other periods, suggesting a temporary dip in trust during mid-pandemic phases.

As can be seen in Figure 23, in the first semester of 2022, people’s trust has decreased, with a significantly higher percentage of them responding that they would probably recommend this hospital to others in need, compared to other periods of the COVID-19 pandemic, when they stated that they would definitely recommend it. (Figure 22, Figure 23). Respondents said that they would "probably return" compared to other semesters of the COVID-19 pandemic. Also, in the same semester, patients reported that they would probably recommend this hospital to others in need, compared to other periods of the COVID-19 pandemic, when they stated that they would definitely recommend it. (Figure 22. Figure 23).

Figure 24: The percentage of patients who would recommend the hospital to others

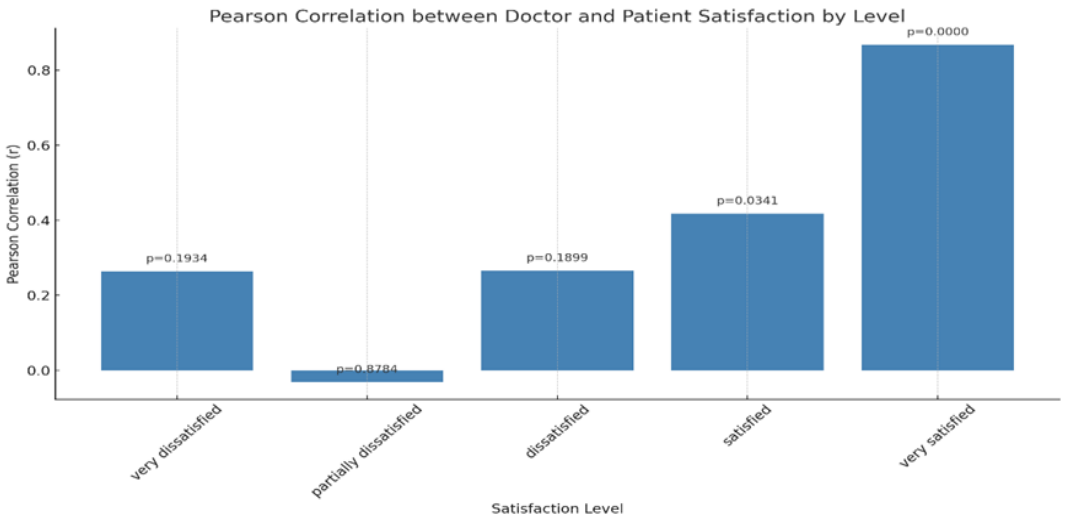


Patients were asked about overall satisfaction, willingness to return if needed, and likelihood of recommending the hospital to others. Overall, patient satisfaction strongly correlated with willingness to return and recommend the hospital, reinforcing its role as a key indicator of perceived quality of care, and 91,87% would recommend the hospital, 94.98% would return to the hospital, if necessary, and overall patient satisfaction was 92.76%.

Comparative analysis across medical departments

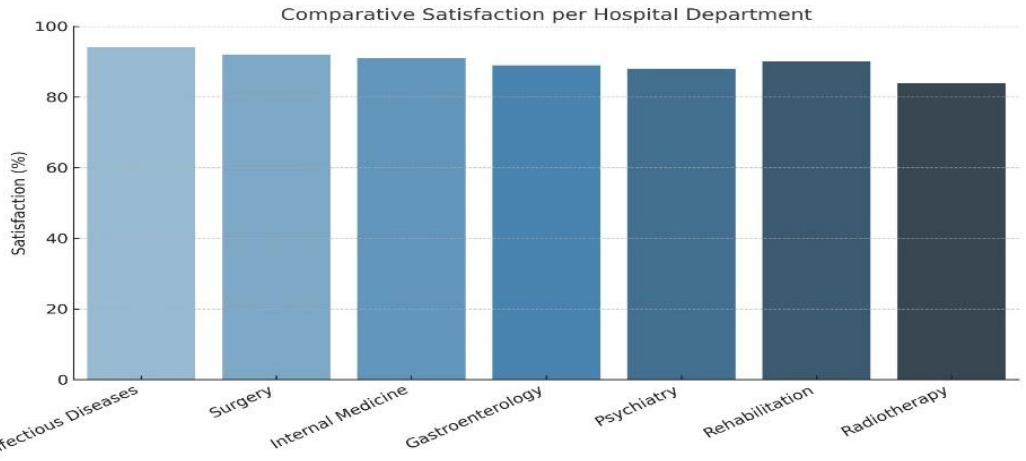
The Pearson correlation analysis revealed a strong positive relationship between the percentage of “very satisfied” patients and satisfaction with doctor care across departments ($r = 0.867$, $p < 0.00000001$). A moderate positive correlation was observed for the "satisfied" category ($r = 0.417$, $p \approx 0.034$) (Figure 26).

Figure 25: Pearson correlation between doctor satisfaction scores and overall patient satisfaction



p< 0.05 (statistically significant), p < 0.01 (very significant), p < 0.001 (highly significant); r-Pearson correlation coefficient

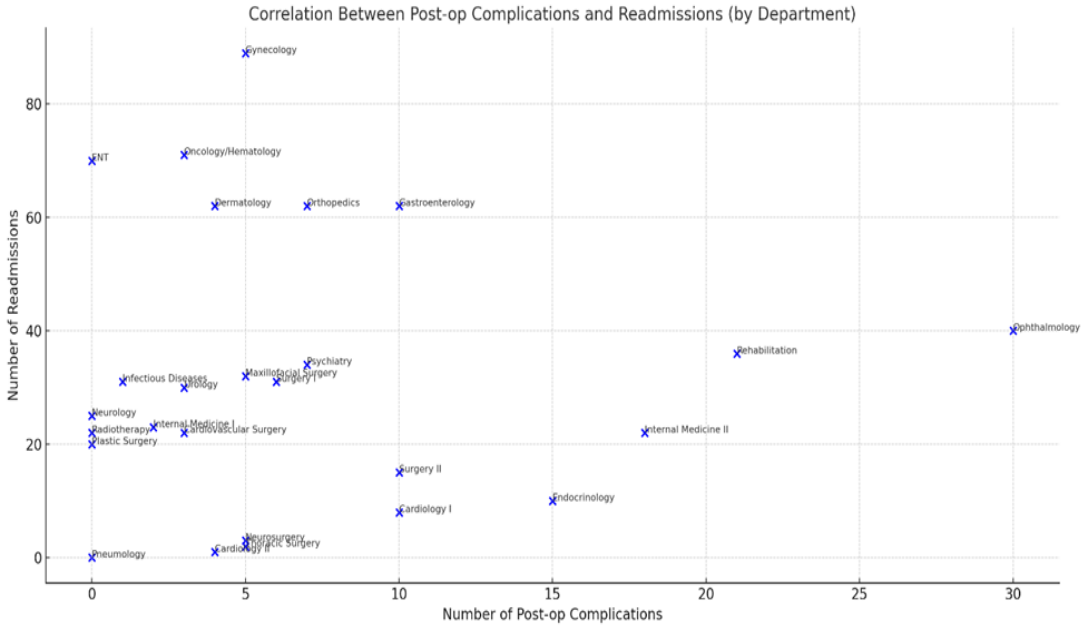
Figure 26: Comparative satisfaction levels across major hospital departments during the COVID-19 Pandemics



Comparative satisfaction rates across major hospital departments showed the Infectious Diseases department achieving the highest satisfaction (above 92%), followed by the Surgical departments and Internal Medicine (close to 91%). Gastroenterology and Psychiatry scored around 88-89%, while Physical Medicine and Rehabilitation maintained high satisfaction at around 90%, likely reflecting both the importance of rehabilitation post-infection and strong patient-provider relationships. Radiotherapy recorded slightly lower satisfaction (around 84%), possibly reflecting challenges faced by oncology patients during pandemic-related disruptions (Figure 26).

Correlation between overall satisfaction and readmission count per department indicated a moderate negative relationship ($r = -0.48$, $p = 0.012$), suggesting that higher satisfaction was associated with fewer readmissions. This supports the hypothesis that quality of care impacts clinical outcomes (Figure 27).

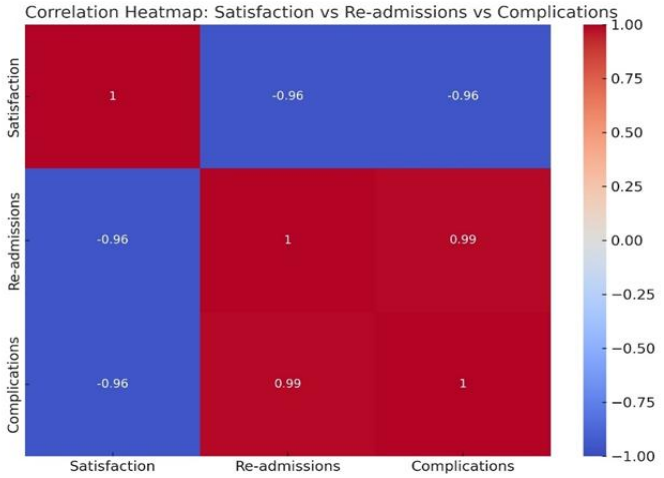
Figure 27: Correlations between post-op complications and readmissions



Analysis of post-operative complications and readmissions revealed a very weak, non-significant correlation ($r = 0.041$, $p = 0.84$), indicating that complications alone do not predict readmission rates (Fig.27). Other factors, such as discharge practices, follow-up care, and comorbidities, likely play a role. Departments like Gynecology, Onco-hematology, and Psychiatry showed high readmission rates despite low complication numbers, while Surgery I, Internal Medicine II, and Cardiology I exhibited more aligned patterns. Plastic Surgery and Maxillofacial Surgery had zero complications and zero readmissions, suggesting effective treatment or less complex cases.

The strongest statistically significant correlation was observed between Internal Medicine I and Thoracic Surgery (r = 0.997, p = 0.0002), Internal Medicine I and Radiotherapy (r = 0.997, p = 0.0002) and Cardiology II and Plastic Surgery also exhibited perfect correlation (r = 1.000, p < 0.0001), indicating near identical patient satisfaction distributions across these departments.

Figure 28: Interrelationships Between Patient Satisfaction, Readmissions, and Complications



A correlation analysis was performed to assess the relationships between overall patient satisfaction, readmission rates, and postoperative complication rates across hospital departments (Figure 30). The results demonstrated a strong negative correlation between patient satisfaction and both readmission rates (r = -0.96) and complication rates (r = -0.96), meaning that higher satisfaction was linked to fewer readmissions and fewer complications. Readmission rates and complication rates were highly positively correlated (r = 0.99), meaning that more complications were closely associated with more readmissions. These findings highlight a robust interdependence between perceived quality of care, clinical outcomes, and patient experience within the hospital setting (Figure 28).

Ideal Hospital Standards versus "Dr. Carol Davila" Central Military Emergency University Hospital during COVID-19

We compared our hospital with a theoretical surge-ready hospital model [16] to determine which system-level deficiencies most strongly influence patient experience and safety during pandemics. This comparison shows where resources should be directed (ICU surge capacity, admission control, staffing reserves, telemedicine) and establishes measurable goals (Composite Risk Index ≤0.70, reduced Emergency department congestion, improved team recognition) for future preparedness.

Hospitals behave like complex adaptive systems[17]: small changes (staff stress, bed occupancy) can have disproportionately large effects on patient safety. Fractal concepts capture how similar patterns repeat from ward to unit to hospital, and how consistency at each level helps keep the system stable. To build a mathematical model, based on nonlinear dynamics and fractal theory of a hospital operating with near-zero risk and to compare it with the Central Military Emergency University Hospital "Dr. Carol Davila," we first defined the parameters of the fractal, nonlinear model:

A. Mathematical model for a near-zero risk hospital [18],

Integrating fractal theory with nonlinear dynamical systems allows us to treat patient safety and hospital workflow as a complex adaptive system. Its main components are:

-Self-similarity: The health system should function coherently and predictably at all levels [19].

-Fractal dimension: The degree of hospital complexity can be expressed througha fractal measure. Efficient systems operate at an optimal complexity, where resources and patient needs are in balance [20].

-Strange attractors: The evolution of medical errors and hospital infections can be framed as a dynamical system

characterized by several stable and unstable configurations [21].

-Controlled chaos theory: Maintains a dynamic balance between fixed protocols and flexible responses to new situations like pandemics [22].

A fundamental equation for an ideal hospital patient safety management system could be:

$\frac{dS}{dt} = -\alpha S + \beta P - \gamma E$. S = patient safety, α = the rate of safety degradation driven by systemic risks, β = effect of prevention and of the improvement measures taken, P = proportion of patients who comply proportion of patients who follow safety and hygene rules, γ = the rate at which medical errors and hospital aquired infections rise, E= stress level among medical staff, a non linear

determinant with a direct effect on performance and error risk.

If we model the hospital as a fractal system, the fractal dimension *D* can be calculated as: $D = \lim_{r \to 0} \frac{\log N(r)}{\log (1/r)}$

N(r) is the number of repeating units of the hospital (wards, teams, checkpoints) at scale r. For an ideal hospital, this ratio should be optimized so that the organizational structure minimizes chaos. An ideal hospital should optimize this dimension to prevent bottlenecks in patient flows.

Table 1: Comparison of Ideal Hospital vs. "Dr. Carol Davila" CMEUH During COVID-19 [23], [24], [25]

Criterion	Ideal Hospital	"Dr. Carol Davila" Central Military Emergency University Hospital
ICU capacity and infrastructure	Flexible infrastructure with the ability to rapidly expand ICU beds.	ICU expansion achieved, but with logistical challenges and increased pressure on staff.
Risk management	Early implementation of integrated risk plans, fractal simulations, and predictive scenarios.	Reactive protocols adapted as the situation evolved; limited predictability initially.
Transmission control	Strict control via selected teams and advanced triage, reducing in-hospital transmission risk.	Triage was partially applied; selected teams implemented to a limited extent; some wards experienced internal outbreaks.
Composite Risk Index (ICR)	Maintained below θ ≈ 0.7, indicating epidemiologic stability.	Elevated values, especially in ICU and Internal Medicine (ICR ≈ 0.85), exceed the critical threshold.
Adverse events	Mean density ≈ 3,000 per unit area, with minimal variation across wards.	ICU and Internal Medicine showed extreme densities (>10,000), indicating overload.
Fractal complexity	D_x ≈ 1.2, indicating a more uniform distribution of cases and good cluster control.	D_x ≈ 1.5 in the Emergency Department and Surgery → heterogeneous distribution, concentrated clusters, hard to control.
Admission control	Time-slotted appointments, digital scheduling flows, and reduced pressure on the Emergency Department.	Sudden surges in patient inflow- significant congestion periods in the Emergency Department.
Workforce	Additional support teams, intensive training, and minimal burnout.	Elevated fatigue, stress, and burnout, with accelerated turnover among ICU staff.
Technology and telemedicine	Integrated remote-monitoring systems and full teleconsultation capabilities.	Telemedicine was partially implemented; many acute cases required in-person evaluation.

B. Comparison of the model with the "Dr. Carol Davila" Central Military Emergency University Hospital

To compare the mathematical model of an ideal hospital with the real situation at the "Dr. Carol Davila" Central Military Emergency University Hospital, we extracted relevant information from documents on nosocomial (hospital-acquired) infections, patient safety, and the hospital's performance during the pandemic. Neural networks and machine-learning systems are used to detect patterns in the occurrence of infections and to automatically identify and correct their sources. Risk-adjustment formula for infections: $R_t = R_0 e^{-\delta t}$. Rt is the infection rate at time t, $R0$ is the initial infection rate, and δ is the attenuation coefficient representing the reduction of risk through prevention measures.

The analysis is based on data from the document "Quality of care during the COVID-19 pandemic patients' perspective" ("Dr. Carol Davila" Central Military Emergency University Hospital, 2020-S1 2023), which describes the data-collection methodology, indicators, and results on satisfaction and perceived quality.

The Composite Risk Index (CRI) consolidates clinical pressure (occupancy, adverse events), distribution complexity (fractal proxy), and operational factors (flow, readmissions)[26] into a 0-1 scale. For S.U.U.M.C., the profile was composed from patient questionnaire results and operational indicators from the beginning of 2020 to the first semester of 2023, while the theoretical hospital profile assumes ward values between 0.30 and 0.50, and ICU <0.65.

The analysis links the CRI benchmarking (S.U.U.M.C. versus ideal hospital) with all CRI correlation outputs, such as event density, readmissions, utilization and fractal complexity (D_n or Df). Results are reported using Pearson correlation for linear and Spearman correlation for monotonic correlations. Threshold: $p < 0.05$.

C. Comparing the theoretical model with the empirical data and identifying the differences

According to CRI, risk is clearly stratified across medical services in the hospital, ICU being above the critical threshold of θ ≈ 0.85 and also beyond the ideal theoretical hospital target, which makes it a priority for urgent intervention. According to the report, they should introduce timed admission slots, strict cohorting with defined intervention teams, and maintain a capacity buffer in order to minimize the chaos.

Surgery and Internal medicine were the wards that showed intermediate CRIs, approximately 0.58- 0.59, with positive deviation from the target. These units should be prioritized for optimization.

The Emergency Department (ED) shows a moderate risk, with a Cri approximately of 0.54, meaning that they could improve or implement digital triage and better coordinate with the outpatient clinic in order to manage arrival peaks.

Gynecology and Orthopedic surgery have a good CRI, suggesting that they don't need a major change in their practice.

Ambulatory services showed the lowest CRI (approx. 0.24) and can relieve pressure from the ED.

These priorities are based on CRI from 0 to 1, which include occupancy, adverse event density, and readmissions, and they are consistent with resilience principles of reducing ICU and ER overload and developing ambulatory capacity in order to absorb demand.

DISCUSSION

This study presents a comprehensive evaluation of quality of care (QoC) in a military hospital during the COVID-19 pandemic, based on patient satisfaction data from the "Patient Satisfaction Questionnaire- Continuous Hospitalization", clinical outcome and qualitative data collected across all medical wards across the S.U.U.M.C. "Dr. Carol Davila." Data were extracted from all medical hospital departments because COVID-19 is a multisystem disease, affecting cardiovascular, neurological, renal, and musculoskeletal systems, thereby increasing demand across diverse specialties, including medical, surgical, and rehabilitation services [27]. Our findings align with international reports and highlight how patient perspectives can inform the reorganization of medical services during health emergencies. Similar observations have been reported in tertiary care studies during the pandemic, where effective communication and physician engagement were key drivers of patient experience [28].

Across departments, the percentage of patients who reported being "very satisfied" with doctor care strongly correlated with overall satisfaction. Similar observations have been reported in tertiary care studies during the pandemic, where effective communication and physician engagement were key drivers of patient experience [28].

Nursing care consistently achieved high satisfaction levels (>94%), reflecting strong leadership, multidisciplinary teamwork and effective communication, factors repeatedly identified as determinants of QoC in the literature. Across most wards, nursing care was achieved [29].

In our hospital, patient satisfaction was lower in the first year of the pandemic (2020) and improved thereafter (2021- first semester of 2023), a trend likely explained by initial operational shocks (surges, staff shortages, reconfigured pathways) followed by organizational learning and stabilization. This pattern mirrors findings from HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) -based studies reporting declines in staff responsiveness and cleanliness during the early pandemic phase [30].

In our cohort, 66.63% of patients reported knowing the identity or professional role of the clinicians involved in their care. This decrease may be attributed to infection-control measures, including masks, visors, or gowns, which obscured faces and badges. Literature confirms that protective equipment can hinder recognition and communication, and interventions such as photo badges, transparent masks, and standardized introductions improve identification [31]. Higher patient satisfaction correlated with willingness to return and recommend the hospital, reinforcing its role as a proxy for QoC. This is consistent with standardized programs such as HCAHPS, where global items-overall rating and "would recommend"-summarize patient perceptions of care quality. Hospitals performing well on these measures tend to show stronger recommendation intent, supporting our findings [32].

Departments such as Infectious Diseases and ROL2 experienced significant strain, managing the highest COVID-19 caseloads between 2020 and 2023. Peak admissions during initial waves necessitated resource reallocation, staff redeployment and establishment of new facilities (such as the COVID-19 Evaluation Center). Similar strategies were reported globally, including ICU extensions, rapid testing units and triage centers [33].

Surgical wards, gynecology, dermatology and ENT experienced a significant reduction in patient volume due to restrictions on non-urgent procedures. The COVIDSurg Collaborative estimated that approximately 28.4 million elective operations were canceled globally during a 12-week peak, with a median of 45 weeks required for recovery, explaining the marked volume reductions observed in Surgery, Gynecology, Dermatology, and ENT[34].

Across wards, patients' satisfaction and clinical outcomes varied. At our tertiary military hospital, Infectious Diseases achieved the highest satisfaction (92%), consistent with literature reports that COVID-dedicated units maintained high ratings and strong recommendation intent despite operational strain, likely reflecting clear communication, visible infection-control measures and cohesive workflows in cohorted departments [35].

Patients in some wards reported difficulties obtaining tests and treatments, contributing to perceptions of lower service quality. Crowding and resource constraints were noted, consistent with studies showing that COVID surges drove crowding, diagnostic delays, and care interruptions as bed occupancy and ICU load increased, reducing operational performance and patient experience [36].

Our results show marked changes in hospitalization types during the pandemic. Between 2020 and 2021, most COVID-19 patients were admitted for continuous care due to deteriorating clinical conditions and the absence of effective outpatient therapies. From 2022 onward, the implementation of antiviral medicines, expanded testing and vaccination [37], increased day hospitalization, altering treatment strategies and patient profiles; this trend was also reported in other studies [38]. Since 2023, the sharp decline in COVID-19 admissions led to the relaxation of previously established safety regulations. This shift demonstrates the healthcare system's adaptability in modifying protocols and optimizing hospital resources.

Despite systemic stress, 94% of patients reported staff care as “good” or “very good” and over 94% were satisfied with care provided by physicians, nurses and aides. While room cleanliness and comfort scored well, bathrooms and toilets were rated “very good” by only 60% of patients. These findings are consistent with reports that staff professionalism and clinical care remained highly valued under surge conditions, even when operational stress degraded facility aspects such as responsiveness or cleanliness [28,30,39,40].

Patient perspectives served not only as a mirror but also as an indirect driver of QoC during the pandemic. High satisfaction levels correlated with fewer readmissions and complications, suggesting that positive patient experiences may promote better communication, adherence, and early identification of complications. This relationship is supported by multiple studies, including among adults with chronic health conditions[41].

Our results suggest that patientwith high scores in doctor communication, discharge clarity and coordinated follow-up had lower readmission rates and smoother recovery. From a system perspective, these findings may reduce long-COVID functional limitations by accelerating rehabilitation access, preventing deconditioning and enabling self-management. Implementing timed admissions, dedicated staff, digital triage, standardized discharge, early follow-up, and telerehabilitation provides a practical pathway to lowering the post-COVID disability burden [42]. These findings mirror international evidence, suggesting that patient-reported experience measures (PREMs) influence QoC, with measurable effects on clinical outcomes, safety and resource utilization[43].

The comparison between S.U.U.M.C.’s department level of CRI and an ideal theoretical hospital highlighted specific opportunities linked to patient-facing outcomes. Wards exhibiting higher fractal complexity (heterogeneous, highly variable flow) show higher CRI at similar occupancy levels, suggesting that arrival variability and fragmented processes increase operational risk. This explains why the Emergency Department and perioperative pathways, which are more variable, showed a higher risk than ambulatory areas (where most people were scheduled) at similar overall volumes. Lower CRI values were associated with smoother communication and higher satisfaction. This highlights that strengthening admission control and expanding outpatient capacity reduces risk and improves patient experience.

CONCLUSION

However, staff identification during the pandemic could have been improved, as protective equipment obscured visual cues and hindered recognition.

Our findings demonstrate that patient perspectives on physician care serve as a strong marker and enabler of high-quality care, even during stressful periods such as the COVID-19 pandemic. Overall, patients reported high levels of general satisfaction, particularly in their interaction with medical staff. However, staff identification during the pandemic could have been improved, as protective equipment obscured visual cues and hindered recognition.

The direct relationship between perceived quality of care and readmission rates underscores the value of patient experience as a metric for quality management. The results can help plan for future health emergencies, highlighting the need for operational flexibility, clear communication, empathy, and teamwork.

Benchmarking “Dr. Carol Davila” Central Military Emergency University Hospital against an ideal surge-ready hospital profile identified actionable priorities: stabilizing ICU risk through timed admission and strict cohorting, standardising high-variability pathways in departments (like Surgery and Internal medicine), digitalising front-end triage (in the Emergency Department), and integrating all departments with ambulatory scheduling to prevent demand spikes.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors’ contribution

Conceptualization, C.U. and M.B.; methodology, C.U.; software, R.I.N.; S.B; data curation, R.I.N.; writing-original draft preparation, C.U. and I.C.; writing-review and editing, C.U., S.B., and I.C.; supervision, E.C.; project administration, R.I.N.; visualization, M.N.P. All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Ethics Committee of S.U.U.M.C. "Dr Carol Dvila" according to P.V. 824/09.10.2025

Patient consent for publication

Not applicable

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REVIEW

The diagnostic value of cone-beam computed tomography (CBCT) in the evaluation of sinonasal pathology: a narrative review

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Abstract: Cone-beam computed tomography (CBCT) has expanded from dento-maxillofacial radiology to otorhinolaryngology, being proposed as a low-dose alternative to multidetector computed tomography (MDCT) for evaluating uncomplicated sinonasal disease and for surgical planning. Major guidelines (EPOS, ICAR-RS, ACR) recommend native high-resolution CT for bone and MRI for loco-regional complications, while the role of CBCT remains focused on bone anatomy and the oro-sinusal interface. The objective of this review was to systematically synthesize the evidence on the diagnostic performance, radiation dose, indications/contraindications, and limitations of CBCT in sinonasal pathology, and to propose a practical algorithm for its use. The methodology consisted of searching PubMed/Medline and "gray" literature (professional society positions, guidelines) until September 2025; relevant guidelines/consensuses and original/comparative studies reporting the utility of CBCT for rhinosinusitis (acute/chronic), odontogenic sinusitis, fungal pathology, anatomical variations, pre- and intraoperative planning, doses/technical parameters were included. Papers focused exclusively on non-sinonasal pathology or on contrast-enhanced CBCT were excluded. The synthesis is narrative, oriented towards clinical questions. The key results were: (1) CBCT provides an excellent representation of the bone anatomy of the osteomeatal complex, with superior spatial resolution to MDCT, but with clearly inferior tissue contrast (limiting the evaluation of complications, soft tissues, and perisinusal extension); (2) the effective dose of CBCT for sinuses typically varies ~0.05–0.48 mSv depending on the protocol/FOV, usually below conventional MDCT, but not consistently below ultra-low-dose MDCT or photon-counting CT (PCCT) protocols, which can achieve even lower doses with superior image quality; (3) tor uncomplicated chronic rhinosinusitis (CRS), CBCT correlates well with endoscopy and is adequate for scoring (e.g., LM analog), assessing anatomical variations, and planning FESS; for orbital/intracranial complications, suspected tumors, or invasive fungal rhinosinusitis, CBCT does not replace CT/MRI; (4) In odontogenic sinusitis (ODS), CBCT is the first-line investigation because it finely delineates dental pathology, oro-antral defects, and foreign bodies, and consensus recommendations support its use guided by indications; (5) Intrinsic limitations: poor tissue contrast, uncalibrated/unreliable HU values, metal artifacts, and sometimes restrictive FOV; (6) In the clinical setting, "point-of-care" CBCT shortens the diagnostic pathway and can reduce costs/delays, but careful case selection and adherence to the justification principle are essential. In conclusion, CBCT has robust diagnostic value for uncomplicated rhinosinusal disease and for the dento-sinusal interface, with the advantage of dose and access, but it does not substitute MDCT/MRI in risk/complication scenarios. Responsible implementation, according to guidelines and radioprotection principles, maximizes benefits and minimizes risks.

Keywords: CBCT; chronic rhinosinusitis; osteomeatal complex; odontogenic sinusitis; radiation dose; FESS

INTRODUCTION

Rhinosinusal inflammation is highly prevalent and generates a significant burden of disease and system costs. EPOS 2020 remains the European reference for diagnosis and management, emphasizing the role of imaging in selected situations, such as preoperative anatomical confirmation, clinical-endoscopic discrepancies, suspicion of complications, or alternative causes. The ICAR-RS 2021 consensus statements and the ACR Appropriateness Criteria (2022) converge: high-resolution native CT is the standard for bone, and MRI is preferred for soft tissues, orbit, and intracranial structures; plain radiography has limited utility. In the last decade, CBCT has gained

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ground due to its high spatial resolution, lower cost, and compact "office-based" infrastructure. However, its performance in soft tissues and density standardization (HU) is limited, and its rational adoption requires clarity on the clinical question and technological alternatives [4–8].

At the population level, chronic rhinosinusitis (CRS) is associated with a significant prevalence, affecting quality of life, productivity, and the use of medical resources, with a disproportionate impact on subgroups with comorbidities (asthma, nasal polyposis, allergies). In this context, the role of imaging is not to "diagnose" CRS in isolation—which remains a clinical diagnosis supported by endoscopy—but to inform the therapeutic decision: delineating the anatomy before functional endoscopic sinus surgery (FESS), confirming alternative suspicions (e.g., odontogenic causes), or clarifying situations with clinical-endoscopic discordance [1–3]. Thus, the choice of imaging modality must stem from a well-formulated clinical question (of the type "what will I change if I find out X?"), respecting the principles of justification and dose minimization (ALARA).

CBCT has positioned itself as an attractive option in the evaluation of the bony compartment of the osteomeatal complex, where high spatial resolution and the possibility of fields of view (FOV) adapted to the region of interest can provide fine details of relevant anatomical variants (agger nasi, Haller/Onodi cells, concha bullosa, vascular tracts) with favorable cost and logistics in an outpatient setting [4–6]. In addition, the "point-of-care" (POC) availability in some clinics reduces the time between consultation, imaging, and therapeutic decision, which can increase the efficiency of the clinical workflow. However, these advantages must be weighed against its intrinsic limitations: weaker tissue contrast than MDCT, reduced sensitivity for complications in soft tissues (orbital, intracranial), variability of HU values, and susceptibility to dental metallic artifacts [5–8]. Consequently, CBCT does not replace CT/MRI in alarm scenarios (orbital/neurological signs, suspected tumor, invasive fungal rhinosinusitis), where guidelines explicitly recommend MDCT and/or MRI.

An area where CBCT has particular added value is the dento-sinus interface. A significant proportion of maxillary sinusitis has an odontogenic etiology, and CBCT offers superior visualization of the sinus wall, dental apices, periapical lesions, and possible oro-antral communications, with direct relevance for planning the interdisciplinary ENT–dentistry therapeutic sequence [1–3,4–6]. At the same time, in uncomplicated CRS, CBCT can support FESS planning by mapping anatomical variants and assessing the degree of obstruction of the osteomeatal complex, when endoscopy and the response to medical treatment leave the next step in suspense [1–3].

Radioprotection considerations are central. In practice, CBCT tends to offer lower effective doses than standard MDCT in usual protocols; however, the comparison becomes closer with the emergence and dissemination of "ultra-low-dose" MDCT (ULD-CT) protocols, demonstrated even in early clinical studies as being able to maintain diagnostic utility at very low doses, and with the adoption of photon-counting CT (PCCT), which, in the evaluation of paranasal sinuses, has shown the possibility of doses even below many CBCT protocols, while maintaining or improving image quality. In sensitive populations (young patients, repeated examinations), the choice between CBCT, optimized MDCT (ULD), and PCCT must be based on clear clinical benefits, in the spirit of EPOS/ICAR-RS/ACR [1–3,9,10].

Finally, reporting standardization and integration with clinical practice are essential: the use of reporting schemes (such as LM or structured descriptions of critical variants), and making explicit the method's limitations and the situations that require escalation to CT/MRI. At the same time, specific training for prescribing physicians and CBCT interpreters (including awareness of artifacts and interpretation pitfalls) remains a condition for safe and effective implementation [4–8].

The purpose of this article is a clinically oriented systematic synthesis of the value of CBCT in rhinosinusal pathology, compared to MDCT/MRI, with an emphasis on performance, dose, indications, limitations, and practical implementation. In particular, we will address: (i) situations where CBCT is appropriate as a first-line test (e.g., suspicion of odontogenic sinusitis or FESS planning in uncomplicated CRS), (ii) alarm signals that directly require CT/MRI, (iii) the pragmatic comparison of dose and information quality between CBCT and modern MDCT/PCCT, and (iv) operational recommendations for integrating CBCT into clinical workflows, aligned with the principles of justification and optimization defined in European and North American guidelines [1–3,9,10].

MATERIALS AND METHODS

We performed a systematic search (until September 7, 2025) on PubMed/Medline and consulted guidelines and society positions (EPOS 2020, ICAR-RS 2021, ACR 2022; AAO-HNS positions). Terms: cone-beam computed tomography, sinonasal, chronic rhinosinusitis, odontogenic sinusitis, fungal sinusitis, radiation dose, photon-counting CT, point-of-care CT, anatomic variations, endoscopic sinus surgery, navigation. We included: guidelines/consensuses; original/comparative studies relevant to CBCT in rhinosinusitis; papers on doses and image quality; reports on artifacts/limitations. Exclusions: non-sinonasal applications, series without clinically useful data, contrast-enhanced CBCT. A narrative synthesis on clinical questions is presented, and no formal meta-analysis was performed.

RESULTS

Technical principles, image quality, and inherent limitations

CBCT uses a conical beam and a flat detector, reconstructing volumetrically with a single arc or partial rotation. The major advantage is the high spatial resolution for fine bone structures (ethmoidal laminar plane, lamina papyracea, uncinate processes, Haller/Onodi cells), often surpassing MDCT at the same target dose; in contrast, soft tissue contrast is inferior due to noise, scatter, and beam hardening artifacts, especially in the presence of dental metals [4–6,31,32]. HU values are not standardized in CBCT (gray-level), so quantitative density estimates are unreliable and should not be used for inferences of tissue composition; recent literature confirms the variability of HU between devices and software [7,8]. Metal artifacts can be mitigated by reconstruction techniques/MAR algorithms and FOV settings, but remain a limiting factor in the dento-maxillary region [31–33].

Radiation dose: CBCT vs MDCT and new generations (ULD-CT, PCCT)

Clinical data report effective CBCT doses for sinuses of the order of 0.05–0.48 mSv (mean ~0.27 mSv), dependent on FOV, kVp/mAs, filtration, and protocol [11,21]. Optimization studies show scenarios for sinusitis diagnosis with ~77 µSv and protocols for surgical planning at ~0.21 mSv, confirming the potential for low-dose with adequate quality [14]. A systematic review (2024) on non-dental applications reported average dose reductions of ~12× for CBCT compared to MSCT in 19 studies, with wide variability (1.7–50×) [18]. However, advances in clinical CT — "ultra-low dose" MDCT and photon-counting CT (PCCT) — can lower the dose below many CBCT protocols while maintaining/superiorizing image quality; a 2024 sinus PCCT study reported 0.038 mSv (PCCT) vs 0.14 mSv (CBCT), with superior CNR and subjective appreciation for PCCT [15]. The pragmatic conclusion: CBCT has a dose advantage over classic MDCT, but not always over optimized ULD/PCCT protocols; the device-protocol selection must be local-specific and respect the principles of justification and ALARA. For context, a chest radiograph has ~0.1 mSv [5].

Uncomplicated chronic rhinosinusitis (CRS): diagnosis, scoring, planning

Guidelines indicate native high-resolution CT for anatomical confirmation and FESS planning. CBCT, as a technology, meets these requirements for bone and provides details of the osteomeatal complex, septum, concha bullosa, and accessory cells; the accuracy for bone lesions/anatomy is very good [1–3,17]. Studies correlate CBCT with endoscopy and show agreement in detecting CRS and OMC variations [17]; one study suggested that the accuracy of CBCT approaches that of endoscopy for the evaluation of CRS in certain clinical contexts, with the potential for an alternative to endoscopy in selected cases (patients with contraindications) [18].

Scoring: the Lund–Mackay (LM) system remains the reporting standard on CT, being robust inter-observer; however, the correlation with symptomatic severity is modest, and volumetric scoring or endoscopic phenotyping may have stronger links to quality of life [19,20]. CBCT allows for LM-analogous scoring (on reconstructed coronal/sagittal-axial images), but does not provide contrast to non-invasively differentiate mucosal subtypes or soft tissue complications. In practice, for uncomplicated CRS requiring anatomical confirmation and planning, CBCT is adequate, especially if available "point-of-care" and if there is no suspicion of complication. For complicated CRS (orbital pain, neurological signs, fever, immunosuppression), MDCT/MRI is required according to ACR/EPOS [1–3].

Anatomical variations of the OMC and critical structures

Documenting variations — Haller/Onodi cells, agger nasi, septal deviations, thin lamina papyracea, prominent anterior ethmoidal artery — is essential preoperatively [21–23]. CBCT excellently highlights these variants and reports prevalences similar to CT, including in patients with dental or orthognathic indications [3,17,21–23]. These findings must be integrated into standardized reports (e.g., the CLOSE/RELEVANT scheme) to reduce intraoperative risks [22,23].

Odontogenic sinusitis (ODS): the ideal example for CBCT

ODS represents a significant proportion of maxillary sinusitis and requires a particular diagnostic/therapeutic algorithm [24]. CBCT is the investigation of choice to identify dental sources (periapical lesions, resorptions, post-extraction complications), oro-antral communications, foreign bodies, and involvement of the sinus walls, all with superior precision to panoramic radiography [24,25]. Recent consensuses recommend multimodal diagnosis (clinical-endoscopic-imaging), but emphasize that indication-guided CBCT accelerates management and correctly directs the sequence of dental therapy/FESS [24,25].

Fungal pathology: "fungal ball" vs. invasive fungal rhinosinusitis

CBCT can capture intralesional densities/calcifications in a maxillary "fungal ball," a classic radiological sign; however, complete detection requires a sufficiently large FOV and, in case of doubt, confirmation by MDCT [26]. For invasive fungal rhinosinusitis, ACR algorithms and recent reviews emphasize that MRI (with contrast) is more sensitive for perisinusal invasion and orbitocranial extension; CT remains useful for bone and calcifications, and CBCT is not indicated as the primary modality in this context [3,27].

Suspicion of tumor, orbital/intracranial complications

In the presence of sinonasal masses, suspicious bone erosion, signs of orbital cellulitis/abscess, or neurological symptoms, CBCT is not sufficient: ACR recommends high-resolution CT and MRI for soft tissue characterization and extensions; CBCT may miss subtle signs in soft tissue and does not allow for vascular/meningeal evaluation [3].

Preoperative planning and navigation; intraoperative role

For uncomplicated FESS, CBCT provides the necessary bone map, including anatomical variants and critical relationships; the risk-benefit equation may favor CBCT in patients without comorbidities/complications. In the operating room, intraoperative CBCT has demonstrated registration accuracy and utility for updating navigation, especially in skull base surgery; however, availability is limited, and the benefits on complications/reinterventions are heterogeneous [28]. Interfacing with augmented reality solutions based on intraoperative CBCT has achieved sub-millimeter errors in experimental models [33].

Pediatrics and "point-of-care" (POC)

In children, guideline-based practice discourages imaging in uncomplicated acute sinusitis; when images are necessary, selection is made strictly by indication [3]. POC CBCT in adults — and, occasionally, in adolescents — has logistical advantages: rapid scanning, seated/upright position, reduced sedation, integration into the same consultation, shortening the diagnostic path; recent AAO-HNS positions support the use of POC-CT when it aids management, with attention to justification, training, and interpretation quality [29]. Early data from public clinics suggest reduced time to therapeutic decision and fewer visits when CBCT is available in the outpatient setting, but robust economic evaluations are needed [30].

DISCUSSION

Key advantages of CBCT in sinonasal disease

Superior bone spatial resolution, ideal for mapping the osteomeatal complex, anatomical variations, and sinus wall defects; 2) Compact infrastructure and relatively low cost, including POC availability; 3) Lower dose than standard MDCT in most common protocols; 4) Excellently visible dento-sinusal interface, which positions CBCT as the first choice in odontogenic sinusitis; 5) Short acquisition time and good patient tolerance (useful in the clinic/outpatient workflow). These benefits can increase treatment adherence (by reviewing images with the patient) and can reduce time and cost investments in some clinical pathways [24,25,29,30].

Intrinsic limitations and critical considerations

CBCT has poor tissue contrast and artifacts (beam hardening, scatter), which reduce sensitivity for mucosa, collections, subtle fluid emissions, and perisinusal extensions. HU values are uncalibrated, with variability dependent on the manufacturer/protocol/algorithm; quantitative uses should be avoided [5,7,8,31–33]. In invasive fungal rhinosinusitis, orbital/intracranial complications, masses, and CSF fistulas, CBCT is inadequate; CT (sometimes with contrast) and MRI are standard [1–3,27]. Finally, it should not be assumed that CBCT always offers lower doses than all alternatives: ULD-CT/PCCT can achieve doses below CBCT with superior quality — an important decision point in centers with such technologies [15,18].

In diabetic patients, rhinosinusitis can rapidly evolve into loco-regional and systemic complications with lethal potential[34]. For this reason, in situations where such an evolution is suspected, CBCT does not provide sufficient information for a complete evaluation of the pathology. In these cases, the use of computed tomography (CT), with or without magnetic resonance imaging (MRI), is necessary to accurately determine the extent of sinonasal involvement and to correctly guide therapeutic management.

Integration with guidelines and radioprotection aspects

Justification of the examination is essential. EADMFR recommendations and European/national positions require that CBCT be indicated only when it changes management and after adequate clinical triage; training for prescribers and interpreters is required [13]. In ENT, ACR provides clear scenarios: CBCT may be appropriate for uncomplicated CRS and planning; CT/MRI is used in suspicion of complications, tumors, and IFRS [3]. EPOS/ICAR-RS confirm these orientations, emphasizing integration with endoscopy and clinical phenotyping [1,2].

Proposed practical algorithm (indicative)

A practical, indicative algorithm for the use of imaging in sinonasal pathology must start from the presence or absence of alarm symptoms. In cases presenting orbito-neurological signs, immunosuppression, high fever, severe pain, suspicion of tumor or invasive fungal rhinosinusitis (IFRS), the recommended imaging investigation is emergency computed tomography, with or without contrast administration, supplemented by magnetic resonance imaging with contrast for an adequate evaluation of soft tissues. In these situations, CBCT is not indicated.

For uncomplicated forms of chronic rhinosinusitis (CRS), imaging is not mandatory for diagnosis. However, if anatomical reconstruction is anticipated or FESS intervention is planned, or in case of clinical-endoscopic discrepancies, CBCT can be used, especially when point-of-care (POC) is available. The imaging report must be standardized and include details about critical anatomical variants. In centers where superior performance ultra-low dose (ULD) CT or photon-counting CT (PCCT) protocols are available, these may be preferred, especially if soft tissue evaluation is anticipated.

In case of suspected odontogenic sinusitis (ODS), CBCT is the first-line investigation, integrated with dental and endoscopic evaluation, requiring close collaboration between ENT specialists and dentists.

For suspected maxillary "fungal ball," CBCT with an adequate field of view (FOV) is recommended, but if atypical signs appear, confirmation by CT or MRI is necessary. In cases of suspected IFRS, the imaging protocol must obligatorily include CT and MRI; CBCT is not recommended.

Implications for Practice and Research

CBCT may shorten the diagnostic and treatment pathway for patients with uncomplicated chronic rhinosinusitis (CRS) and odontogenic sinusitis (ODS), especially in point-of-care (POC) models. The following are needed:

1. standardization of reports (critical anatomy, scoring systems),
2. comparative studies between optimized CBCT and ULD-CT/PCCT regarding clinical outcomes and cost-effectiveness,
3. development and validation of MAR/AI algorithms to reduce metal artifacts and improve soft-tissue surrogates,
4. ENT-specific guidelines for training and quality interpretation in CBCT.

Recent studies have shown that CBCT can have comparable sensitivity to conventional CT in detecting sinonasal anatomical variations in patients with chronic rhinosinusitis [35]. In addition, the use of CBCT is supported by less expensive infrastructure and superior ergonomics in outpatient clinical settings, which can contribute to optimizing patient flow [36]. At the same time, recent advances in image reconstruction and artifact correction contribute to improving the diagnostic value of CBCT, including for otorhinolaryngological applications [37].

CONCLUSION

CBCT has strong diagnostic value in uncomplicated sinonasal disease, in FESS planning, and especially in odontogenic sinusitis, where bony detail and the dento-sinusal interface are crucial. Its dose advantage compared to standard MDCT and its point-of-care (POC) accessibility are real, though not universal: in centers equipped with ULD-CT or PCCT, these technologies may offer lower radiation doses and superior image quality—particularly when soft tissue assessment is required.

CBCT does not replace CT or MRI in the context of complications, tumors, or invasive fungal rhinosinusitis (IFRS).

An implementation guided by the clinical question, adherence to EPOS/ICAR/ACR guidelines, and respect for radiation safety principles maximizes patient benefit. In practice, careful case selection must be coupled with standardized reports (e.g., CBCT-adapted LM-type scoring and inventory of critical anatomical variants), optimized dose protocols, and training for prescribers/interpreters. The integration of CBCT into interdisciplinary ENT-dentistry pathways can shorten the time to therapeutic decision in ODS and reduce costs, conditioned by local quality audit and re-exposures. Direct comparisons between CBCT vs ULD-CT/PCCT are needed on clinical outcomes, cost-effectiveness, and quality of life, as well as the evaluation of MAR/AI algorithms for artifact control. Phased implementation, with monitoring of performance indicators and patient satisfaction, supports sustainable use.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

Conceptualization, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA; methodology, CV, CA.; software, CV, CA; validation, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA.; formal analysis, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA; investigation, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA; resources, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA; data curation, CV, CA; writing—original draft preparation, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA; writing—review and editing, CV, VZ, RH, LG, AS, AR, ORP, IGI, CA; visualization, CV, VZ, IGI, CA.; supervision, CV, VA. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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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 office@rjmm.ro.

EDITORIAL AND CONTENT CONSIDERATIONS

Aims and Scope

Romanian Journal of Military Medicine (RJMM) is the official journal of the Romanian Association of Military Physicians. The Journal publishes peer-reviewed original papers, reviews, meta-analyses, systematic reviews, and editorials concerned with clinical practice and research in the fields of medicine. Papers may cover the medical, surgical, radiological, pathological, biochemical, physiological, ethical, and historical 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 may 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 Academic Editor. The Editor-in-Chief 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), available at: 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:

– Accessible to the public at no charge;

– Searchable by standard, electronic (Internet-based) methods;

– Open to all prospective registrants free of charge or at minimal cost;

– Validates registered information;

– Identifies trials with a unique number; and

– 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, a 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 200 words. Abstracts for original articles should be formatted as detailed in the Word form. Titles must not be longer than 120 characters (including spaces). In every article, there must be three to ten pertinent keywords specific to the article yet reasonably common within the subject discipline.

Editorials

These are invited by the Editor-in-Chief or their delegated editor and should be a brief review of the subject concerned, with reference to 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): [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 “miniseries” 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 suggested to limit to 3500–5000 words, with an abstract of up to 200 words and up to 100 references and 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-analyses and Systematic Reviews are similar to other reviews, and articles are subject to the usual peer review process. Meta-analyses and Systematic Reviews are suggested to be limited to 3500–5000 words, with an abstract of up to 200 words and up to 100 references and 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 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 suggested to be limited to 3000 words, with an abstract of up to 200 words and up to 100 references and figures or 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 the diagnosis of unusual cases. Contributions will be reviewed by the Executive 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 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 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 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

Abbreviations should be used sparingly and only where they ease the reader's task by reducing the repetition of long technical terms. Initially, use the word in full, followed by the abbreviation in parentheses. Thereafter, use the abbreviation.

Trade names

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: the title page and the main text file according to the Word model.

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 an 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 according to the word model. 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 200 words or fewer the purpose, basic procedures, main findings, and principal conclusions of the study. If appropriate, divide the abstract with the headings: Background and Aim, Methods, Results, and Conclusions. The abstracts of reviews need not be structured. The abstract should not contain abbreviations or references. Three to ten 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/meshhhome.html.

Text

Authors should use the word form in editing the submitted material.

References

The Vancouver system of referencing should be used. In the text, references should be cited using Arabic numerals in square parentheses 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 fewer; when seven or more, list the first three followed by et al. Names of journals should be abbreviated in the style used in MEDLINE. References to unpublished data and personal communications should appear in the text only.

Use Index Medicus as the style guide for references and other journal abbreviations.

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 and legend must be understandable without reference to the text. 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.

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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.

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Manuscripts should be submitted online at office@rjmm.ro. A cover letter containing an authorship statement should be included. The cover letter should include a statement covering each of the following areas:

– Confirmation that all authors have contributed to and agreed on the content of the manuscript, and the respective roles of each author. It is not accepted that the idea of equal contribution.

– Confirmation that the manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere.

– 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.

– For research involving pharmacological agents, devices, or medical technology, a clear Conflict of Interest statement about any funding from or pecuniary interests in companies that could be perceived as a potential conflict of interest in the outcome of the research.

– For clinical trials, these have been registered in a publicly accessible database (see more under 'ETHICAL CONSIDERATIONS (Further Information)' later in these guidelines).

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 the Word model that is to be found on the web page (http://revistamedicinamilitara.ro/wpcontent/uploads/2022/07/Macheta-articole.docx).

Each figure should be supplied as a separate file, with the figure number incorporated in the file name. For submission, high-resolution figures (at least 300 d.p.i.) saved as .eps, .jpg, or .tif files are required.

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Proofs

Once the paper has been typeset, the corresponding author will receive an email alert containing the proof of acceptance. It is therefore essential that a working e-mail address is provided for the corresponding author.

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