Romanian Journal of
Military Medicine

Founded 1897 • New Series

Vol. 129 • No. 3/2026 • May

REVISTA DE MEDICINĂ MILITARĂ

REDACTION

Strada Mircea Vulcanescu, Nr. 88, Sector 1, București, Email: office@rjmm.ro
www.revistamedicinamilitara.ro

Romanian Journal of Military Medicine, New Series, vol. 129, No 3/2026, May
ISSN-L1222-5126; eISSN 2501-2312; pISSN 1222-512

Romanian Journal of
Military
Medicine

Founded 1897•New Series
Vol. 129 • No. 3/2026, May

Contents

https://doi.org/10.55453/rjmm.2026.129.3.1

ARTICLE

An exploratory study on microarray technology-based biomarkers in post-menopausal women with obesity: focus on blood levels of adipsin, adiponectin and agouti-related peptide

Oana-Claudia Sima[1,2], Sorina Violeta Schipor[3], Veronica Cumpata[4], Luminita Suveica[3], Dana Manda[3], Ana Valea[5,6*], Emi Marinela Preda[7,8*], Mihai Costachescu[9], Mara Carsote[2,10], Mihai-Lucian Ciobica[11,12]

[1] PhD Doctoral School of "Carol Davila" University of Medicine and Pharmacy, 020021 Bucharest, Romania
[2] Department of Endocrinology V, "C.I. Parhon" National Institute of Endocrinology, 011863 Bucharest, Romania, O.-C.S. oana-claudia.sima@drd.umfcd.ro
[3] Department of Research, "C.I. Parhon" National Institute of Endocrinology, 011863 Bucharest, Romania, S.V.S. sorina.schipor@parhon.ro, D.M. dana.manda@parhon.ro
[4] Department of Family Medicine, State "Nicolae Testemiţanu" University of Medicine and Pharmacy, 2004 Chisinau, Republic of Moldova V.C. veronica.cumpataciorba@gmail.com, L.V. luminita.suveica@usmf.md
[5] Department of Endocrinology, "Iuliu Hatieganu" University of Medicine and Pharmacy, 400012 Cluj-Napoca, Romania
[6] Department of Endocrinology, County Emergency Clinical Hospital, 400347 Cluj-Napoca, Romania, A.V. ana.valea@umfcluj.ro
[7] Department of Radiology, "Carol Davila" University of Medicine and Pharmacy, 050474 Bucharest, Romania
[8] Department of Radiology and Medical Imaging, "Foisor" Clinical Hospital of Orthopedics, Traumatology and Osteoarticular TB, 021382 Bucharest, Romania, E.M.P. emi.preda@umfcd.ro
[9] Department of Radiology and Medical Imaging, "Dr. Carol Davila" Central Military University Emergency Hospital, 010825 Bucharest, Romania, M.K. mihai.costachescu@drd.umfcd.ro
[10] Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, 020021 Bucharest, Romania, M.C. mara.carsote@umfcd.ro
[11] Department of Internal Medicine and Gastroenterology, "Carol Davila" University of Medicine and Pharmacy, 020021 Bucharest, Romania
[12] Department of Internal Medicine I and Rheumatology, "Dr. Carol Davila" Central Military University Emergency Hospital, 010825 Bucharest, Romania, M.-L.C. lucian.ciobica@umfcd.ro

*Correspondence to: A.V. ana.valea@umfcluj.ro and E.M.P. emi.preda@umfcd.ro

Abstract: Background. A novel framework to assess obesity and its complications involves the evaluation of fat-derived factors as potential biomarkers of the cardio-metabolic outcome and long-term management. In this exploratory study, we aimed to evaluate microarray-based circulating levels of adiponectin, adipsin, and AgRP in menopausal women with obesity. Methods. This is a pilot, bi-centric study according to a protocol based on Quantibody® Human Obesity Array 3 (RayBiotech, Norcross, GA, USA). Patients with obesity-associated complications (hypertension, diabetes, dyslipidaemia) were excluded. Results. In the study population (N = 24, median age of 60 years) adiponectin correlated with lipocalin-2 (r = 0.943, p = 0.0048) and plasminogen activation inhibitor-1 (r = 0.829, p = 0.0416). Adipsin correlated with inteleukin-8 (r = 0.786, p = 0.0362), and leptin (r = 0.832, p = 0.0008). Conclusion. Apparently healthy obese menopausal individuals present a landscape of circulating adipokines that might be placed in relationship with the inflammatory and coagulation panel, across a complex inter-play. In addition, agouti-related peptide, despite being a well-known central orexigenic factor, might serve as circulating biomarker, too, noting its correlations with interleukin-6 and glycaemia at 120 minute during oral glucose tolerance test.

Keywords: biomarker, body mass index, adipokine, menopause, blood, assay, ELISA, leptin, interleukin

Citation: Sima OC, Schipor SV, Cumpata V, Suveica L, Manda D, Valea A, et al. *An exploratory study on microarray technology-based biomarkers in post-menopausal women with obesity: focus on blood levels of adipsin, adiponectin and agouti-related peptide* R. J. Mil. Med. 2026, CXXIX(3): 227-234 https://doi.org/10.55453/rjmm.2026.129.3.1

Academic Editor: Octavian Vasiliu

Received: 02 February 2026
Revised: 20 March 2026
Accepted: 09 April 2026

INTRODUCTION

Obesity represents a worldwide health issue with an alarming increasing incidence in the modern era [1-3]. Hence, multiple concerns of the medical community involve, not only addressing new drugs, but, also the development of new panels of

biomarkers to highlight the cardio-metabolic risk, long-term outcomes in order to be integrated in a targeted strategy of life-long management [4-6].

Under these circumstances, microarray analysis for blood factors represents a cutting edge exploration of the potential biomarkers, including in obesity, pointing out more than an interesting tool beyond the well-known genetic and epigenetic exploration amid this lab method [7-9]. Notably, there are no standardized panels of microarray-based biomarkers detection at this point in daily approach of obesity, thus the importance of exploratory researches to pinpoint their true value for the everyday practice of different clinicians with various backgrounds who treat numerous obesity-related complications [10-12].

Adipokines, adipocyte-derivate molecules, [e.g. adiponectin, adipsin, leptin, resistin, chemerin, omentin, visfatin, vaspin, osteonectin, PAI-1 (Plasminogen Activator Inhibitor), TNF-alpha (Tumor Necrosis Factor), IL-6 (Interleukin), IL-8, IL-10, IL-18, angiopoietin 1 and 2, etc.] are released by the adipose tissue, which represents an active endocrine organ, serving multiple functions others than the traditional role of lipids storage. The fat tissue-derived molecules interplay with all body organs and systems, both centrally and peripherally. The detection of some adipokines levels might serve as indicators of metabolism homeostasis and regulation amid physiological circumstances, but, also, in type 2 diabetes, obesity, arterial hypertension, fatty liver disease, metabolic syndrome, and some other endocrine diseases (e.g. primary hyperparathyroidism, acromegaly, Cushing's syndrome, adrenal tumours, etc.) [13-15].

Adipectin is an insulin sensitizing protein that also is prone to anti-inflammatory effects, while adipsin, less known than adiponectin, prior named "complement factor D" (CFD) involves an alternative pathway in complement activation with immune and inflammatory effects. Moreover, its deficiency has been found in relationship with metabolic impairment, specifically, type 2 diabetes, due to its actions of stimulating insulin release and glucose uptake in the muscle. Agouti-related peptide (AgRP), another fat-derived molecule, works both centrally and peripherally. The central role is to serve as orexigenic peptide (the hypothalamus-released factor), which increases the appetite and decreases the body energy expenditure. These actions of the neurotransmitter are prone to increased body fat and overall weight. In addition to the central production (next to the neurons that also produce neuropeptide Y), AgRP represents an adipokine that induces fat accumulation and reduces the cleavage of lipids by its peripheral effects. While AgRP might be dysregulated in obesity, it has been suggested to correlate with anomalies of the glucose profile [16-19].

Objective

Noting that in the modern medical era the search for novel panels of obesity biomarkers is continuously expanding, we aimed to explore the microarray-based circulating levels of adiponectin, adipsin, and AgRP in menopausal women with obesity.

MATERIALS AND METHODS

Study design & ethical aspects

This was an exploratory, pilot, prospective, bi-centric study in post-menopause adults confirmed with obesity based on the body mass index calculation, between December 2024 and December 2025. The ethical approval was provided by both centres: a tertiary centre of endocrinology in Romania and a medical university in Moldova. Ethical Boards approvals were: number 32 from 30 September 2024 for Bucharest, Romania, respectively, number 97 from 20 November 2024 for Chisinau, Republic of Moldova.

Study population

Inclusion criteria: adults over 50 years, body mass index of 30 kg/m2 or above, confirmed menopause, signed informed consent.

Exclusion criteria: any endocrine cause of obesity (e.g. acromegaly, Cushing's syndrome), endocrine tumours, type 1 diabetes, type 2 diabetes, dyslipidaemia of any type, arterial hypertension, prior or current medication such as anti-diabetes drugs, anti-obesity medication, corticotherapy, lipids lowering drugs, anti-hypertensive medication, bariatric surgery, anti-osteoporotics, malignancies, active infections, autoimmune and immune disorders, bone metabolic disorders, osteoporosis, (hereditary) syndromes with central obesity, obesity with paediatric onset, regardless of the syndromic or non-syndromic presentation.

Study protocol

After the informed consent was signed, the patients underwent fasting morning blood testing in addition to oral glucose tolerance test. We excluded the subjects with type 2 diabetes confirmation based on fasting glycaemia above 125 mg/dL or glycaemia at 120 min during 75-gram oral glucose tolerance test equal or above 200 mg/dL.

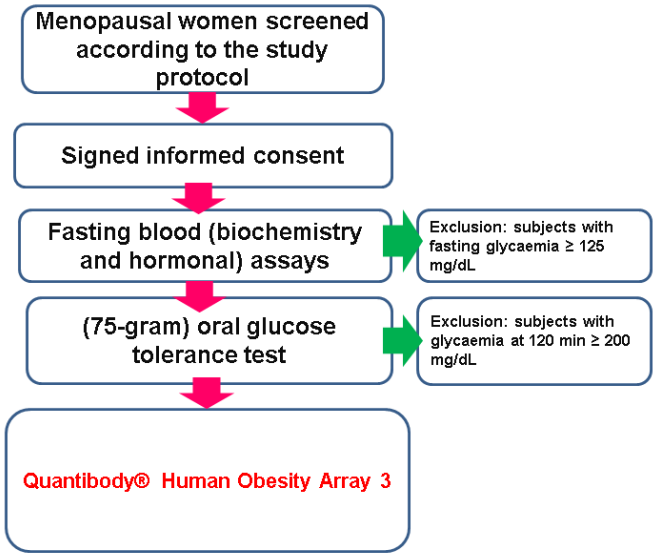
The collected data included: age (years), menopause (years since last menstruation), and body mass index [weight (kg) / height (m2)].

The panel of standard biochemical and hormonal markers included: glycaemia (mg/dL), uric acid (mg/dL), glycated haemoglobin A1c (%), HDL-cholesterol (mg/dL), triglycerides (mg/dL), fibrinogen (mg/dL), PTH (parathromone) in pg/mL, 25OHD (25-hydroxyvitamin D) in ng/mL, cortisol (µg/dL), as well as HOMA (Homeostasis Model Assessment) of insulin resistant with a calculation formula: fasting glycaemia (mg/dL) X fasting insulin (mU/L)/ 405.

Quantitative measurement of adipokines

Quantibody® Human Obesity Array 3 (RayBiotech, Norcross, GA, USA) was used. Quantibody® array represents a multiplexed sandwich enzyme-linked immunoserovent assay (ELISA)-based quantitative array platform that accurately determines the concentration of multiple cytokines simultaneously. It combines the advantages of the high detection sensitivity and specificity of immunoassay and the high throughput of arrays. The assay uses a pair of cytokine specific antibodies for detection. Firstly, a capture antibody is bond on the solid surface of a glass slide. Secondly, the target molecule is linked to the antibody. Then, a second antibody biotin-labeled is added and attached to the antigen-antibody complex. This complex is visualized by adding a streptavidin-conjugated Cy3 dye on a laser fluorescent scanner (GenePix 4400, Molecular Devices LLC, San Jose, CA, USA). For quantitation the array specific cytokine standards, whose concentration has been predetermined, are provided to generate a standard curve for each cytokine. The slide has a 16-well removable gasket which allows for the process of 16 samples on one slide or 8 standard samples and another 8 unknown samples. The samples are based on human serum. Adiponectin, adipsin and AgRP associate a CV (coefficient of variation) of less than 20% per each molecule assay. The panel of analysis also included IL-1Ra (Receptor Antagonist) in ng/mL, IL-6 (ng/mL), IL-8 (pg/mL), leptin (ng/mL), lipocalin-2 (ng/mL), PAI-1 (ng/mL), and TNF-RII (receptor II), which all show the same CV. The sample volume is 50 to 100 µl per array. (Figure 1)

Figure 1: Study protocol



Statistical analysis

MedCalc® Statistical Software version 23.3.7 was applied for data interpretation. Kolmogorov-Smirnov test was done for normality. Comparison of independent samples included t-test for normal distribution and Mann-Whithey test for non-normal distribution. The data were presented as mean ± standard deviation (SD) or median and interquartile interval (IQR), depending on normal or non-normal distribution. Pearson correlation was used for normal distribution, respectively, Spearman rank correlation for non-normal distribution. The cut-off < 0.05 showed statistical significance.

RESULTS

We enrolled in this exploratory study 24 patients with a median age of 60 years, and a median menopause duration of 7 years. Body mass index showed a median of 32.47 kg/m2. (Table 1)

Table 1: Study population' characteristics

Clinical parameters (units)	Study population
Age (years), median (min, max)	60 (53.00, 73.00)
Years since menopause, median (Q1, Q3)	7.00 (5.00, 13.00)
Body mass index (kg/m^2), median (95% confidence interval)	32.47 (32.32 to34.34)

The baseline panel of biochemical and hormonal markers was performed in order to analyse the correlations of the mentioned array-based adipocytes. (Table 2)

Table 2: Biochemical and hormonal assessments in study population

Parameter, unit	Median
	95% confidence interval
Uric acid, mg/dL	5.37
	4.65 to 6.03
Cortisol, µg/dL	9.02
	8.9 to 21
Glycaemia (120'), mg/dL	155
	126.79 to 175.03
Glycaemia (60'), mg/dL	186
	170.48 to 236.72
Glycaemia (0'), mg/dL	104
	97.61 to 110.48
Glycated haemoglobin A1c, %	5.69
	5.59 to 6.00
HDL-cholesterol, mg/dL	64.6
	42.85 to 72.85
HOMA-IR	1.98
	1.44 to 3.91
Triglycerides, mg/dL	97
	81.69 to 114.62
PTH, pg/mL	40.94
	32.55 to 52.55
25OHD, ng/mL	26.8
	17.79 to 32.94
Fibrinogen, mg/dL	441.65

Median values for adiponectin, adipsin and AgRP were of 279.98 ng/mL, 12.01 ng/mL, respectively, 260.3 ng/mL. (Table 3)

Table 3: Human Obesity Array 3-based biomarkers (adipokines) in obese menopausal females

Parameter, unit	Median
	95% confidence interval
Adiponectin, ng/mL	279.98
	144.59 to 486.13
Adipsin, ng/mL	12.01
	7.68 to 17.30
AgRP, pg/mL	260.3
	99.85 to 536.65
IL-1Ra, ng/mL	7.51
	1.05 to 10.76
IL-6, ng/mL	0.36
	0.21 to 1.18
IL-8, pg/mL	169.3
	99.34 to 240.08
Leptin, ng/mL	55.61
	26.45 to 642.61
Lipocalin-2, ng/mL	2.42
	1.88 to 3.62
PAI-1, ng/mL	58.27
	51.09 to 89.95
TNF-RII, ng/mL	1.32

All mentioned parameters from Table 2 and 3 were analysed with respect to the potential correlation with one another. Table 4 introduces the statistically significant results ($p < 0.05$). Adiponectin positively and statistically significantly correlated with lipocalin-2 ($r = 0.943$, $p = 0.0048$) and PAI-1 ($r = 0.829$, $p = 0.0416$). Adipsin displayed statistically significant and positive correlation coefficients for Il-1Ra ($r = 0.691$, $p = 0.0186$), IL-8 ($r = 0.786$, $p = 0.0362$), leptin ($r = 0.832$, $p = 0.0008$), and lipocalin-2 ($r = 0.786$, $p = 0.0208$). AgRP showed a positive association with the level of glycaemia at 120 minute during oral glucose tolerance test ($r = 0.829$, $p = 0.416$), and IL-6 ($r = 0.886$, $p = 0.0188$) and a negative correlation with TNF-RII ($r = -0.820$, $p = 0.04$). (Table 4)

Table 4: Statistically significant correlations between study parameters

Parameter 1, units	**Parameter 2, units**	**r**	**p**
Adiponectin, ng/mL	Lipocalin-2, ng/mL	0.943	0.0048
Adiponectin, ng/mL	PAI-1, ng/mL	0.829	0.0416
Adipsin, ng/mL	IL-1Ra, ng/mL	0.691	0.0186

Adipsin, ng/mL	IL-8, pg/mL	0.786	0.0362
Adipsin, ng/mL	Leptin, ng/mL	0.832	0.0008
Adipsin, ng/mL	Lipocalin-2, ng/mL	0.786	0.0208
AgRP, pg/mL	Glycaemia (120'), mg/dL	0.829	0.0416
AgRP, pg/mL	TNF-RII, ng/mL	-0.820	0.0400
AgRP, pg/mL	IL-6, ng/mL	0.886	0.0188

DISCUSSION

In this exploratory study of array-based adipokines detection amid the presence of obesity in menopausal women, we only included the subjects who did not present a large area of obesity-related complications (e.g. diabetes, high blood pressure, dyslipidaemia, osteoporosis, and even malignancies across a general screening of evaluation based on patients' medical records). This was designed in order to avoid the bias than comes from additional interferences such as insulin resistance or chronic inflammation [20]. One of the most important applications of the adipokines assays might be in so-called "healthy obesity" whereas a panel of circulating biomarkers (which are easily tested by fasting blood assays) may indicate the need of an active strategy to control the cardio-metabolic outcomes, which are not obvious at this stage [20,21].

This present kit of human array allows a rapid testing of numerous adipokines and in this analysis we focused on three of them, none of which being a matter of a standardized guideline or protocol so far. Adiponectin shows anti-diabetic effects via its receptors AdipoR1 and AdipoR2 [22]. In this study, we found it to be strongly correlated with the circulating lipocalin-2. Similarly, Daoud et al. [23] published a study in 2025 that identified the same correlation ($r = 0.54$, $p = 0.001$) in 80 adults participants (50% of them were females). Of note, the correlation was statistically significant only in obese subgroup, not in the normal-weight subjects [23]. Centrally, lipocalin-2 acts as an important appetite suppressor and gender-related differences in high-fat diet obese mice have been found, with indeterminate significance in humans so far [24].

Moreover, the correlation between adiponectin and PAI-1 potentially links the fat tissue hormonal activity with chronic inflammation and coagulation anomalies, including in some malignancies [25-27]. A recent prospective study from 2025 found that individuals with a persistent high glucose during oral glucose tolerance test had higher PAI-1 and lower adiponectin [28], hence, the positive correlation for the current study might involve alternative pathways of connection, a multi-factorial influence or a different metabolic profile in the study population diagnosed with obesity [28]. Notably, we found no correlation between adiponectin and glucose profile (from fasting to the values at one hour and two hours following glucose administration).

In the current exploratory array, lipocalin-2 was also correlated with adipsin, which might show a synergic effect with adiponectin, while direct correlation adipsin-adiponectin was not confirmed. Recently, Lee et al. [29] showed that adiponectin, adipsin and lipcalin-2 are predictors of diabetic retinopathy in type 2 diabetic patients, which suggest interplay of their actions to the endothelium level [29].

The fact that fat-secreted molecules interfere with inflammation is reflected in this study by the correlation with IL-6 and Il-8, which are also released by the muscle, not only by the adipose tissue, and they might all be involve to the crosstalk between glucose metabolism and bone turnover, as well as overall bone health [30]. Notably, we excluded the patients diagnosed with osteoporosis and associated anti-osteoporotic medication in order to the bias of skeletal anomalies.

Additionally, AgRP was the single biomarker to be associated with glycaemia at two hours after oral glucose was provided to the subjects. Thus, a glycaemia increase under these circumstances is associated with a high AgRP that further on might increase the appetite, a similar effect of elevated insulin stimulation by glucose. Yet, we tested the peripheral level, and the central effects (involving the neurons from arcuate nucleus) might not be tidily correlated with the circulating level [31-33].

Limits of the current study and future directions

We are aware of the sample size and a distinct study population in terms of including only menopausal women with uncomplicated obesity. Yet, this is an exploratory analysis and a further expansion involves a larger cohort presenting a complex panel of obesity-related complications and longitudinal surveillance to address the predictive value of these biomarkers under conservative lifestyle intervention, anti-obesity medication as glucagon-like peptide-1 (GLP-1) agonists medication or anti-obesity surgery.

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible.

Future research directions may also be highlighted.

CONCLUSION

In this exploratory study in apparently healthy obese menopausal individuals, we identified by applying an novel adipokines detection panel (Quantibody® Human Obesity Array 3) the correlation between adiponectin, respectively, adipsin, with lipocalin-2, while adiponectin also associated with PAI-1, respectively, adipsin with IL-8. AgRP, despite being a well-known central orexigenic factor, might serve as circulating biomarker, noting its correlations with IL-6 and glycaemia at 120 min during oral glucose tolerance test.

Funding:
This work was supported by a grant of the Ministry of Research, Innovation and Digitization, UEFISCDI "Crossroad of metabolism and bone: the impact of irisin, bone turnover and inflammatory markers in patients with menopausal osteoporosis and obesity"; PN-IV-P8-8.3-ROMD-2023-0262.

Institutional Review Board Statement:
The research was conducted in accordance with the Declaration of Helsinki. The study was approved by the Ethical Boards of both centres (number 32 from 30 September 2024 – Bucharest, Romania, respectively, number 97 from 20 November 2024 – Chisinau, Republic of Moldova).

Informed Consent Statement:
The patients signed the informed consent to participate to this study.

Data Availability Statement:
All available data are in the article.

Acknowledgments:
This is part of the project PN-IV-P8-8.3-ROMD-2023-0262 in addition to collaboration with the PhD research according to the following theme "Non-invasive techniques for identification of osteoporotic fracture risk in menopause" (contract number 28086 from 9 September 2024).

Conflicts of Interest:
The authors declare no conflict of interest.

References

1. Nicolucci A. Obesity as a chronic disease: the key role of new therapies. Assist Inferm Ric. 2025;44(4):166-172. doi:10.1702/4616.46253.

2. Dos Santos Rodrigues Vaz ML, da Silva Sousa AB, Ribeiro CM, Bellozi PMQ, Amato AA. A systematic review of exposure to endocrine disruptors and energy expenditure in mice. Environ Health. 2025. doi:10.1186/s12940-025-01207-1

3. Banerjee D, Mani A. Obesity's systemic impact: exploring molecular and physiological links to diabetes, cardiovascular disease, and heart failure. Front Endocrinol (Lausanne). 2025;16:1681766. doi:10.3389/fendo.2025.1681766.

4. Dollar JM, Leerkes EM, Shriver LH, Eagleton SG, Wideman L. Protocol for the infant growth and development (iGrowUp) study: the role of food and non-food self-regulation in children's obesity-related risk. BMC Public Health. 2025;25(1):4070. doi:10.1186/s12889-025-25217-3.

5. Zhang N, Xie G, Jian G, Jiang K, Lu Z, Wang Z, et al. Association of cumulative changes in atherogenic index of plasma and its obesity-related derivatives with cardiovascular disease: emphasis on incremental risk of diabetes status. Cardiovasc Diabetol. 2025;24(1):435. doi:10.1186/s12933-025-02990-4.

6. Chianelli M, Busetto L, Attanasio R, Guglielmi R, Cozzi R, Grimaldi F, et al. From awareness to action: evolving endocrinologist practices in obesity treatment in Italy.Front Endocrinol (Lausanne). 2025;16:1705670. doi:10.3389/fendo.2025.1705670.

7. Benfica MA, Ribeiro TC, Silva KSO, Oliveira MRN, Maia ELM, et al. Relationship Between Sleep Duration and Overweight/Obesity: A Comprehensive Overview of Meta-Analyses. Clin Obes. 2026;16(1):e70051. doi:10.1111/cob.70051.

8. Vallianou NG, Kounatidis DC, Geladari EV, Evangelopoulos A, Kaldis V, Stratigou T, et al. Climate Change, Air Pollution and the Global Obesity Syndemic: a Review of Current Evidence. Curr Obes Rep. 2025;14(1):78. doi:10.1007/s13679-025-00671-7.

9. Peri K, Eisenberg M. Review on obesity management: bariatric surgery. BMJ Public Health. 2024;2(2):e000245. doi:10.1136/bmjph-2023-000245

10. Liu Y, Wang Y, Tian X, Jiang T, Tang C, Zhu L, et al. Mapping the research landscape of the interactions between obesity and five major complications of diabetes: a bibliometric analysis using knowledge graph visualization. Front Endocrinol (Lausanne). 2025;16:1626191. doi:10.3389/fendo.2025.1626191.

11. Pearson-Stuttard J, Treharne C, King R, Harper H, Pokhilenko I, Gomes M, et al. A novel framework to assess the prevention value of a health intervention.Diabetes Obes Metab. 2026;28(1):584-592. doi:10.1111/dom.70232.

12. Kim D, Highland HM, Smit RAJ, Hysong MR, Buchanan VL, Young KL, et al. Genetic underpinnings of the heterogeneous impact of obesity on lipid levels and cardiovascular disease. Genome Med. 2025;17(1):113. doi:10.1186/s13073-025-01522-9.

13. Bulló M, Casas-Agustench P, Amigó-Correig P, Aranceta J, Salas-Salvadó. Inflammation, obesity and comorbidities: the role of diet. Public Health

Nutr. 2007;10(10A):1164-72. doi:10.1017/S1368980007000663.

14. Jiang M, Stifel U, Blüher M, Lefebvre H, Bornstein SR, Bechmann N. Adrenal-adipose tissue crosstalk in health and disease. Eur J Endocrinol. 2025;193(6):R83-R96. doi:10.1093/ejendo/lvaf252.

15. Naderian R, Mehrabipari S, Hemmati MA, Eslami M. Exploring the pathophysiological links between obesity, diabetes, and myocardial dysfunction: an in-depth narrative review. J Diabetes Metab Disord. 2025;24(2):287. doi:10.1007/s40200-025-01802-6.

16. He Z, Zhao L, Liu J, Zheng W, Gong C, Gong C, et al. Adipokine-mediated crosstalk between metabolic dysregulation and inflammatory pathways. Pathol Res Pract. 2025;278:156312. doi:10.1016/j.prp.2025.156312.

17. Luo C, Yu XM, Hua LY, Zeng MQ, Xu H, Duan CZ, et al. Targeting adipose remodeling: Synergistic mechanisms of drugs and adipose-derived stem cells in obese type 2 diabetes mellitus. World J Stem Cells. 2025;17(11):111162. doi:10.4252/wjsc.v17.i11.111162.

18. Purnell JQ, Le Roux CW. Metabolic and appetitive regulation of adipocyte mass during treatment of obesity. J Intern Med. 2026;299(1):66-78. doi:10.1111/joim.70045.

19. Xie C, Yuan Y, Wang Y, Qi C, Wang W, An C, et al. Beyond Discrete Diagnoses: Conceptualizing Obesity-associated Metabolic Disorders as a Unified, Dynamic Continuum. Curr Obes Rep. 2025;14(1):81. doi:10.1007/s13679-025-00673-5.

20. Saadati S, Godini R, Reddy A, Teede H, Mousa A. Metabolic crossroads in insulin resistance: exploring lipid dysregulation and inflammation. Front Immunol. 2025;16:1692742. doi:10.3389/fimmu.2025.1692742.

21. Jakubiak GK, Badicu G, Surma S, Waluga-Kozłowska E, Chwalba A, Pawlas N. The Visceral Adiposity Index and Its Usefulness in the Prediction of Cardiometabolic Disorders. Nutrients. 2025;17(14):2374. doi:10.3390/nu17142374.

22. Iwabu M, Okada-Iwabu M, Yamauchi T, Kadowaki T. Adiponectin/adiponectin receptor in disease and aging.NPJ Aging Mech Dis. 2015;1:15013. doi:10.1038/npjamd.2015.13.

23. Daoud MS, Alshareef FH, Alnaami AM, Amer OE, Hussain SD, Al-Daghri NM. Prospective changes in lipocalin-2 and adipocytokines among adults with obesity. Sci Rep. 2025;15(1):28794. doi:10.1038/s41598-025-14091-z.

24. Miao L, Tian C, Xiong Q, Zhao J, Feng Y, Yu H, et al. Sex-Specific Appetite Regulation of Lipocalin-2 in High-Fat-Diet-Induced Obese Mice.Neuroendocrinology. 2024;114(5):468-482. doi:10.1159/000536116.

25. Nistor CE, Bugala NM, Daguci C, Daguci L, Diaconu OA, Rica AM. Multiple endocrine neoplasia type 2 syndrome and osteoporosis. Aging Clinical and Experimental Research. 2023;35(S1):S387-S387.

26. Chele D, Sirbu CA, Mitrica M, Toma M, Vasiliu O, Sirbu AM, et al. Metformin's Effects on Cognitive Function from a Biovariance Perspective: A Narrative Review. Int J Mol Sci. 2025;26(4):1783. doi:10.3390/ijms26041783.

27. Porr C, Harris DM, Vidrighin A, Catana A, Diaconu C, Preda E, et al. Etoricoxib-Induced Fixed Erythema.J Clin Med. 2025;14(23):8504. doi:10.3390/jcm14238504.

28. Hernandez-Moreno CJ, Falkner B, Keith SW, Gidding SS, Thaker VV. Association of Glucose Response Shape in OGTT With Markers of Pancreatic Health and Inflammation Across Diverse Ages. J Clin Endocrinol Metab. 2025:dgaf435. doi:10.1210/clinem/dgaf435.

29. Lee YJ, Kim JJ, Kim J, Cho DW, Won JY. The Correlation between Waist Circumference and the Pro-Inflammatory Adipokines in Diabetic Retinopathy of Type 2 Diabetes Patients. Int J Mol Sci. 2023;24(3):2036. doi:10.3390/ijms24032036.

30. Jaśkiewicz Ł, Romaszko-Wojtowicz A, Chmielewski G, Kuna J, Krajewska-Włodarczyk M. Effect of myokines on bone tissue metabolism: a systematic review. Bone. 2025;201:117654. doi:10.1016/j.bone.2025.117654.

31. Oladun B, Mall S, Kim MH. Epigenetic modification of hypothalamic neuropeptides and metabolic hormone receptors in metabolic health. Front Endocrinol (Lausanne). 2025;16:1645474. doi:10.3389/fendo.2025.1645474.

32. Fu Y. Regulation of Feeding Behavior and Body Weight by Orexigenic Neurons in the Arcuate Nucleus. J Obes Metab Syndr. 2025;34(3):213-223. doi:10.7570/jomes25059.

33. Chen J, Cai M, Zhan C. Neuronal Regulation of Feeding and Energy Metabolism: A Focus on the Hypothalamus and Brainstem. Neurosci Bull. 2025;41(4):665-675. doi:10.1007/s12264-024-01335-7.

https://doi.org/10.55453/rjmm.2026.129.3.2

ORIGINAL ARTICLE

Risk Factors Associated With Acute Myocardial Infarction In The Romanian Population

Alexandra-Valentina Ene[1], Oana-Andrada Alexiu-Toma[2], Mihai Toma[2,3*], Lavinia Mariana Berca[4], Ortansa Elisabeta Csurtak[1]

[1] University of Bucharest, Faculty of Biology, Bucharest, Romania; alexandra-valentina.danciu@s.unibuc.ro; ortansa.csutak@bio.unibuc.ro
[2] Titu Maiorescu University, Faculty of Medicine, Bucharest, Romania; oana.alexiu@prof.utm.ro; mihai.toma@prof.utm.ro
[3] Central Military Emergency University Hospital "Dr. Carol Davila", Emergency Department, Bucharest, Romania; mihai.toma@prof.utm.ro
[4] National Research and Development Institute for Food Bioresources - IBA, Bucharest, Romania; laviniamariana.berca@bioresurse.ro

*Correspondence: mihai.toma@prof.utm.ro

Abstract: Acute myocardial infarction (AMI) is a multifactorial condition and a leading cause of morbidity and mortality worldwide. This study aimed to assess the distribution of clinical and demographic characteristics among AMI patients and compare these findings with data from the RO-STEMI program for the Romanian population. We performed a case-control analysis of 138 patients presenting with chest pain at the Emergency Department of "Dr. Carol Davila" Central Military Emergency University Hospital between November 2021 and April 2022. The AMI group (n = 69) included patients with STEMI-specific ECG changes and elevated cardiac biomarkers, while the control group (n = 69) was represented by patients with chest pain but normal ECG and biomarkers. Men with AMI were 8.66 years younger than women, exceeding the 6.51-year difference reported by RO-STEMI. Hypertension and dyslipidemia were strongly associated with AMI (OR = 8.20 and OR = 7.36, $p < 0.0001$). During the pandemic, early presentation (<6 h) decreased by 15%, while arrivals within 6–12 h increased by 19.02%. Primary percutaneous coronary intervention was performed in 81.16% of cases versus 12.94% previously. Killip class and reduced left ventricular ejection fraction correlated with mortality and hospitalization duration. These findings indicate significant changes in AMI onset age, treatment strategies, and presentation delays compared to pre-pandemic data.

Keywords: ST-elevation myocardial infarction (STEMI), dyslipidemia, hypertension, Killip's classification, cardiac risk factors, acute myocardial infarction (AMI) prevention

INTRODUCTION

The Global reports estimates that ischemic heart disease is the leading cause of cardiovascular death in the world (9.44 million deaths in 2021 alone). Coronary artery disease (CAD) was the main cause of death in both the Romanian female (379 deaths per 100.000) and male (362 deaths per 100.000) in 2019 [1]. Acute Myocardial Infarction (AMI) is a heterogeneous group of diseases with similar clinical manifestations [2]. The complex predisposition for AMI includes medical history (e.g., hypertension, dyslipidemia), genetic (e.g., prothrombin FII or ADAMTS7 polymorphisms), epigenetic, anthropometrical (e.g., obesity), behavioral (e.g., sedentary lifestyle, smoking), and other factors (e.g., age, gender, ethnicity) [3].

The RO-STEMI study was the first Romanian registry for AMI with ST-segment elevation (STEMI) published in 2010 and had 3 phases: RO-STEMI-1 (1997-2001), RO-STEMI-2 (2002-2005), and RO-STEMI-3 (2006-2009) [4]. During the 13 years of follow-up, there was an increasing trend in the number of AMI patients with comorbidities (e.g., hypertension, type 2 diabetes, dyslipidemia) and a slight decrease in the percentage of smokers [4]. Based on the results obtained in this study, in August 2010, the Romanian National Program for primary angioplasty in AMI was implemented, which is still ongoing.

A subsequent study from RO-STEMI carried out between 2011-2015 identified new predictive factors for in-hospital mortality in AMI patients who underwent interventional treatment (e.g., Killip class, depressed left ventricular ejection fraction - LVEF, anterior location of infarction) [5].

Citation: Ene AV, Alexiu-Toma OA, Toma M, Berca LM, Csurtak OE. *Risk factors associated with acute myocardial infarction in the Romanian population*. R. J. Mil. Med. 2026, CXXIX(3): 235-240
https://doi.org/10.55453/rjmm.2026.129.3.2

Academic Editor: Remus Nica

Received: 22 January 2026
Revised: 17 March 2026
Accepted: 23 March 2026

During the global crisis caused by the COVID-19 pandemic, it became evident that the prevention and management of CADs need to be improved [6].

Percutaneous coronary intervention (PCI) is an invasive procedure that aims to revascularize ischemic myocardial tissue. "Dr. Carol Davila" Central Military Emergency University Hospital represents one of the 6 medical units from Bucharest that are involved by weekly rotation in PCI of patients with AMI, according to the management guide for AMI of the Ministry of Health.

This study aims to analyze the risk factors' distribution for AMI in a group of subjects and to compare results with data published in the last 15 years for the Romanian population.

MATERIALS AND METHODS

This study was based on medical records of the patients with AMI (the AMI group) or with suspicion of AMI (the control group). All subjects presented themself to the Emergency Department of "Dr. Carol Davila" Central Military Emergency University Hospital, Bucharest between 01.11.2021 and 30.04.2022. The AMI group refers to patients with suggestive acute clinical symptoms (e.g., chest discomfort, pain, pressure, tightness, heaviness, or burning), AMI-specific EKG morphology, and elevated cardiac enzymes [7]. The control group included subjects with symptoms suggestive of AMI but with normal EKG and cardiac enzymes. Echocardiography, Killip stage and echocardiographic LVEF were interpreted according to international criteria during their hospital admission [8]. The LVEF values were distributed in 3 groups according to international criteria: heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF) [8]. Levels of creatine kinase (CK) >145U/L, creatine kinase-MB fraction (CK-MB) >25 U/L, and high sensitive troponin T (hs-cTn) > 1.3 pg/ml were considered abnormal levels. Subjects who were under 18 years of age, not able to consent, or pregnant were not included.

We used odds ratios (O.R.) with 95% confidence intervals (CI) for comparing categorical variables, and the significant values were considered if the p-value was lower than 0.05. Statistical analysis was done using R Studio, version 2023.09.1 Build 494.

RESULTS

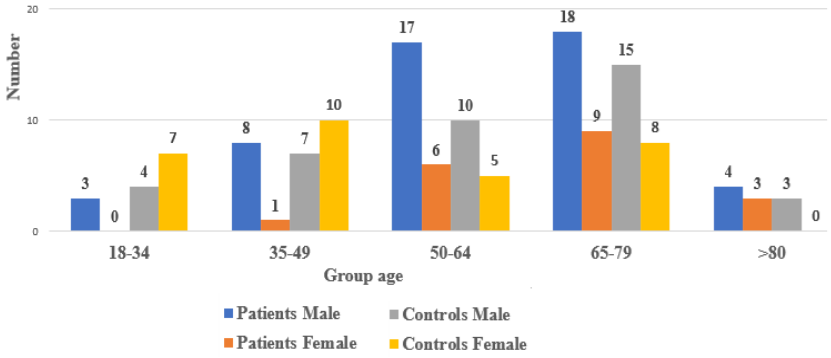
The characteristics of subjects included in the study are presented in Table 1. The gender distribution in patients and control groups presents no statistically significant difference. The average patient's age was higher than in the control group ($p<0.05$). We identified three individuals with COVID-19 infection in the AMI group and 6 individuals in the control group ($p>0.05$). We found no statistical differences between the groups of patients who lived in the urban or rural areas regarding the risk for AMI. Also, the risk factors associated with CAD were investigated in the medical records of 138 patients (Table 1).

Table 1: Characteristics of subjects included in the study.

Characteristics	AMI group	Control group
Male: Female	50/19	39/30
Average age	61.66±14.42 (19-92)	54.20±18.25 (18-87)
Male age	59.28±14.65 (19-84)	58.64±17.72 (18-87)
Female age	67.94±11.96 (41-92)	48.43±17.56 (19-78)
Rural / Urban	23/46	24/45
Covid Yes/No/Unknown	3/66/0	6/11/52
Hypertension	58	27
Dyslipidemia	45	14
Smoking	34	18
Diabetes	17	10
Heart failure	15	12
Cardiac pathological antecedents	16	11
Neurological pathological antecedents	8	6

The majority of AMI patients have had at least one traditional risk factor for this disease. We observe statistically significant differences between the two groups (Figure 1), for females in the 35-49 age group ($p<0.05$), and for females in the 18-34 age group ($p<0.001$). Anterior chest pain was the most frequent clinical symptom reported by AMI patients (91% vs 14% in subjects from the control group).

Figure 1: Distribution of patients and control subjects by gender and age range



Almost half of patients presented to the Emergency Department in the first six hours after the onset of acute symptoms (49% presented in the first 6 hours; 33% within 6-12 hours; 17% more than 12 hours after the onset of symptoms). We observed that in the first 12 hours from the onset of symptoms, 94% of male patients and 52.6% of female patients presented in the ED ($p<0.001$). The EKG morphology analysis showed that the most frequent localization of AMI was anterior (39.1%) and inferior (23.1%). The values for CK [663 U/L (range 11-4024) vs 90 U/L (range 17-3443)], CK-MB [88.5 U/L (range 6-586) vs 13 U/L (range 6-107)] and hs-cTn [4658 pg/ml (range 1.3-50000) vs 1.3 pg/ml (range 1.3-66.5)] levels were higher in AMI than in control group (Table 2).

Table 2: Paraclinical parameters in AMI and control groups.

Cardiac markers	Subgroups	AMI male	AMI female	Control male	Control female
CK	CK1 (10-145 U/l)	4	6	29	28
	CK2 (146-2000 U/l)	32	12	9	2
	CK3 (> 2000 U/l)	14	1	1	0
CK-MB	CK-MB1 (≤ 25 U/l)	10	4	34	30
	CK-MB2 (25-200 U/l)	27	14	5	0
	CK-MB3 (> 200 U/l)	13	1	0	0
hs-cTn	hs-cTn (≤1.3 pg/ml)	0	0	17	24
	hs-cTn (1.4-50000 pg/ml)	39	15	22	6
	hs-cTn (> 50000 pg/ml)	11	4	0	0

The CK values showed statistically significant differences between the CK1 and CK3 subgroups ($p < 0.001$). The values of hs-cTn show significant differences between AMI patients with CK MB 1 and CK-MB 2 values ($p<0.001$). We observed that in the group of patients, the median CK values are related to gender, with men having 870.5 U/L (range 54-3781) and women having 456 U/L (range 11-4024) ($p<0.05$). The values for CK-MB and hs-cTn were not related to the subject's gender. The majority of patients investigated were treated with PCI (81.16% that went primarily to PCI and 18.84% of patients received thrombolysis before PCI) and 4.36% died before receiving interventional treatment. Regarding the result of PCI, it is observed that 4 out of 66 AMI patients who presented with clinical signs and symptoms of infarction had no obstructive lesions of the coronary arteries; these patients were included in the category of AMI with non-obstructive coronary artery (MINOCA).

From the AMI group, 61 patients were discharged with improved status (the median hospitalization period was 7 days; range 1-70 days), and 5 patients died during hospitalization (median 7 hospitalization days; range 1-19 days). Sixteen subjects from the control group were hospitalized (23.2%) and had a median of 6 hospitalization days (range 2-24 days). No deaths were reported in this subgroup of patients.

LVEF was preserved only in 17.4% of AMI patients and Killip 1 was established for 73.9% of patients from them (Table 3). The bivariate analysis of the number of deaths shows that it is statistically associated with the Killip and LVEF class at admission ($p<0.01$) and also with the number of hospitalization days ($p<0.05$) (Table 3).

Table 3: Relation between number of deaths, Killip class, LVEF class and number of hospitalization days in patients' group.

Cardiac markers	Subgroups	AMI male	AMI female	Control male	Control female
CK	CK1 (10-145 U/l)	4	6	29	28
	CK2 (146-2000 U/l)	32	12	9	2
	CK3 (> 2000 U/l)	14	1	1	0
CK-MB	CK-MB1 (≤ 25 U/l)	10	4	34	30
	CK-MB2 (25-200 U/l)	27	14	5	0
	CK-MB3 (> 200 U/l)	13	1	0	0
hs-cTn	hs-cTn (≤1.3 pg/ml)	0	0	17	24
	hs-cTn (1.4-50000 pg/ml)	39	15	22	6
	hs-cTn (> 50000 pg/ml)	11	4	0	0

1 Fisher exact, p 2-tails: * Killip I+II vs. III+ IV: $p < 0.01$; ** HFpEF + HFmrEF vs. HFrEF: $p < 0.01$; *** Number of hospitalisation days: I + II vs. III: $p < 0.05$.

DISCUSSION

The period of the study covers the winter period and the fourth wave of the pandemic in Romania, which had the highest mortality reported for COVID-19 in our country [9].

In our study, the percentage of men is comparable to that reported in the RO-STEMI study (72.46% vs. 68.56%) [4]. The median age of patients was approximately 1.5 years lower than reported in the RO-STEMI study (61.66±14.42 vs. 63.39±12) [4]. Also, we observe a decrease in age, especially in men; in our study, the age of men compared to that of women is 8.66 years lower, compared to the RO-STEMI study, where it was only 6.51 years lower [4]. This trend is concordant with those reported for other populations [10].

Treatment of dyslipidemia and hypertension is a key step for reducing the risk of atherosclerotic cardiovascular disease; populations with hypertension and dyslipidemia are associated with an increased risk of AMI. For example, Anderson et al. reported that from AMI patients, 73.7% have hypertension and 73.4% have dyslipidemia [11]. Our data shows that compared to RO-STEMI, the frequency of hypertension (84.05% vs. 52.20%), smoking (49.27% vs. 47.00%), and dyslipidemia (65.21% vs. 38.4%) increased in patients with AMI from Romania in the last 10 years [4]. In our study, hypertension (O.R.= 8.20, $p<0.0001$) and dyslipidemia (O.R.= 7.36, $p<0.0001$) were strongly associated with AMI, although all AMI patients had specific treatment for hypertension or dyslipidemia. More subtle differences were observed for diabetes (24% vs 21.80%) and personal history of AMI (11.6% vs. 9.80%) [4].

Overall, the percentage of active or former smokers in the AMI group (49.27%) is concordant with figures reported by RO-STEMI (47.06%) [4]. However, we observed an increasing frequency of smoking at young ages (78.3% in the 18-34 age group and 76.4% in the 35-49 age group) in contrast with RO-STEMI (75% vs 73.25%). The frequency of smokers in the control group (26.1%) was higher than the value reported for the Romanian population (19.8%) or in other European populations [12]. In our control group, we don't observe any significant difference between smoking and gender, although such differences were reported in Romania (30.6% of men and 7.5 % of women) [4] and in other European countries [12].

The frequency of anterior AMI is much higher compared to data previously reported for the Romanian population (31%), but the frequency of inferior AMI is similar (22%) [13]. There is a significant increase in patients who were treated by direct PCI (81.16% vs. 12.94%) and a halving of the percentage of patients treated with thrombolytic medication before the intervention (18.84% vs. 35.07%) compared to the RO-STEMI study [4]. In the year 2009, when a percentage of 30.82% of patients who benefited primarily from PCI within the RO-STEMI program was reported, the number of patients was continuously increasing, a fact that was confirmed by other reports [5,13]. The frequency of patients diagnosed with MINOCA identified in our study group is within the limits reported in the specialized literature of 5-15% [14].

Compared to the RO-STEMI 3 study, the percentage of patients with Killip 1 (73.9% vs. 68.34%), Killip 2 (13.04% vs. 17.65%), Killip 3 (2.9% vs. 7.93%), or Killip 4 (10.16% vs. 6.06) was similar [4]. The values of LVEF are different from those reported by others [15] and may represent a characteristic of the subjects included in this study. For patients with HFmrEF after STEMI, a need for specific attention and appropriate management was reported [15]. The percentage of patients who presented more than 12 hours after the onset of symptoms decreased by 5.18%. Compared to the pre-COVID-19 period, the percentage of patients who presented in less than 6 hours decreased by approximately 15%, and the percentage of patients who presented between 6 and 12 hours increased by 19.02%.

The values of patients from our study who were discharged with improved status were comparable to those reported by another study (9.20 ± 5.47 days) [13]. The percentage of 7.24% of deaths during hospitalization is below that reported by the RO-STEMI study

(11.84%) and similar to that reported by other studies [5,13]. We did not observe statistical differences regarding the evolution of this AMI related to patients' gender, although in other studies such associations were reported [16].

Also, the relation between the number of deaths and the Killip, LVEF class at admission, and the number of hospitalization days is in concordance with another report [5].

During the COVID-19 pandemic, a considerable reduction in hospitalization for AMI, more complex catheterization laboratory protocols, an increase in time to the catheterization laboratory associated with an increase in door-to-balloon times, which finally led to increased rates of in-hospital mortality [17]. These remarks can be explained by the fact that patients did not activate emergency medical systems because hospitals were perceived as dangerous places regarding the infection risk, and by the fact that patients with AMI had a significantly higher mortality in-hospital compared to those admitted before COVID-19, potentially due to late arrival to the hospital [17]. The complications determined by the COVID-19 infection and the difficulties in accessing the ambulance services during the lockdown period could increase the mortality due to AMI. All these observations can explain, at least partially, the reduced incidence of COVID-19 in patients with AMI from our Emergency Department. The decrease in the age of AMI onset observed during the COVID-19 pandemic can be explained by the increase in the incidence of cardiovascular risk factors and the fact that young people probably had more courage to call on medical services [18].

The COVID-19 pandemic created a subsequent impact on mortality in patients with AMI. In Romania, the difference in time delay and clinical outcome in patients with AMI during the pre-pandemic and COVID-19 pandemic period was not investigated in detail [19]. Several studies performed in different countries revealed significant differences in accessing medical care related to gender, population density, socioeconomic status, and infrastructure [20].

Limitations

The main limitation of our study was that the number of patients and controls was relatively low in that period of time, so there should be further studies that include a larger number of subjects and investigate the connection between risk factors, COVID-19 infection, and myocardial infarction in the Romanian population.

CONCLUSION

The analysis of the data included in this study highlighted that the age at which AMI symptoms begin has decreased (men diagnosed with AMI were 8.66 years younger than women), and this can be explained by the increase in the incidence of some cardiovascular risk factors (e.g., hypertension, dyslipidemia, smoking). Compared to the RO-STEMI study, the number of patients presenting within 6-12 hours from the onset of symptoms has increased and most of the patients diagnosed with AMI had reduced and slightly reduced LVEF. The number of patients that received interventional treatment has increased compared to the RO-STEMI study and Killip class and LVEF are associated with mortality and hospitalization days. All these results of this study are useful for prospective studies regarding risk factors for myocardial infarction in the Romanian population.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. The study was supported by the Ministry of Research and Education, grant number PN 23 01 03 03.

Acknowledgments

No generative AI was used during the production of this article.

Authors' contribution

Conceptualization, D.A.-V., A.-T.O.-A and C.O.E.; methodology, D.A.-V.; software, T.M.; validation, D.A.-V., B.L.M., and T.M.; formal analysis, D.A.-V.; investigation, D.A.-V. and T.M.; resources, B.L.M. and T.M.; data curation, T.M.; writing-original draft preparation, D.A.-V.; writing-review and editing, A.-T.O.-A., T.M., and C.O.E.; visualization, T.M.; supervision, C.O.E.; project administration, B.L.M.; funding acquisition, B.L. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

As a University Hospital, patients and controls sign informed consent upon admission, confirming their explicit acceptance of the use of their personal data and blood samples for scientific research purposes and clinical studies.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of the Central Military Emergency University Hospital "Dr. Carol Davila" (protocol number 641/07.11.2023).

Patient consent for publication

Not applicable.

References

1. Vaduganathan M, Mensah GA, Turco JV, Fuster V, Roth GA. The Global Burden of Cardiovascular Diseases and Risk: A Compass for Future Health. J Am Coll Cardiol, 2022, 80, 25, 2361-2371, doi: 10.1016/j.jacc.2022.

2. Singh YS, Wada H, Ogita M, Takamura Y, Onozato T, et al. Clinical outcomes of ST elevation myocardial infarction patients without standard modifiable risk factors. J Cardiol, 2024, 84(1), 41-46, doi: 10.1016/j.jjcc.2023.11.007.3. Katz AE, Gupte T, Ganesh SK. From atherosclerosis to

spontaneous coronary artery dissection: defining a clinical and genetic risk spectrum for myocardial infarction. Curr Atheroscler Rep, 2024, 26, 7, 331-340, doi: 10.1007/s11883-024-01208-4.

4. Tatu-Chițoiu G, Arsenescu-Georgescu C, Babeş K, Benedek I, Căpâlneanu R, et al. Report of the Romanian Registry for ST-Elevation Acute Myocardial Infarction (ROSTEMI) (1997-2009). Final report. Available online: https://www.cardioportal.ro/files/RO_STEMI_EN.pdf (accessed 15.10.2025).

5. Cretu DE, Udroiu CA, Stoicescu CI, Tatu-Chitoiu G, Vinereanu D. Predictors of in-hospital mortality of ST-segment elevation myocardial infarction patients undergoing interventional treatment. An analysis of data from the RO-STEMI registry. Maedica (Bucur), 2015, 10, 4, 295-303.

6. Kazi SN, Von Huben A, Marschner S, Chong JJH, Denniss AR, et al. Trends in Modifiable Risk Factors Amongst First Presentation ST Elevation Myocardial Infarction Patients in a Large Longitudinal Registry. Heart Lung Circ, 2023, 32, 4, 480-486, doi: 10.1016/j.hlc.2022.12.012.

7. ESC Guideline for the management of acute coronary syndromes. Available online: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Acute-Coronary-Syndromes-ACS-Guidelines (accessed on 10.10.2025).

8. ESC Guideline for the diagnosis and treatment of acute and chronic heart failure. Available online: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Focused-Update-on-Heart-Failure-Guidelines (accessed on 10.10.2025)

9. Dascalu S, Geambasu O, Valentin Raiu C, Azoicai D, Damian Popovici E, et al. COVID-19 in Romania: What Went Wrong? Front Public Health, 2021, 9, 813941, doi: 10.3389/fpubh.2021.813941.

10. Liang MT, Pang Y, Gao LL, Han LJ, Yao HC. Clinical risk factors and outcomes of young patients with acute ST segment elevation myocardial infarction: a retrospective study. BMC Cardiovasc Disord, 2023, 23, 1, 353, doi: 10.1186/s12872-023-03392-8.

11. Anderson JL, Knight S, May HT, Le VT, Bair TL, et al. Frequency and outcomes of patients presenting with non-ST elevation myocardial infarction (NSTEMI) without standard modifiable risk factors: a US Healthcare Experience. J Clin Med, 2023, 12, 9, 3263, doi: 10.3390/jcm12093263.

12. Eurostat. Smoking of Tobacco Products by Sex, Age and Country of Citizenship. Available online: https://ec.europa.eu/eurostat/databrowser/view/hlth_ehis_sk1c/default/table?lang=en (accessed on 10.10.2025)

13. Alexiu Toma OA, Arnăoute A, Simion L, Opriță B. Analiza retrospectivă a factorilor de risc și demografici asociați cu infarctul miocardic acut cu supradenivelare de segment ST. Revista de Medicina de Urgența, 2018, 7, 1-6.

14. Sykes R, Doherty D, Mangion K, Morrow A, Berry C. What an interventionalist needs to know about mi with non-obstructive coronary arteries. Interv Cardiol. 2021, 16, e10, doi: 10.15420/icr.2021.

15. Ma Y, Wang L, Jin W, Zhu T, Liu J, et al. Left ventricular function and coronary microcirculation in patients with mild reduced ejection fraction after STEMI. BMC Cardiovasc Disord, 2022, 22, 1, 423, doi: 10.1186/s12872-022-02846-9.

16. Stehli J, Duffy SJ, Burgess S, Kuhn L, Gulati M, et al. Sex disparities in myocardial infarction: biology or bias? Heart Lung Circ, 2021, 30, 1, 18-26, doi: 10.1016/j.hlc.2020.06.025.

17. Choi H, Lee JH, Park HK, Lee E, Kim MS, et al. Impact of the COVID-19 pandemic on patient delay and clinical outcomes for patients with acute myocardial infarction. J Korean Med Sci, 2022, 37, 21, e167, doi: 10.3346/jkms.2022.37.e167.

18. Esposito L, Cancro FP, Silverio A, Di Maio M, Iannece P, et al. COVID-19 and acute coronary syndromes: from pathophysiology to clinical perspectives. Oxid Med Cell Longev, 2021, 4936571, doi: 10.1155/2021/4936571.

19. Hodas R, Benedek I, Rat N, Kovacs I, Chitu M, et al. Impact of COVID-19 Pandemic on STEMI Networks in Central Romania. Life (Basel), 2021, 11, 10, 1004, doi: 10.3390/life11101004.

20. Hillerson D, Li S, Misumida N, Wegermann ZK, Abdel-Latif A, et al. Characteristics, process metrics, and outcomes among patients with ST-elevation myocardial infarction in rural vs urban areas in the US: A report from the US National Cardiovascular Data Registry. JAMA Cardiol, 2022, 7, 10, 1016-1024 doi: 10.1001/jamacardio.2022.2774.

https://doi.org/10.55453/rjmm.2026.129.3.3

REVIEW

The Multidimensional Impact of Mental Health Literacy in Military Personnel: A Narrative Review

Sadegh Kazemi[1], Mojtaba Fattahi Ardakani[2], Reza Faryabi[3], Morad Ali Zareipuor[4*]

[1] Ph.D. in Disaster& Emergencies Health, Research Center for Emergency and Disaster Resilience, Red Crescent Society of the Islamic Republic of Iran, Fars, Iran; info.sadeghkazemi@gmail.com
[2] Social Determinants of Health Research Center, Non-communicable Diseases Research Institute, Department of Health Education and Promotion, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran; mjfattahi57@gmail.com
[3] Department of Public Health, School of Public Health, Jiroft University of Medical Sciences, Jiroft, Iran; rfphdjmu@gmail.com
[4] Department of Public Health, University of Medical Sciences of Khoy, Khoy, Iran. z.morad@yahoo.com

*Correspondence: z.morad@yahoo.com

Abstract: Background: This narrative review explores the multidimensional impact of Mental Health Literacy (MHL) among military personnel, a population frequently exposed to high-stress environments and associated psychological risks. It aims to synthesize evidence on how MHL influences various individual, organizational, and social outcomes. Methods: A narrative review was conducted by analyzing relevant peer-reviewed articles published between 2015 and 2025. Comprehensive searches were performed across major databases, including PubMed, Web of Science, Scopus, the Scientific Information Database (SID), and MagIran. From an initial pool of 43 records, 8 duplicates were removed, leaving 35 articles for screening. After full-text assessment, 7 studies met the inclusion criteria. The review process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)reporting guidelines, and the methodological quality of the included studies was appraised using the Mixed Methods Appraisal Tool (MMAT). Results: The results demonstrate that the impact of MHL in military personnel spans five core dimensions: (1) Education and Awareness, (2) Prevention and Treatment, (3) Performance Improvement, (4) Leadership and Social Support, and (5) Societal and Family Impact. Enhanced MHL not only reduces stigma and promotes help-seeking behavior but also improves stress management, early crisis identification, and timely intervention, contributing to overall psychological resilience. Conclusions: Strengthening MHL is essential for improving the quality of life, operational performance, and psychological well-being of military personnel. Commanders and military managers should prioritize developing and implementing targeted educational programs and interventions to foster mental health awareness and resilience.

Keywords: Military Personnel, Armed Forces, Mental Health Literacy, Narrative Review, Multidimensional Impact, Psychological Well-being, Health Education

INTRODUCTION

Health literacy refers to an individual's ability to access, understand, evaluate, and apply health-related information and services, enabling them to make informed health decisions [1]. In today's world, health literacy has become a fundamental necessity and plays a crucial role in health-related decision-making [2,3]. Low health literacy is considered one of the major challenges in public health. Individuals with inadequate health literacy often face difficulties in accessing, understanding, and interpreting essential health information, which limits their ability to make informed decisions and adopt preventive behaviors [4,5]. Low health literacy is associated with inappropriate use of the healthcare system, lower participation in screening and prevention programs, poor treatment adherence, ineffective management of chronic diseases, increased hospitalizations, greater use of emergency services, treatment delays, and poorer health outcomes. Moreover, such individuals are less able to recognize health risks in a timely manner and often lack confidence in communicating effectively with healthcare professionals, leading to worsening health conditions and increased healthcare costs [6,7].

Citation: Kazemi S, Ardakani MF, Faryabi R, Zareipuor MA. The Multidimensional Impact of Mental Health Literacy in Military Personnel: A Narrative Review R. J. Mil. Med. 2026, CXXIX(3): 241-250 https://doi.org/10.55453/rjmm.2026.129.3.3

Academic Editor: Octavian Vasiliu

Received: 17 September 2025
Revised: 2 December 2025
Accepted: 1 January 2026

Mental Health Literacy (MHL), as a subset of health literacy, refers to the ability to understand and manage mental health issues, recognize signs and symptoms of mental disorders, and identify resources and services needed to support mental well-being. In other words, MHL encompasses the knowledge and skills that enable individuals to effectively address psychological challenges and seek appropriate actions such as counseling and treatment [8]. Numerous studies on the concept of MHL have demonstrated that adequate MHL is associated with disease management, information-seeking behavior, prevention of long-term complications, and reduction of chronic harm [9,10]. Furthermore, it serves as a powerful predictor and mediator for all health-promoting behaviors and quality of life [9].

Military personnel, due to exposure to high levels of stress, physical risks, and traumatic experiences in combat zones, are at a heightened risk of mental health disorders. The prevalence of mental health disorders among military personnel is significantly higher compared to the general population [11]. This issue not only affects the personal quality of life of these individuals but can also lead to broader social and economic consequences [12]. Therefore, MHL is of critical importance among military personnel. However, evidence from research indicates that the level of MHL in this population remains insufficient. For instance, a study conducted among military college students in China reported that only 21% of participants demonstrated adequate mental health literacy [13]. Similarly, low levels of MHL have also been observed among healthcare providers serving military personnel [14].

In recent years, attention to MHL as a key factor in improving military personnel's overall health has increased. However, in many countries, educational programs and interventions related to MHL remain insufficient [15,16]. Studies have shown that neglecting mental health can lead to increased rates of suicide, addiction, and other social problems [17]. One of the main challenges in this field is the lack of sufficient information about the importance of MHL and its impact on the performance of military personnel. Implementing mental health interventions in military forces to enhance psychological well-being, with a focus on principles such as job-specific training, cohesion, and repeated skill practice, is essential [18]. Support for mental health during military operations is often inadequate due to insufficient training for commanders and mental health professionals. Advanced training is necessary to address the unique mental health challenges faced during deployment [19].

Additionally, the impact of MHL on factors such as stress, anxiety, and depression among military personnel needs to be examined. Therefore, neglecting MHL can have serious consequences for military forces. Higher levels of mental health literacy (MHL) can reduce and prevent mental health problems throughout life. The ACP model—emphasizing assertiveness, clear communication, and positivity—offers a practical framework for enhancing MHL programs across diverse contexts [20]. MHL is particularly crucial in military settings due to the high-stress, psychologically demanding, and uniquely challenging nature of the work environment. Military personnel are frequently exposed to critical and high-risk situations that can adversely affect their mental well-being, leading to conditions such as anxiety, depression, and stress. Enhancing MHL among military personnel not only promotes their psychological resilience and quality of life but also contributes to the overall effectiveness and operational performance of the armed forces. This study serves as a valuable resource for researchers and military officials seeking to strengthen mental health support systems and reduce related challenges. The present narrative review explores the significance of MHL, the key factors influencing it, and summarizes current evidence on mental health literacy among military personnel, identifying existing gaps and proposing directions for future interventions.

MATERIALS AND METHODS

The present narrative review was guided by PRISMA principles to enhance transparency. Although PRISMA is primarily designed for systematic reviews, this study adopted a narrative approach due to methodological heterogeneity among eligible studies and the limited number of publications on the topic, while following PRISMA principles to enhance transparency. It includes articles published in Persian and English in domestic and international scientific journals from 2015 to 2025, with the final search conducted on 6 August 2025.

Search Strategy

Databases searched included PubMed, Web of Science, Scopus, SID, and MagIran. Keywords included “health literacy”, “mental health literacy”, “mental health”, “military personnel”, “armed forces”, and “strategies”. Boolean operators AND / OR were used to construct search strings. A representative PubMed query was ("mental health literacy"[MeSH] OR "health literacy" OR "mental health") AND ("armed forces" OR "military personnel").

Screening and Selection

Two independent reviewers screened titles and abstracts. Duplicates were removed prior to screening.

Inclusion criteria: studies examining MHL in military personnel, full-text available in Persian or English, and relevant keywords in the title or abstract. Exclusion criteria: studies not aligned with research objectives, unavailable full texts, or letters to the editor (Table 1).

Disagreements were resolved by discussion among the authors.

Out of 43 retrieved articles, 7 met the inclusion criteria. The selection process is shown in Figure 1.

Data Extraction and Analysis

The information extracted included the author, year, location, population, methodology, intervention, and main findings. Due to heterogeneity in methods and results, quantitative synthesis was not performed; data were analyzed qualitatively.

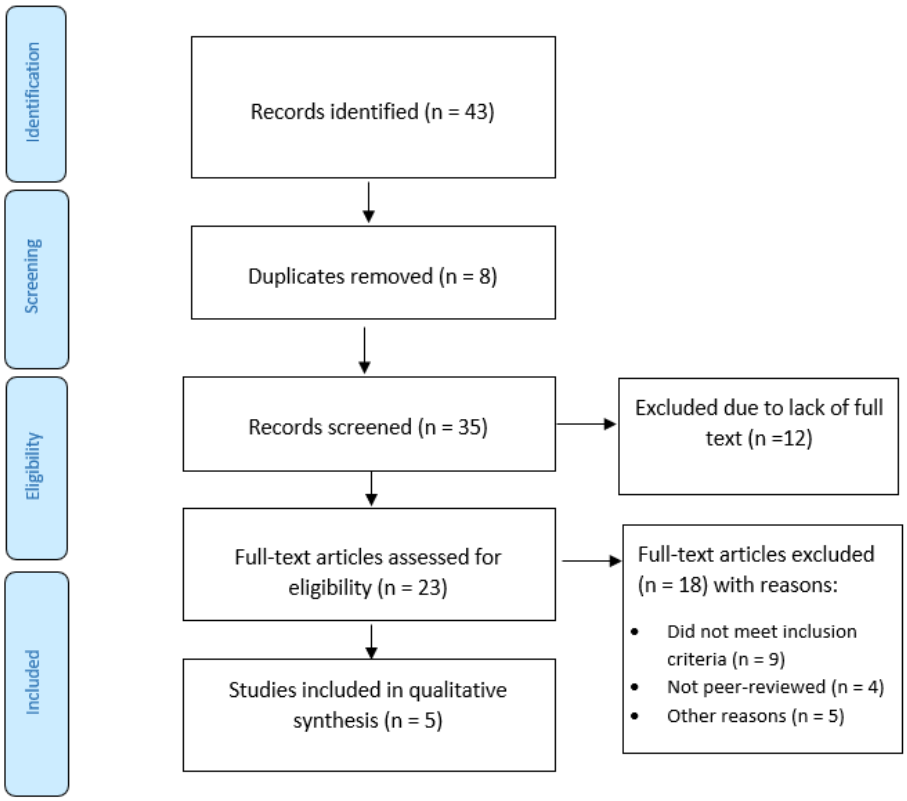
Table 1: Inclusion/Exclusion Criteria Table (PICO)

Element	Inclusion Criteria	Exclusion Criteria
Population	Military personnel	Civilian population
Intervention	MHL interventions, educational programs	Non-mental health studies
Comparison	Any	N/A
Outcome	MHL level, psychological well-being, help-seeking	Unrelated outcomes
Study design	Quantitative, qualitative, mixed methods, narrative/systematic reviews	Letters, commentaries, unavailable full texts

Quality Assessment

The Mixed Methods Appraisal Tool (MMAT, McGill University) was used to assess the methodological quality of quantitative, qualitative, and mixed-method studies (Table 2).

Figure 1: PRISMA Flow Diagram



RESULTS

In this study, five articles related to MHL among military personnel were selected, and their findings were analyzed. Regarding the research settings, one study was conducted in India, one in the United States, and one each in the United Kingdom, Spain, and Iran. In terms of study design, four studies were cross-sectional, one was mixed-methods, and two were quasi-experimental. The results of these studies are summarized in Table 3.

Based on the reviewed articles, MHL in the armed forces enables personnel to identify mental health issues and respond to them effectively. This type of literacy includes the ability to recognize signs and symptoms of mental health problems, understand supportive strategies, and make informed decisions to manage stress and psychological crises. Personnel with higher MHL are generally better equipped to maintain their own mental health and that of their colleagues, and they can perform more effectively in psychologically challenging and stressful situations. MHL plays a crucial role in the armed forces.

Table 2: Quality Assessment of Included Studies

No.	Author	Year	Article Title	Location	Design	Population	Sample Size	Randomization	Blinding	Selection Bias	Data Analysis	Overall Quality Score
1	Saini	2023	Augmenting Mental Health Literacy of Troops in a Large Military Station: A Novel Approach	India	Quasi-experimental	Soldiers	1200	No	No	Low	Adequate	High
2	Iago Portela	2023	Evaluation of Health Literacy and Its Predictive Formative Factors Among Spanish Military Personnel	Spain	Cross-sectional	Spanish military personnel	-	N/A	N/A	Medium	Adequate	Medium
3	Crone	2020	Mental Health First Aid for the UK Armed Forces	UK	Quasi-experimental	UK Armed Forces personnel	602	No	No	Low	Adequate	High
4	Soleimani-Sefat	2022	Development and Psychometric Properties of the Mental Health Literacy Questionnaire (MHLQ) Among Young Iranian Soldiers	Iran	Psychometric	Young Iranian soldiers	-	N/A	N/A	Medium	Adequate	Medium
5	Thomas	2021	Mental Health Literacy in U.S. Soldiers: Knowledge of Services and Processes in the Utilization of Military Mental Health Care	USA	Cross-sectional	U.S. soldiers	-	N/A	N/A	Medium	Adequate	Medium

Randomization and Blinding: Applicable only for experimental or quasi-experimental studies.
Selection Bias: Assessed based on study design and reported details (Low = low risk, Medium = moderate risk).
Data Analysis: All studies employed appropriate data analysis methods (Adequate).
Overall Quality Score: Determined based on a combination of the above dimensions and the overall reliability of each study.

First, increasing awareness of mental health helps personnel better recognize the symptoms of mental disorders and coping methods. This awareness can reduce stigma and taboos associated with mental health issues and frame help-seeking as a sign of strength. Conducting training programs on stress and crisis management also empowers personnel [21]. In terms of prevention and treatment, MHL allows personnel to manage psychological and emotional pressures better. Identifying warning signs of psychological crises and taking timely action can prevent more serious problems. Additionally, increased awareness of early signs of mental disorders facilitates early identification and treatment of these issues [22-25].

Table 3: Summary of the Importance and Role of Mental Health Literacy in the Armed Forces

No.	Author	Year	Article Title	Location	Design	Population	Sample Size	Main Findings
1	Saini (21)	2023	Augmenting Mental Health Literacy of Troops in a Large Military Station: A Novel Approach	India	Quasi-experimental	soldiers	1200	This study demonstrated that augmenting mental health literacy (MHL) among troops through a novel approach could enhance their ability to manage stress and improve mental health outcomes. The intervention was well-received and effective.
2	Iago Portela (22)	2023	Evaluation of Health Literacy and Its Predictive Formative Factors Among Spanish Military Personnel	Spain	Cross-sectional	Spanish military personnel	-	The study evaluated health literacy and its predictive factors among Spanish military personnel. Results indicated that higher health literacy was associated with better mental health outcomes and resilience.
3	Crone (19)	2020	Mental Health First Aid for the UK Armed Forces	UK	Quasi-experimental	UK Armed Forces personnel	602	The study assessed the effectiveness of Mental Health First Aid (MHFA) training for UK Armed Forces. Findings showed that MHFA training improved mental health literacy and encouraged help-seeking behavior among participants.
4	Soleimani-Sefat (23)	2022	Development and Psychometric Properties of the Mental Health Literacy Questionnaire (MHLQ) Among Young Iranian Soldiers	Iran	Psychometric	Young Iranian soldiers	-	The study developed and validated the Mental Health Literacy Questionnaire (MHLQ) for young Iranian soldiers. Results indicated that the MHLQ is a reliable tool for assessing mental health literacy in this population.
5	Thomas (24)	2021	Mental Health Literacy in U.S. Soldiers: Knowledge of Services and Processes in the Utilization of Military Mental Health Care	USA	Cross-sectional	U.S. soldiers	-	The study found that mental health literacy among U.S. soldiers ranged between 27% and 74%. Soldiers with higher literacy levels and more deployments had better responses to mental health items. No difference was observed between those seeking treatment and those who were not. This study documented soldiers' mental health literacy for the first time and identified educational and promotional targets. Future studies should explore comprehensive factors and correlations of mental health literacy.

Table 4: Summary of the Role and Importance of Mental Health Literacy in Military Forces

Role	Description
Education and Awareness	- Increasing Awareness: Recognizing symptoms of mental disorders and coping methods. - Changing Attitudes: Reducing stigma and taboos, framing help-seeking as a sign of strength. - Training and Empowerment: Conducting educational programs for stress and crisis management.
Prevention and Treatment	- Stress Management: Identifying and managing psychological and emotional pressures. - Crisis Prevention: Recognizing warning signs and taking timely action. - Preventing Mental Disorders: Early identification of issues and preventing their progression. - Early Diagnosis and Treatment: Timely identification and treatment of mental health issues.
Performance Improvement	- Reducing Absenteeism and Turnover: Creating a healthy and stable environment. - Decision-Making Ability: Making rational decisions in critical situations. - Improving Efficiency: Increasing accuracy and effectiveness in task performance.
Leadership and Social Support	- Facilitating Interpersonal Interactions: Strengthening communication skills and empathy. - Social Support: Creating support networks and reducing feelings of loneliness. - Developing Effective Leadership: Establishing supportive and positive work environments.
Impact on Society and Family	- Impact on Families: Improving family relationships and quality of life. - Developing a Culture of Psychological Safety: Creating a space for discussing mental health issues. - Post-Service Support: Assisting military personnel in adapting to post-service life and managing stress.

From a performance improvement perspective, focusing on mental health can reduce absenteeism and turnover, creating a healthy and stable environment. Personnel with good mental health are typically able to make rational and effective decisions in critical situations, which enhances efficiency and accuracy in task performance [20]. In the context of leadership and social support, MHL strengthens communication skills and empathy, facilitating the creation of supportive networks. These positive relationships can reduce feelings of loneliness and enhance team morale. Additionally, leaders who are aware of mental health issues can create supportive and positive work environments [26]. Finally, the mental health of armed forces personnel not only impacts them but also benefits their families. Improving mental health can lead to the development of a culture that respects and addresses mental health issues, while also supporting soldiers in adapting to post-service life [27]. (Table 4).

DISCUSSION

MHL in the armed forces refers to the ability to understand and manage psychological issues, which is of significant importance. This literacy can positively impact the performance and well-being of military personnel by reducing stress and its associated complications, thereby enhancing individual and collective capabilities. This study examines the importance of MHL in the armed forces and, through a narrative review, analyzes and explains its various dimensions.

1. Awareness and Education:

The literature on MHL in military contexts indicates that increased awareness and education can substantially enhance soldiers' understanding of mental health, with effects persisting for up to 6 months post-intervention [21]. Standardized educational programs focusing on MHL—such as symptomatology, stress management techniques, and coping and resilience strategies—can improve psychological awareness and empower military personnel. However, evidence suggests that raising awareness alone is insufficient to ensure the effective utilization of mental health services. For instance, a study among the Canadian Armed Forces revealed that although soldiers demonstrated relatively high levels of mental health knowledge, service utilization remained low. This discrepancy was more pronounced among younger soldiers, single personnel, and those perceiving limited support from their commanders [28]. These findings highlight the critical influence of organizational and interpersonal factors, including communication quality with supervisors, institutional norms, and military policies, in translating knowledge into action. Additionally, attitudes toward mental health and fear of stigma can hinder the effectiveness of educational initiatives [21,29]. Therefore, interventions that target cultural and attitudinal change should accompany traditional training programs [30]. Courses such as Mental Health First Aid have been shown to enhance knowledge, improve attitudes, and increase confidence in identifying and supporting individuals with psychological difficulties [31]. As a result, such interventions can strengthen supportive behaviors at the unit level and reduce stigma associated with mental disorders. Integrating these findings suggests a conceptual pathway in which improved attitudes toward mental health reduce stigma-related fears, thereby increasing the willingness to seek help and access professional services. Contextual factors—including age, marital status, type of service, organizational culture, and leadership style—can further facilitate or hinder the development of MHL within military populations.

2. Prevention and Treatment:

Increasing the operational efficiency of military personnel requires focused attention to mental health. Given soldiers' exposure to high-risk, critical situations, effective stress management is an essential competency that must be prioritized within military systems. Promoting mental health awareness among service members and relevant authorities facilitates the early identification of symptoms of psychological disorders and supports the use of evidence-based techniques, such as meditation and mindfulness, to regulate stress [25]. By providing appropriate resources and supportive conditions, psychological resilience can be strengthened, enabling military organizations to prevent serious mental health problems while enhancing the overall mental health literacy of personnel. In turn, this contributes to improved military readiness and performance.

Existing evidence indicates that improvements in mental health literacy lead to increased help-seeking behavior and earlier access to psychological support services. However, the effectiveness of such interventions is influenced by cultural, structural, and organizational characteristics within the armed forces. Preventive strategies that are aligned with military organizational culture and tailored to internal norms and values are more likely to achieve meaningful and sustainable outcomes [32,33]. Therefore, in addition to educational programs, strengthening organizational commitment to mental health and fostering supportive environments is essential for enhancing MHL and promoting psychological well-being among military personnel.

3. Performance Improvement:

One of the key factors in enhancing employee performance, particularly among military personnel, is paying attention to mental health. Promoting mental well-being can reduce absenteeism and even decrease rates of desertion. Focusing on mental health, especially in critical situations, improves decision-making abilities and enhances the operational efficiency of military forces. Psychological support not only strengthens loyalty and a sense of security among personnel but also increases perceived organizational support and reduces the costs associated with recruiting and training new staff [20]. Therefore, systematic planning for mental health screening, management, and the implementation of comprehensive mental health programs within military

organizations leads to improved decision-making capabilities and overall operational performance. To achieve this, military organizations should structurally establish regular training courses or workshops aimed at promoting MHL. Such programs can be conducted in three phases: pre-mission, during-mission, and post-mission. In addition to training, military organizations need to develop adequate infrastructure that ensures rapid access to psychological counseling, referral to specialized centers, and psychological rehabilitation services. In a review study, Fikretoglu et al. also emphasized the importance of establishing appropriate infrastructure to improve the mental health performance of military personnel [34]. Similarly, Wu et al. (2021) highlighted the promotion of a supportive organizational culture, improved access to mental health resources, and the implementation of related policies—findings consistent with the present study [35].

4. Leadership and Social Support:

MHL plays a vital role in shaping the psychological and social dynamics within the armed forces. Beyond its direct influence on individual well-being, MHL contributes to stronger interpersonal relationships, greater social support, and more effective leadership. A closer examination of existing studies reveals several key themes that help explain these interconnections.First, improving MHL enhances communication and empathy among service members. When personnel understand mental health concepts and recognize early signs of distress, they are more capable of offering support to one another. This understanding builds mutual trust and fosters teamwork—factors that are essential for maintaining morale and cohesion in high-pressure military environments [35,36]. Second, the role of social support emerges as a critical mediator between MHL and mental health outcomes. Greater literacy about mental health tends to reduce stigma, making individuals more willing to seek help and share their experiences. This not only prevents feelings of isolation but also strengthens unit solidarity. Some studies have noted that while social support may not directly reduce depressive symptoms, it significantly enhances life satisfaction and resilience among personnel [37]. These findings suggest that the relationship between support and psychological health is complex and may operate through multiple pathways, including perceived belonging and emotional regulation. Third, leadership plays an important bridging role. Commanders and supervisors with higher levels of MHL are better equipped to identify early signs of distress in their teams and to create an environment of psychological safety. Effective leaders can shape a positive organizational culture that encourages open communication about mental health issues and supports timely access to professional care [38]. Consequently, leadership enriched with mental health awareness not only benefits individual soldiers but also enhances unit effectiveness and operational readiness. A possible mechanism underlying these relationships may follow this sequence: Improved MHL → Reduced Stigma → Increased Help-Seeking → Enhanced Mental Health → Greater Operational Effectiveness. This process aligns with broader psychological models emphasizing that awareness and attitude shifts are prerequisites for behavioral change. It is also important to consider contextual factors. Cultural norms, type of military branch, and organizational structure can significantly affect how MHL programs are received and implemented. For example, in more hierarchical or combat-oriented environments, stigma and fear of appearing weak may reduce participation in mental health initiatives. Adapting training materials to local culture and leadership style can therefore increase program effectiveness [39].

5. Impact on Society and Family:

The mental health of military personnel plays a critical role in both organizational effectiveness and the quality of individual and family life. Promoting psychological well-being not only strengthens family relationships and facilitates access to support resources but also fosters a culture in which mental health is valued equally with physical health. In such environments, service members are more likely to express their concerns without fear of stigma and to seek appropriate assistance. Enhancing MHL is essential for cultivating this culture. Improved MHL contributes to individual well-being, supports scientific understanding of psychological issues, and creates a safe environment for open dialogue about mental health. Evidence from previous studies indicates that health promotion initiatives in military settings—such as communication skills and empathy training—can enhance family cohesion, resilience, and social support [34,35]. Furthermore, increased MHL within the broader community can strengthen the mental health of service members and their families by encouraging early identification and treatment of disorders, promoting psychological safety, and improving access to counseling and support systems. These findings align with research emphasizing the central role of family and social factors in maintaining the mental health of military personnel [25,26]. A plausible mechanism underlying these relationships suggests that greater MHL reduces social stigma, enhances help-seeking behavior, promotes the use of supportive resources, and ultimately improves individual and collective resilience. Cultural and organizational factors also influence the effectiveness of such interventions. In certain military branches or societies where mental illness carries a strong stigma, personnel may be less inclined to seek counseling or psychological support(40). Therefore, educational and preventive programs should be tailored to the cultural values and organizational structures of each military context to ensure greater acceptance and effectiveness [27]. Moreover, the integration of digital tools and online training can expand access to mental health services, particularly for families who become geographically distant from military facilities after service. Furthermore, organizational health literacy also plays an important role in promoting psychological well-being within military settings. Organizational health literacy refers to an organization’s capacity to design, coordinate, and implement processes that facilitate members’ access to, understanding of, and effective use of health-related information and services. By investing in this area, military organizations can develop more health-oriented work environments and reduce barriers to access and stigma related to mental health care.

Evidence suggests that improving organizational health literacy enables armed forces to deliver more targeted and effective mental health education and support programs in the field [41]. This enhancement increases the acceptance and utilization of psychological services and interventions, ultimately fostering greater resilience and improving overall organizational performance. This systems-based approach emphasizes that personnel's mental well-being depends not only on individual-level support but also on structural, policy, and cultural determinants within the organization. Therefore, organizational health literacy should be addressed alongside individual mental health literacy to achieve sustainable progress in mental health promotion.

Limitations

This review is limited by the relatively small number of eligible studies and the heterogeneity in study designs, populations, and outcome measures. These factors constrained the ability to perform quantitative synthesis. Future research should utilize standardized assessment tools, employ rigorous study designs, and evaluate the effectiveness of mental health literacy (MHL) interventions specifically within military contexts. Such research will provide more robust evidence to guide policy, training programs, and mental health support strategies for armed forces personnel.

CONCLUSION

MHL among military personnel is essential for fostering psychological resilience, early recognition of mental health problems, and promoting help-seeking behaviors. This review underscores that higher levels of MHL are linked to improved quality of life, operational effectiveness, and overall performance among members of the armed forces. Given the inherently stressful and high-pressure nature of military service, personnel remain vulnerable to various mental health disorders. Strengthening MHL can therefore serve as a preventive and empowering approach—enabling individuals to manage stress more effectively, identify psychological challenges at early stages, and prevent their escalation during critical missions. Furthermore, leadership that acknowledges and integrates mental health awareness into organizational culture can foster supportive and resilient work environments. Based on these findings, it is recommended that military institutions and policymakers develop and implement structured educational programs, continuous training, and evidence-based interventions aimed at improving MHL among service members. Such initiatives not only enhance individual well-being and morale but also contribute to greater organizational performance, readiness, and mission success within the armed forces.

Conflicts of interest and sources of funding

The authors declare no conflicts of interest and no funding

Acknowledgments

The authors of this article would like to express their gratitude to all individuals who assisted in conducting this research.

No generative AI was used in the production of this manuscript.

Authors' contribution

Conceptualization, M.Z. and S.K.; methodology, M.F.A and R.F; software, R.F. and M.F.A.; validation, M.Z and S.K.; formal analysis, R.F. and M.F.A.; investigation, M.Z. and S.K.; data curation, M.Z. and S.K; writing—original draft preparation, M.Z. and S.K.; writing—review and editing M.Z. and S.K.; visualization, R.F. and M.F.A.; supervision, M.Z. and S.K.; project administration, M.Z. and S.K. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

References

1. Zareipour M, Jadgal M-S, Khazir Z, Moradi Z, Amirzehni J. Study of lifestyle and its relationship between health literacy in health ambassadors in Urmia. Journal of Health Literacy. 2021;6(2):33-40. DOI: 10.22038/jhl.2021.58210.1164.

2. Zareipour M, Sadaghianifar A, Moradi Z, Jafari N, Esmzadeh M. Health literacy and its relationship with self-efficacy in health ambassadors. Journal of Health Literacy. 2020;4(4):56-63. DOI: 10.22038/jhl.2020.44789.1090.

3. Movahed E, Zareipour M, Jadgal MS, Rezaee Moradali M, Baljani E. Investigating health literacy and its Relationship with the Social Influences of COVID-19 in Police force employees. Journal of Health literacy. 2024;8(4):43-52. DOI: 10.22038/jhl.2023.73126.1437.

4. Shahid R, Shoker M, Chu LM, Frehlick R, Ward H, Pahwa P. Impact of low health literacy on patients' health outcomes: a multicenter cohort study. BMC Health Services Research. 2022;22(1):1148.DOI: 10.1186/s12913-022-08527-9.

5. Nutbeam D, Lloyd JE. Understanding and responding to health literacy as a social determinant of health. Annual review of public health. 2021;42(1):159-73.DOI: 10.1146/annurev-publhealth-090419-102529.

6. Trutner ZD, Furlough K, Martinez A, Vetter I, Uhler LM, Haynes A, et al. Is health literacy associated with surgical outcomes? A systematic review. Journal of Surgical Research. 2023;291:720-33.DOI: 10.1016/j.jss.2023.06.044.

7. Ghasemi A-H, Lirharani RK, Saki N, Arezoomand M. The Role of Health Literacy in Reducing Healthcare Costs and Referring to the Hospital among Elderly. Journal of Medical Library and Information Science. 2021; 6-21. https://doi.org/10.22037/jmlis.v2i.33107

8. Lam LT, Wong P, Lam MK. Protocol for a phase III wait-listed cluster randomised controlled trial of an intervention for mental well-being through enhancing mental health literacy and improving work friendliness in Hong Kong. Trials.2019;20:1-11. DOI: 10.1186/s13063-019-3748-y.

9. Noroozi A, Khademolhosseini F, Lari H, Tahmasebi R. The mediator role of mental health literacy in the relationship between demographic variables and health-promoting behaviours. Iranian Journal of Psychiatry and Behavioral Sciences.2018;12(2):e.126.3. DOI: https://doi.org/10.5812/ijpbs.12603.

10. Arafat SY, Al Mamun M, Uddin MS. Depression literacy among first-year university students: a cross-sectional study in Bangladesh. Global Psychiatry. 2019; 2(1):.6-31.DOI:10.2478/gp-2019-0002.

11. Stevelink S, Malcolm E, Mason C, Jenkins S, Sundin J, Fear N. The prevalence of mental health disorders in (ex-) military ersonnel with a physical impairment: a systematic review. Occupational and environmental medicine. 2015; 72(4):.51-243. DOI: 10.1136/oemed-2014-102207.

12. Cesur R, Sabia JJ, Tekin E. The psychological costs of war: Military combat and mental health. Journal of Health Economics. 2013;32(1):51-65.DOI: 10.1016/j.jhealeco.2012.09.001.

13. Rong H, Cheng X, Garcia JM, Zhang L, Lu L, Fang J, et al. Survey of health literacy level and related influencing factors in military college students in Chongqing, China: A cross-sectional analysis. PLOS ONE. 2017;12(5):e0177776.DOI: https://doi.org/10.1371/journal.pone.0177776.

14. Rong H, Lu L, Wang L, Liu C, Zhang L, Li F, et al. Investigation of health literacy status and related influencing factors in military health providers of the Chinese People's Liberation Army, a cross-sectional study. BMC Public Health. 2023;23(1):4.DOI: https://doi.org/10.1186/s12889-022-14958-0.

15. Ojio Y, Mori R, Matsumoto K, Nemoto T, Sumiyoshi T, Fujita H, et al. Innovative approach to adolescent mental health in Japan: school-based education about mental health literacy. Early intervention in psychiatry. 2021;22(1):1148.DOI: 10.1111/eip.12959.

16. Saini R, Das RC, Chatterjee K, Srivastava K, Khera A, Agrawal S. Augmenting mental health literacy of troops in a large military station: A novel approach. Industrial psychiatry journal. 2023;32(Suppl 1):S166-S173. DOI: 10.4103/ipj.ipj_233_23.

17. Nematshahi M, Parsaeimehr Z, Roshanzadeh M, Jamalinik M, Hasheminik M, Tajabadi A. Mental health status and its influencing factors in Iranian soldiers: Systematic review. Journal of military medicine. 2020;22(9):95-885. .DOI: 10.30491/JMM.22.9.3.

18. Lawrence EG, Jones N, Greenberg N, Fear N, Wessely S, Michael G, et al. Mental well-being interventions in the military: the ten key principles. British Medical Journal Publishing Group; 2022;80-179.DOI: 10.1136/bmjmilitary-2020-001740.

19. Crone DM, Sarkar M, Curran T, Baker CM, Hill D, Loughren EA, et al. Mental health first aid for the UK Armed Forces. Health Promotion International. 2020;35(1):132-139.DOI: 10.1093/heapro/day112.

20. Morgado TM, Costa TO, de Araújo OL, da Silva RG. Interventions for better mental health literacy. Handbook of Research on Assertiveness, Clarity, and Positivity in Health Literacy: IGI Global; 2022; 187-207.DOI: https://doi.org/10.4018/978-1-7998-8824-6.ch011.

21. Saini R, Das R, Chatterjee K, Srivastava K, Khera A, Agrawal S. Augmenting mental health literacy of troops in a large military station: A novel approach. Industrial psychiatry journal. 2023;32(Suppl 1):S166-S173. DOI: 10.4103/ipj.ipj_233_23.

22. Portela-Pino I, Hernaiz-Sanchez A, Lomba-Portela L. Evaluation of health literacy and its predictive formative factors among Spanish military personnel. Military Psychology. 2025;37(1):14-21.DOI: 10.1080/08995605.2023.2274755.

23. Soleimani-Sefat E, Parandeh A, Rahmati F, Kamalikhah T. Development and psychometric properties of the mental health literacy questionnaire (MHLQ) among young Iranian soldiers. International Journal of Preventive Medicine. 2022;13(1):101.DOI: 10.4103/ijpvm.IJPVM_468_20.

24. Thomas JL, Adrian AL, Penix EA, Wilk JE, Adler AB. Mental health literacy in US soldiers: Knowledge of services and processes in the utilization of military mental health care. Military Behavioral Health. 2016;4(2):9-92.DOI: 10.1080/21635781.2016.1153541.

25. Willing MMP, Nevers J, Nofziger D, Rogers T, Riggs DS. Lessons learned from efforts to prevent behavioral health problems and promote mental wellbeing in the US military. Mental Health & Prevention. 2024;34:200-330.DOI: https://doi.org/10.1016/j.mhp.2024.200330.

26. Liu B, Liu L, Zou M, Jin Y, Song L, Ren L, et al. Relationships between resilience, perceived social support, and mental health in military personnel: a cross-lagged analysis. BMC Public Health. 2024;24(1):33-34.DOI: https://doi.org/10.1186/s12889-024-20907-w.

27. Wadham B, Andrewartha L, Lawn S, Onur I, Edney LC. A scoping review of interventions targeting the mental health of Australian veterans. International journal of environmental research and public health. 2024;21(6):796.DOI: 10.3390/ijerph21060796.

28. Therrien ME, Gottschall S, Wang Z, Daugherty C. Awareness and use of Canadian Armed Forces mental wellbeing programs and resources among Regular Force personnel. Current Psychology. 2024;43(38):19-30.DOI: 10.1007/s12144-024-06607-z.

29. Doody CB, Robertson L, Cox KM, Bogue J, Egan J, Sarma KM. Pre-deployment programmes for building resilience in military and frontline emergency service personnel. Cochrane Database Syst Rev. 2021;12(12):Cd.13242.DOI: 10.1002/14651858.CD013242.pub2.

30. Trompeter N, Rafferty L, Dyball D, McKenzie A, Greenberg N, Fear NT, et al. Gender differences in structural and attitudinal barriers to mental healthcare in UK Armed Forces personnel and veterans with self-reported mental health problems. Social psychiatry and psychiatric epidemiology. 2024;59(5):37-827. DOI: 10.1007/s00127-023-02567-0.

31. Deahl M. Operational mental health... what practitioners and commanders should know. International Journal of Social Psychiatry. 2024;70(7):8-1234. DOI: 10.1177/00207640241261208.

32. Soria-Martínez M, Navarro-Pérez CF, Pérez-Ardanaz B, Martí-García C. Conceptual framework of mental health literacy: Results from a scoping review and a Delphi survey. International Journal of Mental Health Nursing. 2024;33(2):96-281. DOI: 10.1111/inm.13249.

33. Cao F, Li J, Xin W, Yang Z, Wu D. The impact of resilience on the mental health of military personnel during the COVID-19 pandemic: coping styles and regulatory focus. Front Public Health. 2023;11:1240047. DOI: 10.3389/fpubh.2023.1240047.

34. Fikretoglu D, Sharp M-L, Adler AB, Bélanger S, Benassi H, Bennett C, et al. Pathways to mental health care in active military populations across the

Five-Eyes nations: An integrated perspective. Clinical Psychology Review. 2022;91:102100.DOI: 10.1016/j.cpr.2021.102100.

35. Wu A, Roemer EC, Kent KB, Ballard DW, Goetzel RZ. Organizational Best Practices Supporting Mental Health in the Workplace. J Occup Environ Med. 2021;63(12):e925-e.31. DOI: 10.1097/JOM.0000000000002407.

36. McGraw K, Adler J, Andersen SB, Bailey S, Bennett C, Blasko K, et al. Mental health care for service members and their families across the globe. Military medicine. 2019;184(Supplement_1):25-418. DOI: 10.1093/milmed/usy324.

37. Hou C-H, Chen P-L. Optimism, Social Support, and Caregiving Burden among the Long-Term Caregivers: The Mediating Effect of Psychological Resilience. International Journal of Mental Health Promotion. 2024;26(9). DOI: https://doi.org/10.32604/ijmhp.2024.051751.

38. Jones N, Campion B, Keeling M, Greenberg N. Cohesion, leadership, mental health stigmatisation and perceived barriers to care in UK military personnel. Journal of Mental Health. 2018;27(1):8-10. DOI: 10.3109/09638237.2016.1139063.

39. Henderson C, Evans-Lacko S, Thornicroft G. Mental illness stigma, help seeking, and public health programs. American Journal of Public Health. 2013;103(5):80-777. DOI: 10.2105/AJPH.2012.301056.

40. Srivastava K, Chatterjee K, Chauhan VS, Panda SP, Bhat PS. Building psychological resilience among families of service personnel. Industrial Psychiatry Journal. 2024;33(Suppl 1):S242-S5. DOI: 10.4103/ipj.ipj_158_24.

41. Sørensen K, Levin-Zamir D, Duong TV, Okan O, Brasil VV, Nutbeam D. Building health literacy system capacity: a framework for health literate systems. Health Promotion International. 2021;36(Supplement_1):i13-i23. DOI: 10.1093/heapro/daab153.

https://doi.org/10.55453/rjmm.2026.129.3.4

REVIEW

Immunomodulatory Treatment Strategies in Psoriasis Patients with High-Risk Systemic Comorbidities: A Narrative Review and Case Series

Adelina F. Ghilencea[1], Horia Blejan[1], Daniel O. Costache[2*], Adrian Enache[3], Constantin Caruntu[4*], Cristian Scheau[4]

[1] Doctoral School, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; filofteia-adelina.ghilencea@drd.umfcd.ro (AFG), horia.blejan@drd.umfcd.ro (HB)
[2] Dermatology Discipline, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; daniel.costache@umfcd.ro
[3] Department of Pathology, Carol Davila Central Emergency Military University Hospital, Bucharest, Romania; adrianenache20@yahoo.com
[4] Department of Physiology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; costin.caruntu@gmail.com (CC), scheau@umfcd.ro (CS)

*Correspondence: daniel.costache@umfcd.ro (DOC), costin.caruntu@gmail.com (CC)

Abstract: Introduction. Management of moderate-severe psoriasis is challenging in the presence of severe systemic comorbidities, such as HIV infection, recent history of cancer, latent tuberculosis infection, or advanced liver disease. These patients are almost invariably excluded from randomized clinical trials, an aspect that limits the availability of standardized therapeutic options. Material and methods. This narrative review summarizes the current literature on immunomodulatory therapeutic strategies in patients with psoriasis and severe systemic comorbidities, integrating existing evidence in the literature with relevant clinical observations from real-world practice. Results. Available data suggest that therapeutic decisions should be individualized according to the type of comorbidities and severity of the disease. In well-controlled HIV infection, conservative strategies may be preferred. In patients with a history of cancer, systemic therapies may be used with caution and in interdisciplinary collaboration. In latent tuberculosis infection, prophylaxis is necessary, but isoniazid-induced hepatotoxicity is an important limitation. In liver disease, biological therapies may constitute a safer alternative to conventional systemic therapy. Conclusion. In this context, patients with psoriasis and severe associated systemic comorbidities require a personalized, multidisciplinary approach and close monitoring. Real-world data play an essential role in guiding therapeutic decisions in this patient population.

Keywords: psoriasis, biologic therapy, HIV infection, malignancy, latent tuberculosis, immunosuppression

INTRODUCTION

Psoriasis is a chronic, immune-mediated inflammatory disease with an estimated prevalence of approximately 2–3% in the general population (1,2). It is now recognized as a systemic condition, frequently associated with multiple comorbidities, including metabolic, cardiovascular, hepatic, infectious, and neoplastic diseases, which may influence both clinical severity and possible therapeutic options (3,4).

Systemic inflammation plays a central role in the pathogenesis of psoriasis, with complex immunological pathways involved, with the interleukin 23/ T helper 17 axis (IL-23/Th17) playing a central role. These mechanisms have underpinned the development of modern biological therapies, such as tumor necrosis factor alpha (TNF-α) inhibitors, interleukin 17 (IL-17) inhibitors, interleukin 23 (IL-23) inhibitors, and interleukin 12/23 (IL-12/23) inhibitors, which have revolutionized the treatment of moderate and severe forms of the disease (5,6).

In recent years, advances in understanding pathogenic mechanisms, identification of biomarkers, and development of personalized therapeutic strategies have contributed to significant improvements in the prognosis and quality of life of patients with psoriasis (7,8). However, the use of these therapies in certain populations remains limited. Patients with major systemic comorbidities — such as human immunodeficiency virus (HIV) infection, recent oncological history, latent tuberculosis infection, or advanced liver disease — are frequently excluded from

Citation: Ghilencea AF, Blejan H, Costache DO, Enache A, Căruntu C, Scheau C. *Immunomodulatory Treatment Strategies in Psoriasis Patients with High-Risk Systemic Comorbidities: A Narrative Review*. R. J. Mil. Med. 2026, CXXIX(3): 251-263
https://doi.org/10.55453/rjmm.2026.129.3.4

Academic Editor: Octavian Vasiliu

Received: 12 March 2026
Revised: 02 April 2026
Accepted: 06 April 2026

randomized clinical trials, which reduces the availability of solid evidence-based recommendations for these categories (6,7). Consequently, therapeutic decisions in these situations are often based on observational data and clinical experience.

The aim of this article is to review immunomodulatory therapeutic strategies in psoriasis associated with severe systemic comorbidities, integrating data from the literature with observations from real-world clinical practice.

METHODOLOGY

This study was designed as a narrative review combined with a retrospective case series, aiming to synthesize current evidence and real-world clinical experience regarding immunomodulatory therapeutic strategies in psoriasis patients with high-risk systemic comorbidities. A literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science for articles published up to March 2026, using relevant keywords such as “psoriasis,” “biologic therapy,” “HIV,” “malignancy,” “latent tuberculosis,” and “liver disease.” Eligible studies included clinical trials, observational studies, systematic reviews, and case reports addressing treatment approaches and safety in this population, with emphasis on clinically relevant and recent data. Extracted information was qualitatively synthesized according to comorbidity type, therapeutic strategies, and safety outcomes. In parallel, a retrospective case series was realized, including patients with clinically and/or histopathologically confirmed psoriasis and at least one major systemic comorbidity, managed in routine practice. Clinical evaluation included Psoriasis Area and Severity Index score (PASI) and Dermatology Life Quality Index score (DLQI) scores, as well as comorbidity-specific parameters, and therapeutic decisions were individualized based on disease severity and risk–benefit assessment within a multidisciplinary framework. Patients were monitored through regular clinical and laboratory assessments to evaluate treatment response and adverse events. All procedures were conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. The clinical components of the study were approved by the Local Ethics Committee of the Dr. Carol Davila University Emergency Central Military Hospital, Bucharest (registration number 750, 22 January 2025).

PSORIASIS AND HIV INFECTION

People living with HIV (PLWH) have an increased incidence of dermatological conditions, many of which are associated with significant morbidity and reduced quality of life. Psoriasis, in particular, tends to have a more severe and prolonged course in this population compared with the general population (9,10). HIV infection is characterized by a progressive decrease in CD4+ T lymphocytes, which makes the increased frequency of psoriasis exacerbations in these patients quite paradoxical. However, psoriasis can occur at any stage of HIV infection and is considered to be the result of immunological dysregulation, particularly through alterations in the Th1/Th17 axis (11). The introduction of combination antiretroviral therapy (cART) has significantly modified the natural history of both HIV infection and psoriasis, contributing to increased life expectancy and improved quality of life for patients. However, moderate and severe forms of psoriasis frequently require systemic or immunomodulatory treatments, raising important safety concerns (4).

Therapeutic options for psoriasis in HIV-positive patients are limited, with first-line treatment usually including topical therapies associated with antiretroviral therapy, followed by phototherapy in more extensive forms (11,12). As a second-line treatment, oral retinoids can be used, either alone or in combination. Also, immunosuppressive therapies and biological therapies represent a useful alternative in difficult cases (9,10,12). On the other hand, in patients with psoriasis and concomitant HIV or other viral infections like hepatitis B or C viruses, there may be a risk of viral reactivation with the use of biological therapies (10). Nonetheless, recent studies suggest that this risk is not significant, especially in patients with well-controlled HIV infection, and that the therapeutic approach only requires interdisciplinary collaboration, particularly with the infectious disease physician (10,11). Moreover, biological agents targeting the IL-23 pathway, such as guselkumab and risankizumab, have shown promising results in small series of cases, with high efficacy and a favorable safety profile, with no observed effects on viral replication or immune parameters (13,14). Furthermore, a recent systematic review, which included multiple biological therapies (TNF-α inhibitors, IL-17 inhibitors and IL-23 inhibitors), highlighted the consistent improvement of cutaneous manifestations of psoriasis in HIV-positive patients, with rare adverse events (11).

However, despite the accumulation of data supporting the safe use of systemic and biological therapies in patients with psoriasis and HIV infection, the management of psoriasis in this context remains a challenge, and therapeutic decisions require interdisciplinary collaboration (15). Next, we present the case of a young HIV positive man with palmoplantar psoriasis encountered in our clinical practice.

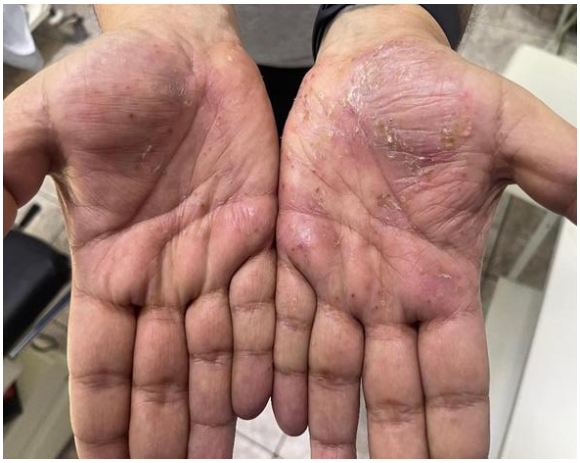
Palmoplantar pustular psoriasis in a patient with well-controlled HIV infection

A 29-year-old man presented in January 2026 with a painful palmoplantar eruption evolving progressively over approximately six weeks. The initial presentation consisted of dryness and mild palmar erythema, attributed by the patient to occupational exposure and frequent disinfectant use. Over time, lesions evolved into painful pustules with scaling and burning sensations. Plantar involvement led to gait impairment, while palmar involvement affected manual daily activities, contributing to anxiety regarding disease progression. The patient had been diagnosed with HIV infection in 2018 and was receiving combined antiretroviral therapy

with dolutegravir/lamivudine (1 tablet/day), with documented excellent adherence since diagnosis. There was no personal or family history of psoriasis and no other known immune-mediated disease. No opportunistic infections were reported in recent years.

At presentation, the immune and virologic status was favorable: CD4 = 1400 cells/mm³ with undetectable viral load. Routine laboratory tests were unremarkable. Dermatologic examination revealed well-demarcated erythematous scaly plaques on both palms, with multiple superficial sterile pustules, some confluent, on an erythematous background (Figure 1). Plantar lesions were more extensive, with hyperkeratosis, painful fissuring, and scattered pustules along the plantar margins and arch. No lesions were observed on the trunk, scalp, or nails.

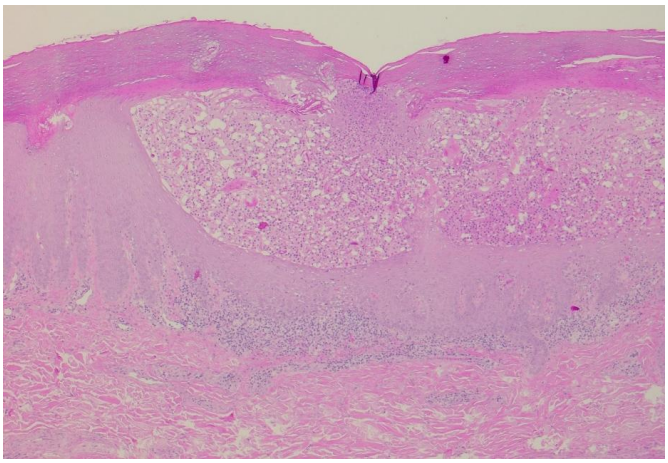
Figure 1: Palmoplantar pustular psoriasis in a patient with well-controlled HIV infection.
Erythematous well-demarcated plaques with superficial sterile pustules on the palms at initial presentation (PASI 7.8).



Taking these aspects into consideration, a clinical diagnosis of palmoplantar pustular psoriasis was made. Despite limited body surface area involvement, PASI was 7.8 and DLQI was 15, reflecting the disproportionate functional impact due to the critical localization. The patient reported occupational difficulties and social avoidance due to visible hand lesions. However, given the clinical context — young HIV-positive patient — histopathologic confirmation was necessary to exclude other pustular dermatoses or drug reactions.

An incisional biopsy was performed under local anesthesia (lidocaine 1%). Histology showed regular acanthosis, elongation of rete ridges, hyperkeratosis with parakeratosis, neutrophilic microabscesses in stratum corneum, and intraepidermal spongiform pustules, consistent with palmoplantar pustular psoriasis (Figure 2).

Figure 2: Palmoplantar pustular psoriasis in a patient with well-controlled HIV infection – Histopathological features.
Regular acanthosis, elongation of rete ridges, hyperkeratosis with parakeratosis, neutrophilic microabscesses in stratum corneum, and intraepidermal spongiform pustules. H&E stain x10.



This diagnosis raised an important therapeutic challenge: HIV-associated psoriasis has been reported to be severe or atypical, possibly related to immune dysregulation and Th1/Th17 axis alterations (7,8,16). Because randomized trials of biologic therapies usually excluded HIV-positive individuals, evidence is limited and decisions must balance cutaneous control against potential immune destabilization. In this case, the presence of significant but localized functional impairment, as well as the absence of systemic involvement, represented factors favoring the choice of a conservative strategy. Despite well-controlled HIV-infection (undetectable viral load and stable immune status), systemic therapies were avoided given the potential risk of immune destabilization. Topical corticosteroids are known to exert potent anti-inflammatory and immunomodulatory effects by binding to intracellular receptors and modulating cellular gene expression (17). Similarly, ultraviolet B phototherapy (UVB) is known to induce apoptosis of pathogenic T lymphocytes, leading to local and systemic immunosuppression (18,19). Therefore, this combination allows effective disease control while providing a safe, non-systemic approach. Based on these considerations, topical treatment with mometasone furoate (1 mg/g) once daily was initiated, combined with narrow band UVB (NB-UVB) phototherapy three times weekly. The choice of NB-UVB was based on its established efficacy in psoriasis and a favorable safety profile in stable HIV patients under appropriate monitoring.

The patient underwent regular dermatologic and infectious diseases follow-up. Clinical evolution was favorable: after approximately four weeks, pustules decreased and erythema improved. By eight weeks, plantar fissuring improved substantially and pain on walking diminished. DLQI decreased to 6. Immunological parameters remained stable, with no decline in CD4+ and no detectable viremia.

This case highlights that severity assessment should include functional and psychosocial impact, not solely extent. In well-controlled HIV infection, a stepwise, non-systemic approach may be effective and safe in localized disease.

PSORIASIS ASSOCIATED WITH A HISTORY OF MALIGNANCY

The relationship between psoriasis, immunomodulatory therapies, and the risk of malignancy is complex and intensively debated, and the lack of solid evidence leads to reluctance to initiate systemic or biologic therapies in patients with a history of cancer (20). Studies have shown that patients with severe psoriasis are at increased risk for certain types of malignancies, particularly lymphomas and non-melanoma skin cancers (21). In addition, associated risk factors, such as smoking, obesity, and alcohol consumption, may further contribute to this risk. On the other hand, a recent meta-analysis did not reveal a significant increase in the risk of breast cancer in patients with psoriasis, regardless of disease severity (22). These results suggest that although psoriasis is associated with an increased risk for certain neoplasms, this risk does not extend uniformly to all types of cancer.

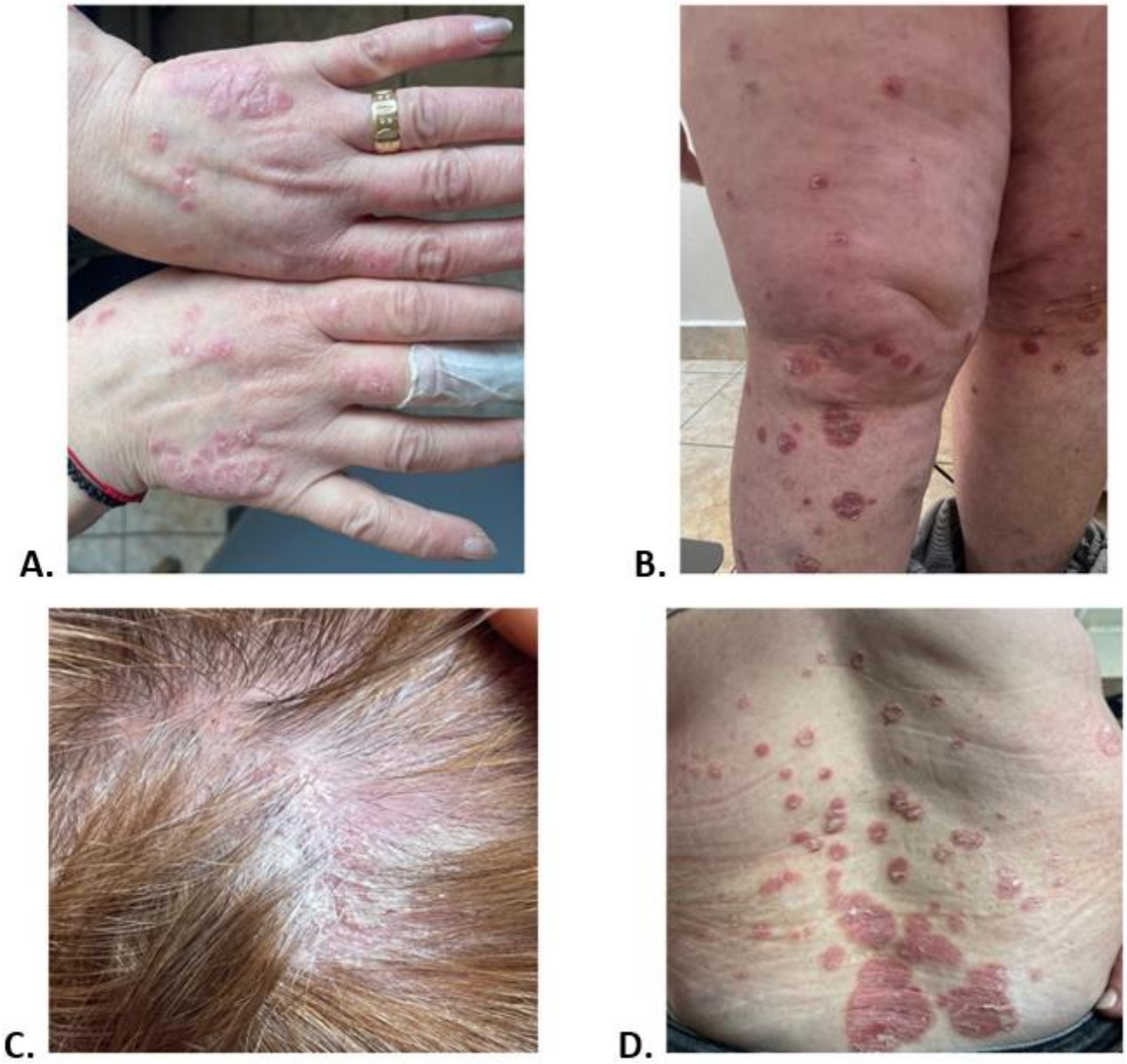
Therapies used in psoriasis may also influence oncological risk differently. Treatment with psoralene and ultraviolet A phototherapy (PUVA) and cyclosporine has been associated with an increased risk of skin cancer, especially squamous cell carcinoma (21). Regarding TNF-α inhibitors, the data are variable, with some studies suggesting a slightly increased risk of non-melanoma skin cancer (23). In contrast, newer biologic therapies, including IL-17 inhibitors and IL-23 inhibitors, appear to have a more favorable safety profile, with no clear association with an increased risk of malignancy (21,23).

A key issue in clinical practice is the risk of tumor recurrence in patients who require systemic treatment for psoriasis but already have a history of malignancy. Current data suggest that biologic therapies are not associated with a significant increase in the risk of tumor recurrence or progression (20). However, management of these patients involves a multidisciplinary approach, particularly a good collaboration between dermatology and oncology (20). Also, regular oncological screening and careful monitoring are essential during treatment. Further, we present a characteristic case for this type of pathological association.

Moderate-to-severe plaque psoriasis in a patient with a recent history of invasive breast carcinoma

A 54-year-old woman presented in November 2024 with progressive worsening of a cutaneous eruption that began approximately four months prior. The onset was subtle, with a few erythematous plaques on the trunk initially interpreted as contact dermatitis. Over time, lesions expanded, became infiltrated, markedly scaly and pruritic, and progressively involved the scalp and limbs (Figure 3). The patient reported mild pruritus, skin tightness, and scaling that significantly impacted daily comfort. Psychosocial burden was evident: she avoided dark clothing due to visible scaling and described anxiety related to body image.

Figure 3: Psoriasis vulgaris – Clinical features.

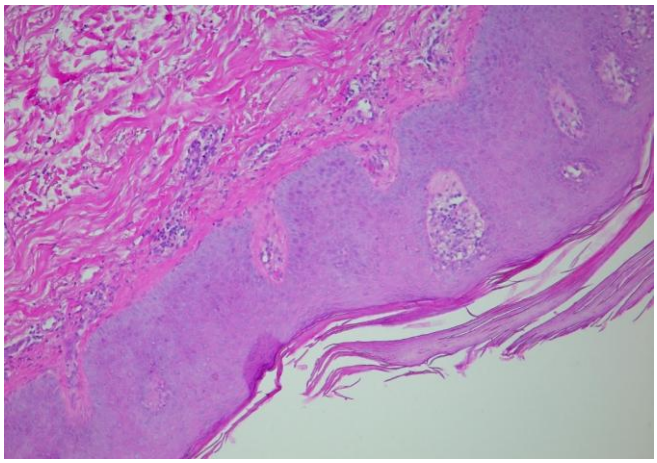


A - Well-demarcated erythematous plaques with adherent silvery scale involving the dorsal hands and forearms at baseline, B - Multiple infiltrated erythematous plaques distributed over the lower trunk and lumbar region, C - Erythematous scaly plaque involving the scalp, D- Thick erythematous plaques with scaling on the lower limbs.

Her medical history was notable for invasive mucinous breast carcinoma, surgically treated in November 2023. Postoperative oncologic evaluation documented remission with no evidence of metastasis or recurrence. At presentation, she was receiving adjuvant endocrine therapy with anastrozole (1mg/day), and periodic oncologic follow-up remained negative.

Dermatologic examination showed well-demarcated erythematous infiltrated plaques covered with adherent silvery scale involving the trunk, upper and lower limbs, and scalp. There were no clinical signs of psoriatic arthritis and no significant nail involvement. PASI score was 16.8 and DLQI score was 18, consistent with moderate-to-severe disease and major quality-of-life impairment. The diagnosis of plaque psoriasis was confirmed histopathologically (Figure 4).

Figure 4: Psoriasis vulgaris – Histopathological features.
Regular epidermal hyperplasia, parakeratosis, suprabasal mitosis, superficial dermal inflammatory infiltrate. H&E stain x10.



The key challenge was not the psoriasis severity alone, but the recent oncologic context. Patients with recent solid malignancies are another type of patient frequently excluded from trials of systemic/biologic therapies, and available evidence is largely observational (24,25). The main clinical dilemma was potential recurrence of neoplasia under systemic immunomodulatory therapies, particularly the conventional immunosuppressants such as methotrexate, as well as the biologic agents. Exerting various mechanisms of action, methotrexate is an effective immunomodulator through disruption of adenosine metabolism, which leads to repressed T-cell activation and B-cell down-regulation (26). Although its immunosuppressive effect is less targeted compared to biologic therapies, caution is advised in patients with recent neoplasia. Regarding a possible therapy with methotrexate, there is no robust evidence that using low doses increases recurrence risk in solid tumors, but caution is warranted, particularly within the first years after cancer treatment.

Because of these aspects, therapeutic decisions were discussed in an interdisciplinary manner with the treating oncologist. Considerations included: approximately one year since surgery, absence of clinical/imaging recurrence, mucinous histology, which has a relatively favorable prognosis, and the significant psoriasis burden. A conservative systemic strategy was chosen: methotrexate 10 mg/week with folic acid supplementation, under strict hematologic and hepatic monitoring, combined with phototherapy to accelerate control. Clinical response was progressive. After approximately eight weeks, erythema and plaque infiltration decreased. At four months, the PASI score decreased to three with marked DLQI score improvement. By August 2025, complete remission was achieved (PASI score 0; DLQI score 0), without significant laboratory abnormalities and without oncologic recurrence during follow-up.

Given remission and the patient's preference to minimize prolonged systemic exposure, methotrexate was temporarily discontinued with close monitoring. However, relapse occurred in January 2026, initially on the scalp and later on the trunk (PASI score 9; DLQI score 11). Concomitant oncologic assessment remained negative. Following renewed interdisciplinary discussion, methotrexate was restarted at the same dose, with plans to consider biologic transition if long-term control becomes necessary, guided by safety profile and available data in post-malignancy populations.

This case underscores the importance of individualized treatment and sustained dermatology–oncology collaboration in patients with recent malignancy.

PSORIASIS AND LATENT TUBERCULOSIS

According to current guidelines, screening for latent tuberculosis infection is an essential step before initiating biologic therapy in patients with psoriasis. In this context, isoniazid prophylaxis is frequently used as an effective bactericidal agent against Mycobacterium tuberculosis. On the other hand, it is associated with a well-known risk of hepatotoxicity, ranging from asymptomatic transient elevations of transaminases to severe, potentially fatal acute hepatitis (27,28).

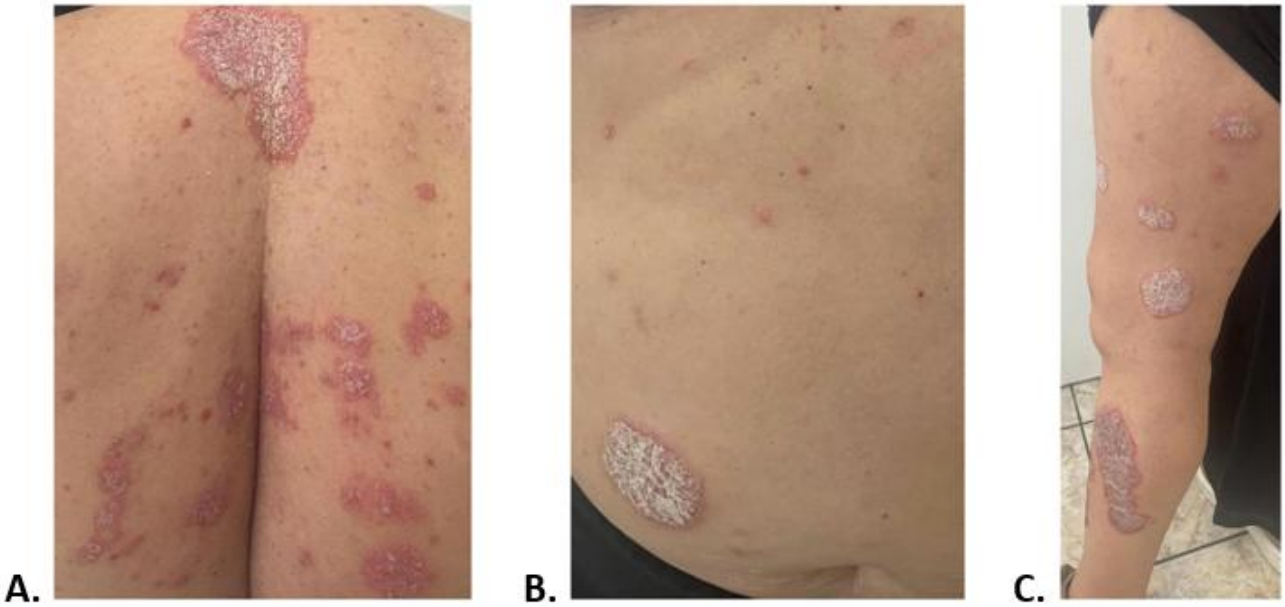
Interestingly, data from the literature indicate a wide variability in the frequency of isoniazid-induced hepatotoxicity. A meta-analysis that included over 22,000 patients treated for latent tuberculosis infection reported a frequency of approximately 2.6% for isoniazid-induced liver damage, with a very low mortality (0.02%) (29). However, real-world data suggest higher rates in certain subgroups of patients. A recent study reported hepatotoxicity in approximately 20% of patients treated with isoniazid, with a significant association with factors such as dyslipidemia, systemic inflammatory diseases including psoriasis, and male gender (27).

Because of these aspects, the correct interpretation of hepatotoxicity in patients receiving biologic therapy and antituberculosis prophylaxis is mandatory, as differentiating between isoniazid-induced toxicity and a potential adverse effect of biologic therapy is essential to avoid unnecessary interruption of effective treatment. Next, we present the challenges associated with concomitant use of biologic therapy and isoniazid in a patient with psoriasis and hepatotoxicity.

SEVERE PLAQUE PSORIASIS TREATED WITH IXEKIZUMAB, COMPLICATED BY ISONIAZID-INDUCED HEPATOTOXICITY

A 62-year-old woman with a 40-year history of plaque psoriasis was evaluated in April 2024 due to progressive worsening of cutaneous lesions. She had previously received multiple topical therapies and intermittent systemic courses (including methotrexate 15 mg/week), with partial responses and frequent relapses. In the months before presentation, plaques became thicker and more extensive on the trunk and limbs, accompanied by intense pruritus, sleep disturbance, and marked emotional distress (Figure 5). PASI score was 18.9, and DLQI score was 22, consistent with severe disease and major quality-of-life impact.

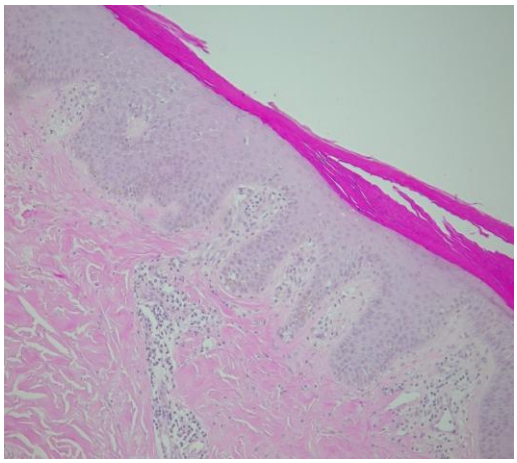
Figure 5: Psoriasis vulgaris – Clinical features.



A. Posterior thorax – multiple well-demarcated erythematous plaques with overlying silvery-white scales, some lesions showing confluence, B. – Abdomen – isolated, well-circumscribed erythematous plaque covered by adherent whitish scales, C. Lateral aspect of the lower limb -several erythematous, scaly plaques of variable size, partially confluent, with thick micaceous scaling.

Given severity, long disease duration and insufficient response to prior treatments, biologic therapy with ixekizumab was initiated per approved regimen: 160 mg loading dose, followed by 80 mg every 2 weeks up to week 12, then 80 mg every 4 weeks. Ixekizumab is a selective IL-17A inhibitor with demonstrated efficacy and safety in pivotal phase three randomized trials UNCOVER-2 and UNCOVER-3 (30). Pre-treatment screening was performed according to current recommendations (31). A skin biopsy was obtained, confirming the diagnosis (Figure 6). Routine blood tests were within normal range and viral hepatitis screening was negative. On the other hand, QuantiFERON-TB Gold was positive, without respiratory symptoms or imaging findings suggestive of active tuberculosis, which made it consistent with latent tuberculosis.

Figure 6: Psoriasis vulgaris – Histopathological features.
Regular acanthosis with elongation of rete ridges, hyperkeratosis with parakeratosis, and thinning of suprapapillary plates, dilated capillaries in dermal papillae and neutrophilic aggregates (Munro microabscesses). H&E stain x10.



In line with guidelines, isoniazid prophylaxis was initiated alongside biologic therapy, with regular hepatic monitoring (31). Dermatologic response was rapid - after three months, complete cutaneous response was achieved (PASI score 0; DLQI score 1). However, during routine monitoring, progressive transaminase elevation was observed:

- March 2024: AST 22 U/L; ALT 25 U/L
- July 2024: AST 138 U/L; ALT 153 U/L
- August 2024: AST 236 U/L; ALT 293 U/L

The patient remained asymptomatic (no jaundice, significant asthenia or abdominal pain). No other hepatotoxic medications were used and no additional toxic exposures were identified.

A key clinical dilemma emerged: isoniazid-induced hepatotoxicity versus a possible biologic therapy-related adverse event. Isoniazid has a well-documented hepatotoxic potential, with increased risk in older patients, while IL-17 inhibitors generally have a favorable hepatic profile (32). However, attribution can be challenging in patients taking multiple medicines. Based on the temporal pattern and progressive rise under isoniazid exposure, a diagnosis of probable isoniazid-induced hepatocellular injury was established. For safety, biologic therapy was temporarily withheld and the patient underwent a gastroenterological evaluation.

Transaminases gradually decreased after discontinuation of anti-tuberculous prophylaxis. On the other hand, in January 2025, a partial psoriasis relapse occurred (PASI score 6; DLQI score 8) during biologic therapy cessation. In March 2025, because the liver enzymes were almost normalized (AST 46 U/L; ALT 51 U/L), biologic therapy with ixekizumab was resumed without isoniazid, under strict monitoring. The subsequent course was very good, with a complete response that was achieved by May 2025 (PASI score 0; DLQI score 1) and maintained through November 2025 without recurrent cytolysis.

The fact that the liver enzymes increased under isoniazid, normalized after discontinuation and did not increase again after reintroduction of biologic therapy strongly supports that isoniazid was the causative agent, rather than IL-17 inhibition. This case highlights the importance of systematic tuberculous screening, awareness of isoniazid hepatotoxicity, careful causality assessment if hepatotoxicity appears, and controlled re-challenge to preserve an effective biologic therapy.

PSORIASIS AND LIVER CIRRHOSIS

Hepatic cirrhosis is a major cause of morbidity and mortality worldwide, frequently caused by hepatic steatosis, chronic alcohol consumption and viral infections (33). The disease progression is characterized by two distinct stages — compensated and decompensated cirrhosis, differentiated by the presence of complications such as ascites, hepatic encephalopathy, or gastrointestinal hemorrhage (33). Cirrhosis is the result of a complex process characterized by hepatocyte injury, stellate cell activation, and progressive fibrosis, in the context of persistent chronic inflammation (35). Metabolic imbalances, oxidative stress and immunological disorders contribute to disease progression and impaired liver function.

Chronic liver disease is frequently encountered in patients with psoriasis due to common systemic inflammatory mechanisms and metabolic dysfunction. Recent data suggest a causal relationship between certain autoimmune liver pathologies, such as primary biliary cirrhosis and psoriasis, supporting the role of immune disorders (34). However, the management of psoriasis in patients with cirrhosis is a major challenge, as many of the conventional systemic therapies are hepatotoxic or metabolized by the liver. Methotrexate, one of the most widely used systemic therapies in psoriasis, is contraindicated in the setting of advanced liver disease due to the risk of fibrosis and worsening liver dysfunction (34). In recent years, biological therapies have become an important therapeutic option, due to their targeted mechanism of action and more favorable safety profile compared to classic systemic therapies. Current data suggest that IL-17 inhibitors, IL-23 inhibitors, and IL-12/23 inhibitors are not associated with an increased risk of severe hepatotoxicity, making them a therapeutic option in patients with compensated cirrhosis, with careful selection and rigorous monitoring (35, 36).

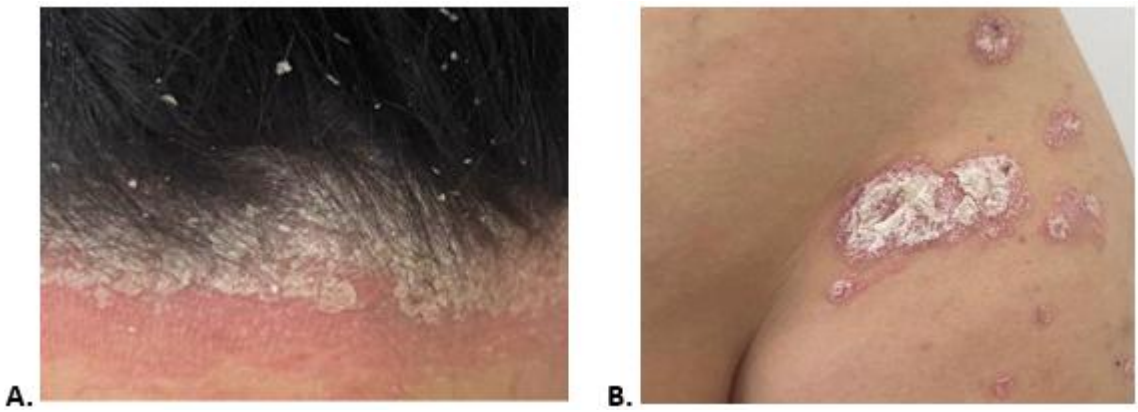
Therefore, the treatment of psoriasis in patients with liver cirrhosis requires a careful assessment of the risk-benefit ratio. In the absence of completely safe therapeutic options, biological therapies may represent an effective alternative in selected patients with compensated cirrhosis. Because of these aspects, a multidisciplinary approach and rigorous monitoring are essential to optimize therapeutic outcomes and prevent complications (36). It is worth mentioning that the evaluation of patients with cirrhosis requires a complex approach, including imaging methods and biological parameters. Abdominal ultrasound is an accessible and noninvasive method for the assessment of liver fibrosis and portal hypertension, and is frequently used in the monitoring of these patients (37).

Lastly, we present a case that highlights the challenges encountered in this type of patient.

Plaque psoriasis in a patient with compensated liver cirrhosis (Child–Pugh A)

A 46-year-old woman with plaque psoriasis diagnosed in 2018 presented in July 2025 due to progressive worsening of cutaneous lesions over recent months. Lesions initially reappeared on elbows and knees, and then extended to limbs and scalp, with prominent scaling (Figure 7). Quality-of-life impairment was severe: DLQI score was 24, while PASI score was 12.6, indicating moderate disease with substantial psychosocial burden.

Figure 7: Psoriasis vulgaris – Clinical features.



A. Scalp – well-demarcated erythematous plaques covered by thick silvery-white scales extending beyond the hairline, B. Extensor surface – erythematous, well-circumscribed plaque with adherent silvery scales, typical of extensor involvement.

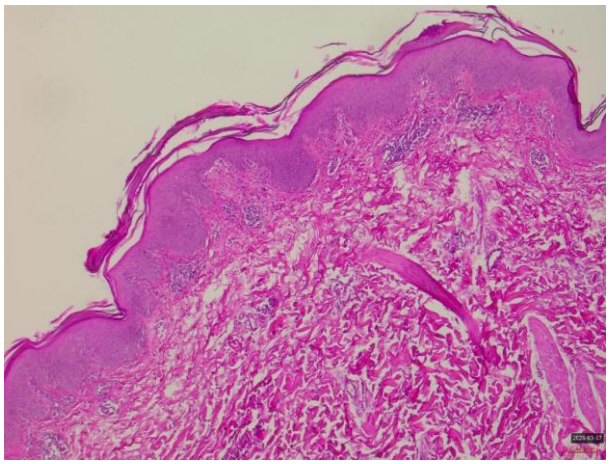
The complexity of this case was given by the hepatic comorbidity. The patient was previously diagnosed with compensated cirrhosis of unclear etiology (Child–Pugh score A, five points). Recent imaging and laboratory data showed advanced fibrosis, third-grade steatosis, and persistent cytolysis: ALT 159 U/L, AST 42 U/L, GGT 650 U/L. There were no clinical signs of decompensation (ascites, encephalopathy, or gastrointestinal bleeding).

Conventional systemic treatment options were severely limited. Methotrexate — commonly used in moderate-to-severe psoriasis — was considered contraindicated due to the risk of worsening liver injury and fibrosis progression (6). Other conventional systemic therapies also raised safety concerns. A careful risk–benefit assessment was performed. Even if psoriasis had a major impact on quality of life and also risk of progression, systemic intervention was needed to avoid further alteration of hepatic function.

The case was discussed with her gastroenterologist at the Carol Davila Central Military University Hospital, Bucharest. Factors supporting biologic therapy included: compensated cirrhosis, absence of severe portal hypertension/decompensation, regular liver monitoring capacity, and lack of safer alternatives. Therefore, biologic therapy with an IL-12/23 inhibitor (ustekinumab biosimilar)

was initiated, given a relatively favorable hepatic safety profile in available data and no direct known association with severe hepatotoxicity. Baseline evaluation included viral hepatitis tests, infectious screening, complete blood count, and full liver panel. A strict monitoring protocol for transaminases and liver function markers was implemented.

Figure 8: Psoriasis vulgaris – Histopathological features.
Marked acanthosis with regular elongation of rete ridges, hyperkeratosis with parakeratosis, dilated capillaries in dermal papillae and inflammatory infiltrate. H&E stain x10.



Under treatment, improvement was observed: by four weeks, pruritus decreased and erythema diminished. At three months, the PASI score decreased to 8.7, and the DLQI score decreased to 12. Although complete remission was not achieved, the response was clinically meaningful given the disease complexity. Importantly, liver parameters remained stable, with no signs of clinical or biological decompensation. The patient received detailed counseling on monitoring and hepatic warning signs, and dermatology – gastroenterology collaboration continued.

This case illustrates that, in compensated cirrhosis, biologic therapy may be a viable alternative to hepatotoxic conventional agents, provided careful patient selection and rigorous interdisciplinary monitoring.

DISCUSSION

The management of psoriasis in the context of severe systemic comorbidities represents a major challenge in current dermatological practice, especially due to the lack of robust evidence from randomized clinical trials. Patients with HIV infection, a history of cancer, latent tuberculosis infection, or advanced liver disease are frequently excluded from these trials, which limits the direct applicability of therapeutic guidelines (5,6). In this context, data from real-world practice and clinical experience become essential to guide therapeutic decisions. The cases analyzed illustrate the significant variability of clinical presentation and the challenges of choosing treatment according to each patient's profile.

In HIV-associated psoriasis, the literature suggests that the severity of the disease is not always directly correlated with the degree of immunosuppression, with complex mechanisms of immunological dysregulation being involved, especially at the level of the Th1/Th17 axis (8,16). In these situations, a stepwise therapeutic strategy is justified, starting with topical therapies and phototherapy, especially in localized forms (7). Clinical experience supports that avoiding systemic therapy when not absolutely necessary can reduce the risk of complications without compromising disease control.

In patients with a history of neoplasia, the main concern is the risk of tumor recurrence under immunomodulatory therapy. Although current data suggest only a modest increase in the overall oncological risk in psoriasis and do not clearly demonstrate a significant increase in recurrence under biological therapies, the level of evidence remains limited and heterogeneous (24,25). In this context, the time interval since oncological diagnosis, the type of tumor and the current status of the disease become critical factors in the choice of treatment. Close collaboration with the oncologist is essential to assess the individual risk and optimize the therapeutic strategy.

For latent tuberculosis infection, isoniazid prophylaxis is standard before initiating biologic therapy, but associated hepatotoxicity remains a relevant concern. Current guidelines recommend screening and appropriate treatment of latent tuberculosis infection before biologic therapy (31). Although the overall frequency of liver involvement is relatively low, it may become significant in certain

subgroups of patients, particularly in the elderly or in the context of comorbidities (32). Careful analysis of the chronology of biological changes and response after treatment discontinuation is essential to establish causality and to avoid unnecessary discontinuation of effective biologic therapy.

In the context of chronic liver disease, especially cirrhosis, therapeutic options are limited by the risk of hepatotoxicity of conventional systemic therapies, especially methotrexate (5,38). Literature data suggest that biologic therapies, particularly IL-12/23 inhibitors, may have a favorable safety profile in patients with compensated liver disease (39).

Therefore, interdisciplinary collaboration between dermatologists, infectious disease specialists, oncologists, and gastroenterologists is absolutely essential in the management of these patients. Monitoring of clinical and biological parameters allows for rapid adjustment of treatment and prevention of complications. In the absence of clear evidence from randomized trials, the integration of real-world data provides valuable insight into the management of psoriasis associated with severe systemic comorbidities.

The management of moderate-to-severe psoriasis in the presence of major systemic comorbidities represents a complex therapeutic challenge in which decisions cannot be guided solely by cutaneous severity. Well-controlled HIV infection, recent malignancy (40-42), latent tuberculosis prophylaxis requirements, or compensated cirrhosis (43-47) should not be considered absolute contraindications to systemic or biologic therapy, but rather risk modifiers requiring careful stratification and dynamic monitoring.

CONCLUSION

The present case series illustrates that therapeutic strategies, including topical, phototherapeutic, and, in selected situations, systemic or biologic therapies, can be safely used in high-risk contexts when patient selection is rigorous, interdisciplinary collaboration is active, and surveillance is tailored to the clinical scenario. Sequential assessment of adverse events and ongoing re-evaluation of the risk–benefit balance is essential to avoid both undertreatment and unnecessary risk exposure. Also, three core principles emerge: individualized decision-making - PASI and DLQI scores are essential, but insufficient without a global patient risk assessment; interdisciplinary collaboration - dermatology, oncology, infectious diseases, gastroenterology and rigorous and dynamic safety monitoring, particularly in the setting of polypharmacy and complex systemic risk.

Taking all of these aspects into consideration, and in the absence of robust randomized evidence for these special populations, real-world experience contributes significantly to a risk-adapted dermatology approach, emphasizing structured vigilance over therapeutic avoidance.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

This research received no external funding.

Authors' contribution

Conceptualization, AFG, DOC, and CC; methodology, ADG, and CC; validation, DOC, CC, and CS; formal analysis, ADG, and CS; investigation, ADG, and HB; resources, ADG, AE, and HB; data curation, DOC, CS, and CC; writing—original draft preparation, ADG, and HB; writing—review and editing, ADG, DOC, and CC; visualization, AE; supervision, CC; project administration, CS. All authors have read and agreed to the published version of the manuscript.

Patient consent for publication

Written informed consent has been obtained from the patients to publish this paper. The study was conducted in accordance with the World Medical Association Declaration of Helsinki (1964) and its later amendments (most recently revised in 2013). The study was approved by the Local Ethics Committee of the Dr. Carol Davila University Emergency Central Military Hospital, Bucharest (registration number 750, 22 January 2025).

References

1. Boehncke WH, Schön MP. Psoriasis. Lancet. 2015 Sep 5;386(9997):983-94. doi: 10.1016/S0140-6736(14)61909-7.

2. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. Lancet. 2021 Apr 3;397(10281):1301-1315. doi: 10.1016/S0140-6736(20)32549-6.

3. Takeshita J, Grewal S, Langan SM, Mehta NN, Ogdie A, Van Voorhees AS, Gelfand JM. Psoriasis and comorbid diseases: Epidemiology. J Am Acad Dermatol. 2017 Mar;76(3):377-390. doi: 10.1016/j.jaad.2016.07.064.

4. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA. 2020 May 19;323(19):1945-1960. doi: 10.1001/jama.2020.4006.

5. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgö Z, Boonen H, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 1: treatment and monitoring recommendations. J Eur Acad Dermatol Venereol. 2020 Nov;34(11):2461-2498. doi: 10.1111/jdv.16915.

6. Nast A, Smith C, Spuls PI, Avila Valle G, Bata-Csörgö Z, Boonen H, et al. EuroGuiDerm Guideline on the systemic treatment of Psoriasis vulgaris - Part 2: specific clinical and comorbid situations. J Eur Acad Dermatol Venereol. 2021 Feb;35(2):281-317. doi: 10.1111/jdv.16926.

7. Kaushik SB, Lebwohl MG. Psoriasis: Which therapy for which patient: Focus on special populations and chronic infections. J Am Acad Dermatol. 2019 Jan;80(1):43-53. doi: 10.1016/j.jaad.2018.06.056.

8. Morar N, Willis-Owen SA, Maurer T, Bunker CB. HIV-associated psoriasis: pathogenesis, clinical features, and management. Lancet Infect Dis. 2010 Jul;10(7):470-8. doi: 10.1016/S1473-3099(10)70101-8.

9. Ceccarelli M, Venanzi Rullo E, Vaccaro M, Facciolà A, d'Aleo F, Paolucci IA, et al. HIV-associated psoriasis: Epidemiology, pathogenesis, and management. Dermatol Ther. 2019 Mar;32(2):e12806. doi: 10.1111/dth.12806.

10. Li L, Jiang X, Fu L, Zhang L, Feng Y. Reactivation rates of hepatitis B or C or HIV in patients with psoriasis using biological therapies: a systematic review and meta-analysis. Clin Exp Med. 2023 Jul;23(3):701-715. doi: 10.1007/s10238-022-00827-y.

11. Shimon SV, Romanelli P. Systematic review of biologic use for psoriasis in HIV-positive individuals from 2018 to 2024. Arch Dermatol Res. 2024 Nov 13;317(1):14. doi: 10.1007/s00403-024-03395-1.

12. Jugovac V, Gulin M, Barić D, Ledić Drvar D, Čeović R. Treatment of plaque-psoriasis in HIV-positive patients. Acta Dermatovenerol Alp Pannonica Adriat. 2024 Mar;33(1):37-40.

13. Maione V, Rovaris S, Romanó C, Bighetti S, Arisi M, Carrera CG, et al. Exploring the Impact of Guselkumab and Risankizumab on Psoriasis in HIV-Positive Patients: Insights From Four Italian Centers. Australas J Dermatol. 2025 Jun;66(4):215-219. doi: 10.1111/ajd.14467.

14. Xu J, Gill K, Flora A, Kozera E, Frew JW. The impact of psoriasis biologic therapy on HIV viral load and CD4+ cell counts in HIV-positive individuals: A real-world cohort study. J Eur Acad Dermatol Venereol. 2023 Mar 10. doi: 10.1111/jdv.19020.

15. Ortegon Blanco AE, Alonzo Canul ME. Successful Biological Treatment of a Patient With Psoriasis and HIV. Cureus. 2024 Oct 20;16(10):e71970. doi: 10.7759/cureus.71970.

16. Menon K, Van Voorhees AS, Bebo BF Jr, Gladman DD, Hsu S, Kalb RE, et al; National Psoriasis Foundation. Psoriasis in patients with HIV infection: from the medical board of the National Psoriasis Foundation. J Am Acad Dermatol. 2010 Feb;62(2):291-9. doi: 10.1016/j.jaad.2009.03.047.

17. Claman HN. Corticosteroids as immunomodulators. Ann N Y Acad Sci. 1993 Jun 23;685:288-92. doi: 10.1111/j.1749-6632.1993.tb35877.x.

18. Sandoval AGW, Mahajan A, Buzney E. Phototherapy for Psoriasis in the Age of Biologics. Dermatol Clin. 2024 Jul;42(3):399-404. doi: 10.1016/j.det.2024.02.002.

19. Damiani G, Pacifico A, Chu S, Chi CC; Young Dermatologists Italian Network (YDIN). Frequency of phototherapy for treating psoriasis: a systematic review. Ital J Dermatol Venerol. 2022 Jun;157(3):215-219. doi: 10.23736/S2784-8671.21.06975-3.

20. Bruni M, Lobefaro F, Pellegrini C, Mastrangelo M, Gualdi G, Esposito M, et al. Psoriasis and cancer: the role of inflammation, immunosuppression, and cancer treatment. Expert Opin Biol Ther. 2025 Apr;25(4):395-411. doi: 10.1080/14712598.2025.2471093.

21. Potestio L, Tommasino N, Lauletta G, Salsano A, Lucagnano G, Menna L, Esposito G, Martora F, Megna M. The Impact of Psoriasis Treatments on the Risk of Skin Cancer: A Narrative Review. Adv Ther. 2024 Oct;41(10):3778-3791. doi: 10.1007/s12325-024-02968-w.

22. Tung TH, Jiesisibieke ZL, Cheng YH, Chi CC. Risk of breast cancer among patients with psoriasis: a systematic review and meta-analysis. Arch Dermatol Res. 2023 Dec 1;316(1):12. doi: 10.1007/s00403-023-02753-9.

23. Krzysztofik M, Brzewski P, Cuber P, Kacprzyk A, Kulbat A, Richter K, Wojewoda T, Wysocki WM. Risk of Melanoma and Non-Melanoma Skin Cancer in Patients with Psoriasis and Psoriatic Arthritis Treated with Targeted Therapies: A Systematic Review and Meta-Analysis. Pharmaceuticals (Basel). 2023 Dec 21;17(1):14. doi: 10.3390/ph17010014.

24. Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, Incidence, and Risk of Cancer in Patients With Psoriasis and Psoriatic Arthritis: A Systematic Review and Meta-analysis. JAMA Dermatol. 2020 Apr 1;156(4):421-429. doi: 10.1001/jamadermatol.2020.0024.

25. Pouplard C, Brenaut E, Horreau C, Barnetche T, Misery L, Richard MA, et al. Risk of cancer in psoriasis: a systematic review and meta-analysis of epidemiological studies. J Eur Acad Dermatol Venereol. 2013 Aug;27 Suppl 3:36-46. doi: 10.1111/jdv.12165.

26. Hanoodi M, Mittal M. Methotrexate. 2024 Dec 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan–.

27. Silva BS, Ferraz B, Faria N, Costa MI, Reis R. Isoniazid-induced hepatotoxicity in patients with latent tuberculosis - experience from a tuberculosis center. Indian J Tuberc. 2025 Apr;72(2):194-197. doi: 10.1016/j.ijtb.2023.12.010.

28. Badrinath M, Chen RJ, John S. Isoniazid Toxicity. 2024 Feb 28. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2026 Jan–.

29. Oscanoa TJ, Vidal X, Luque J, Julca DI, Romero-Ortuno R. Hepatotoxicity induced by isoniazid in patients with latent tuberculosis infection: a meta-analysis. Gastroenterol Hepatol Bed Bench. 2023;16(1):448-457. doi: 10.22037/ghfbb.v16i1.2685.

30. Gordon KB, Blauvelt A, Papp KA, Langley RG, Luger T, Ohtsuki M, et al; UNCOVER-1 Study Group; UNCOVER-2 Study Group; UNCOVER-3 Study Group. Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis. N Engl J Med. 2016 Jul 28;375(4):345-56. doi: 10.1056/NEJMoa1512711.

31. Sterling TR, Njie G, Zenner D, Cohn DL, Reves R, Ahmed A, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recomm Rep. 2020 Feb 14;69(1):1-11. doi: 10.15585/mmwr.rr6901a1.

32. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al; ATS (American Thoracic Society) Hepatotoxicity of Antituberculosis Therapy Subcommittee. An official ATS statement: hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med. 2006 Oct 15;174(8):935-52. doi: 10.1164/rccm.200510-1666ST.

33. Juanola A, Pose E, Ginès P. Liver Cirrhosis: ancient disease, new challenge. Med Clin (Barc). 2025 Mar 14;164(5):238-246. English, Spanish. doi: 10.1016/j.medcli.2024.11.002.

34. Zhao D, Zhao Q, Xu F, Zhang F, Bai W. Primary biliary cirrhosis and psoriasis: a two-sample Mendelian randomization study. Front Immunol. 2024 Jan 4;14:1264554. doi: 10.3389/fimmu.2023.1264554.

35. Wiacek M, Adam A, Studnicki R, Zubrzycki IZ. Exploring Cirrhosis: Insights into Advances in Therapeutic Strategies. International Journal of Molecular Sciences. 2025; 26(15):7226. https://doi.org/10.3390/ijms26157226.

36. Fallowfield JA, Jimenez-Ramos M, Robertson A. Emerging synthetic drugs for the treatment of liver cirrhosis. Expert Opin Emerg Drugs. 2021

Jun;26(2):149-163. doi: 10.1080/14728214.2021.1918099.

37. Han SK, Kim MY, Kang SH, Baik SK. Application of ultrasound for the diagnosis of cirrhosis/portal hypertension. J Med Ultrason (2001). 2022 Jul;49(3):321-331. doi: 10.1007/s10396-022-01191-w.

38. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol. 2009 Oct;51(4):758-64. doi: 10.1016/j.jhep.2009.04.020.

39. Loft ND, Vaengebjerg S, Halling AS, Skov L, Egeberg A. Adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis: a systematic review and meta-analysis of phase III studies. J Eur Acad Dermatol Venereol. 2020 Jun;34(6):1151-1160. doi: 10.1111/jdv.16073.

40. Costache DO, Feroiu O, Ghilencea A, Georgescu M, Căruntu A, Căruntu C, et al. Skin Inflammation Modulation via TNF-α, IL-17, and IL-12 Family Inhibitors Therapy and Cancer Control in Patients with Psoriasis. Int J Mol Sci. 2022 May 6;23(9):5198. doi: 10.3390/ijms23095198.

41. Costache DO, Bejan H, Poenaru M, Costache RS. Skin Cancer Correlations in Psoriatic Patients. Cancers (Basel). 2023 Apr 25;15(9):2451. doi: 10.3390/cancers15092451.

42. Bartos G, Cline A, Beroukhim K, Burrall BA, Feldman SR. Current biological therapies for use in HIV-positive patients with psoriasis: case report of gesulkumab used and review. Dermatol Online J. 2018 Nov 15;24(11):13030/qt3db748cg.

43. Bernardini N, Dattola A, Gemma GPA, Atzori L, Artosi F, Biondi G, et al. Psoriasis severity, comorbidity burden, and biologic therapy: a multicenter observational study using the Charlson Comorbidity Index. J Dermatolog Treat. 2025 Dec;36(1):2562311. doi: 10.1080/09546634.2025.2562311.

44. Mateu-Arrom L, Puig L. Choosing the right biologic treatment for moderate-to-severe plaque psoriasis: the impact of comorbidities. Expert Rev Clin Pharmacol. 2024 Apr;17(4):363-379. doi: 10.1080/17512433.2024.2340552.

45. Costache DO, Blejan H, Cojocaru DL, Ioniță GA, Poenaru M, Constantin MM, et al. Intersecting Pathways: Nonalcoholic Fatty Liver Disease and Psoriasis Duet- A Comprehensive Review. Int J Mol Sci. 2024 Feb 24;25(5):2660. doi: 10.3390/ijms25052660.

46. Jiang Y, Chen Y, Yu Q, Shi Y. Biologic and Small-Molecule Therapies for Moderate-to-Severe Psoriasis: Focus on Psoriasis Comorbidities. BioDrugs. 2023 Jan;37(1):35-55. doi: 10.1007/s40259-022-00569-z.

47. Staub FL, Santos AK, Lima de Braga RS, Scheffer de Souza M, Vigne Duz JV, Souza Ramos G, Catucci Boza J, Rossato Silva D. Latent tuberculosis infection in patients with psoriasis using biologic therapies. Monaldi Arch Chest Dis. 2025 Jun 26. doi: 10.4081/monaldi.2025.3538.

https://doi.org/10.55453/rjmm.2026.129.3.5

ARTICLE

Effects of combined SGLT2i and RAASi therapy in patients with chronic kidney disease

Ileana Adela Vacaroiu[1,2], Elisabeta Badila[3], Daniela Radulescu[1,2], Flavia-Liliana Turcu[1,2], Dan Arsenie Spinu[4,5*], Corina Sporea[6,7*], Daniela Miricescu[8], Andra-Elena Balcangiu-Stroescu[9], Ovidiu Cristian Chiriac[6,10], Larisa Florina Serban-Feier[1,2]

1 Department of Nephrology, Carol Davila University of Medicine and Pharmacy, 020021 Bucharest, Romania; ileana.vacaroiu@umfcd.ro (I.V.) daniela.radulescu@umfcd.ro (D.R.) ; flavia.turcu@umfcd.ro (F.T.); larisa-florina.feier@umfcd.ro (L.-F.F.)
2 Department of Nephrology, Sf. Ioan Clinical Emergency Hospital, 042122 Bucharest, Romania
3 Department of Cardiology, Colentina Hospital, Carol Davila University of Medicine and Pharmacy, 050474 Bucharest, Romania; elisabeta.badila@umfcd.ro (E.B.)
4 Department 3, Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, 8 Eroii Sanitari Blvd., 050474 Bucharest, Romania; arsenie.spinu@umfcd.ro (A.S.)
5 Urology Department, "Dr. Carol Davila" Central Military Emergency University Hospital, 134 Calea Plevnei, 010825 Bucharest, Romania
6 Discipline of Balneophysiokinetotherapy and Recovery, Faculty of Midwifery and Nursing, Carol Davila University of Medicine and Pharmacy, 050474 Bucharest, Romania; corina.sporea@gmail.com (C.S.); ovidiu-cristian.chiriac@drd.umfcd.ro (O.C.C.)
7 Scientific Research Core, National University Center for Children's Neurorehabilitation "Robănescu-Pădure", 44 Dumitru Minca Street, 041408 Bucharest, Romania
8 Discipline of Biochemistry, Faculty of Dentistry, Carol Davila University of Medicine and Pharmacy, 050474 Bucharest, Romania; daniela.miricescu@umfcd.ro (D.M.)
9 Discipline of Physiology, Faculty of Dentistry, Carol Davila University of Medicine and Pharmacy, 050474 Bucharest, Romania; andra.balcangiu@umfcd.ro (A.B.)
10 Department of Rehabilitation, Physical and Balneotherapy Medicine I, Central Military Emergency University Hospital "Dr. Carol Davila", 010825 Bucharest, Romania

*Correspondence: arsenie.spinu@umfcd.ro (A.S.); corina.sporea@gmail.com (C.S.)

Abstract: (1) Background: The aim of this retrospective observational study was to evaluate the effects of sodium–glucose cotransporter-2 inhibitors (SGLT2i) therapy in patients with chronic kidney disease (CKD) who had been receiving renin–angiotensin–aldosterone system (RAAS) inhibitor (RAASi) treatment for at least one year. (2) Methods: The medical records of 73 patients with CKD, staged according to the KDIGO 2012 guidelines, were reviewed at the start of combined therapy (RAASi and SGLT2i), marked as T0, and again after six months (T1). Biochemical parameters assessed at both time points included urinary albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), urinary albumin, urinary proteinuria, serum creatinine, and hemoglobin. (3) Results: A significant reduction in UACR ($p < 0.001$) and 24-hour urine albumin excretion ($p = 0.050$) was observed. Urine protein/24h ($p = 0.074$) and serum creatinine ($p = 0.391$) showed decreasing trends, while eGFR increased ($p = 0.154$), although these changes did not reach statistical significance. Regarding UACR category migration, 25% of patients improved, 74% remained stable, and only 1% worsened. (4) Conclusions: After six months of combined SGLT2i and RAASi therapy, most patients showed stable or improved renal status, suggesting a nephroprotective effect of dual therapy in CKD.

Keywords: chronic kidney disease; SGLT2 inhibitors; RAAS inhibitors; dual therapy; albuminuria

INTRODUCTION

Cardiovascular disease (CVD), chronic kidney disease (CKD), type 2 diabetes (T2D), and cancer are leading causes of morbidity and mortality worldwide [1-6]. CKD affects approximately 37 million people in the United States, with an estimated 726,000 individuals living with end-stage renal disease (ESRD). The annual incidence of ESRD exceeds 350 cases per million population. Although a slight decline in prevalence has been observed in recent years, CKD remains a major public health concern, particularly among older adults and individuals of African American and Hispanic descent [7-10]. While these conditions are often studied separately, they

Citation Vacaroiu IA, Badila E, Radulescu D, Turcu FL, Spinu DA, Sporea C, et al. *Effects of combined SGLT2i and RAASi therapy in patients with chronic kidney disease*. R. J. Mil. Med. 2026, CXXIX(3): 264-275 https://doi.org/10.55453/rjmm.2026.129.3.5

Academic Editor: Raluca Mititelu

Received: 1 March 2026
Revised: 12 April 2026
Accepted: 20 April 2026

frequently coexist due to shared risk factors such as hyperglycemia, hypertension, and obesity, as well as complex organ crosstalk and overlapping pathophysiological mechanisms [11-14]. A key factor driving disease progression in this context is dysregulation of the renin–angiotensin–aldosterone system (RAAS), which leads to hemodynamic alterations, sodium retention, and systemic inflammation [12,15]. RAAS inhibitors (RAASi), including angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), and direct renin inhibitors, have become essential in the management of hypertension, CKD, and heart failure, particularly in patients with albuminuria [16-21] .

More recently, sodium–glucose cotransporter 2 inhibitors (SGLT2i) have gained recognition for their cardio-renal protective effects, initially demonstrated in patients with diabetes. Beyond glycemic control, these agents reduce intraglomerular pressure, proteinuria, and systemic blood pressure, providing significant benefits for patients both with and without diabetes [5,12,19,22,23]. By blocking glucose reabsorption in the proximal tubule, SGLT2i increase urinary glucose excretion through a mechanism that is independent of insulin secretion [19]. An emerging therapeutic strategy involves combining RAASi with SGLT2i in order to exploit their complementary mechanisms of action [24,25]. Preclinical and clinical studies suggest potential synergistic effects between these two drug classes. For example, SGLT2i have been shown to modulate RAAS activity [26] and to enhance antifibrotic effects when used alongside RAASi, as reflected by decreased endotrophin levels [27]. Additionally, SGLT2i may initially activate but subsequently attenuate tubular RAAS pathways and sympathetic nervous system activity [28-30]. Real-world evidence further supports the usefulness of this therapeutic combination. In the Indian SGRASS-DKD study, combination therapy improved blood pressure control and was well tolerated, despite mild electrolyte changes [31]. Vart al. also demonstrated prolonged renal survival and lower mortality in non-diabetic CKD patients with proteinuria treated with both agents, even in the setting of suboptimal treatment adherence [32].

The aim of our retrospective study was to evaluate the clinical and biochemical effects of combined therapy with RAASi and SGLT2i in a cohort of patients with CKD.

MATERIALS AND METHODS

Study Design and Setting

This retrospective observational study was conducted at a single nephrology center between August 2025 and February 2026. The medical records of 73 patients diagnosed with CKD according to the KDIGO 2012 guidelines were retrospectively reviewed. Of these, 54.79% had T2D and 68% had hypertension.

Study Population and Inclusion Criteria

Participants met the following inclusion criteria: an estimated glomerular filtration rate (eGFR) between 25 and 60 mL/min/1.73 m^2 with any stage of albuminuria—A1 (≤30 mg/g), A2 (30–299 mg/g), or A3 (≥300 mg/g), based on the urinary albumin-to-creatinine ratio (UACR)—or an eGFR greater than 60 mL/min/1.73 m^2 with UACR >30 mg/g (A2 or A3).

All patients had been receiving treatment with RAASi, including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), at the maximum tolerated dose for at least one year prior to study inclusion.

Patients were excluded if key clinical or biochemical data were missing or if they experienced major therapeutic changes unrelated to the study treatments (SGLT2i or RAASi).

Treatment Protocol and Study Timeline

Baseline evaluation (T0) was performed at the start of combined therapy with RAASi and SGLT2i (dapagliflozin-DAPA). Follow-up evaluation (T1) was conducted six months after initiating dual therapy [33].

Data Collection and Measurements

Biochemical samples were collected at both time points (T0 and T1). The following parameters were assessed: urinary albumin-to-creatinine ratio (UACR, mg/g) obtained from a spontaneous urine sample, preferably first morning urine; estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI 2021 equation; urinary albumin and urinary protein from 24-hour urine (standardized collection protocol) in a subset of the 73 enrolled patients; serum creatinine (mg/dL); and hemoglobin (g/dL).

Ethical Considerations

The study protocol was approved by the hospital Ethics Committee of Sf. Ioan Clinical Emergency Hospital, Bucharest, Romania (Approval No. 2023/14.02.2025). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

RESULTS

Normality testing indicated a non-parametric distribution for most variables. Therefore, continuous data are reported as median (Q1–Q3). Hemoglobin values at T0 and T1 were normally distributed and are presented as mean ± standard deviation, while the paired differences were analyzed using non-parametric tests.

Descriptive statistics for the study parameters at baseline (T0) and follow-up (T1) are presented in Table 1. Sample size varied across parameters due to missing data (albuminuria: n = 11; proteinuria: n = 10; UACR, eGFR, and creatinine: n = 73; hemoglobin: n = 70).

Table 1: Descriptive statistics of study parameters at baseline (T0) and follow-up (T1).

Parameter	T0	T1	Δ(T0-T1)
Age (years)	70.0 (62.50–75.00)	—	—
eGFR (mL/min/1.73 m²)	45.81 (36.23–57.51)	46.09 (36.72–57.04)	2.15 (−3.18–6.20)
Creatinine (mg/dL)	1.41 (1.14–1.79)	1.35 (1.10–1.90)	−0.03 (−0.17–0.10)
Albuminuria (mg/24h)	523.30 (314.00–1015.00)	260.80 (120.00–1224.00)	−206.00 (−527.40– −40.00)
Proteinuria (mg/24h)	602.35 (384.98–1274.70)	329.75 (179.75–1863.15)	−241.95 (−360.10– −56.85)
UACR (mg/g)	119.45 (17.92–590.09)	56.00 (8.95–244.45)	−43.00 (−152.00– −3.33)
Hemoglobin (g/dL)	12.76±1.70	13.19±1.78	0.20 (−0.50–1.03)

Sample size varied across parameters due to missing data (Albuminuria: n = 11; Proteinuria: n = 10; UACR / eGFR / Creatinine: n = 73; Hemoglobin: n = 70).

Changes in Biochemical Parameters

Changes in renal parameters between baseline (T0) and follow-up (T1) were assessed using the Wilcoxon signed-rank test (Table 2).

Table 2: Changes in renal parameters between baseline (T0) and follow-up (T1) were assessed using the Wilcoxon signed-rank test. (NS=non-significant)

Parameter	Z	p value	Interpretation
eGFR	−1.427	0.154	NS
Creatinine	−0.857	0.391	NS
Albuminuria	−1.956	0.050	Borderline ↓
Proteinuria	−1.784	0.074	NS trend ↓
UACR	−5.981	<0.001	Significant ↓

A statistically significant reduction was observed in UACR values between baseline and follow-up ($Z = -5.981$, $p < 0.001$).

Albuminuria showed a borderline significant decrease (Z = −1.956, p = 0.050), while proteinuria demonstrated a non-significant downward trend (p = 0.074).

No statistically significant changes were observed in eGFR (p = 0.154) or serum creatinine levels (p = 0.391).

KDIGO Risk Category Migration

Migration of patients across KDIGO risk categories between baseline and follow-up is presented in Table 3 and Figure 1.

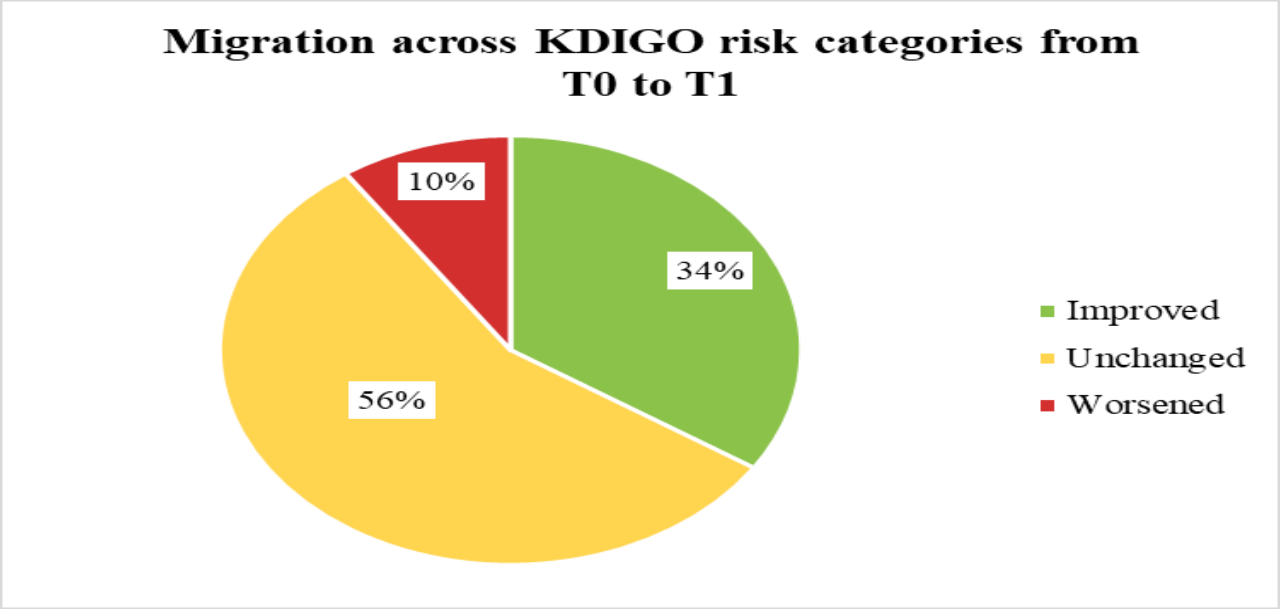
Table 3: Migration of patients between KDIGO risk categories from baseline (T0) to follow-up (T1).

		CKD_Stage_T1			
		Low	**Moderate**	**High**	**Very high**
CKD_Stage_T0	**Low**	0	0	0	0
	Moderate	3	9	4	0
	High	3	8	9	3
	Very high	0	3	8	23

Improvement in KDIGO risk category was primarily driven by reductions in albuminuria rather than changes in eGFR.

Risk category migration analysis showed that 34% of patients improved their KDIGO risk class, 56% remained unchanged, and 10% experienced worsening between T0 and T1. In Table 3, cell background colors illustrate risk category migration, with green indicating improvement, orange indicating worsening, and yellow indicating no change.

Figure 1: Changes in KDIGO risk categories from baseline (T0) to follow-up (T1). Most patients remained stable, with approximately one-third improving their risk category and a smaller proportion experiencing worsening.



UACR Category Changes

Migration across UACR categories is shown in Table 4 and Figure 2.

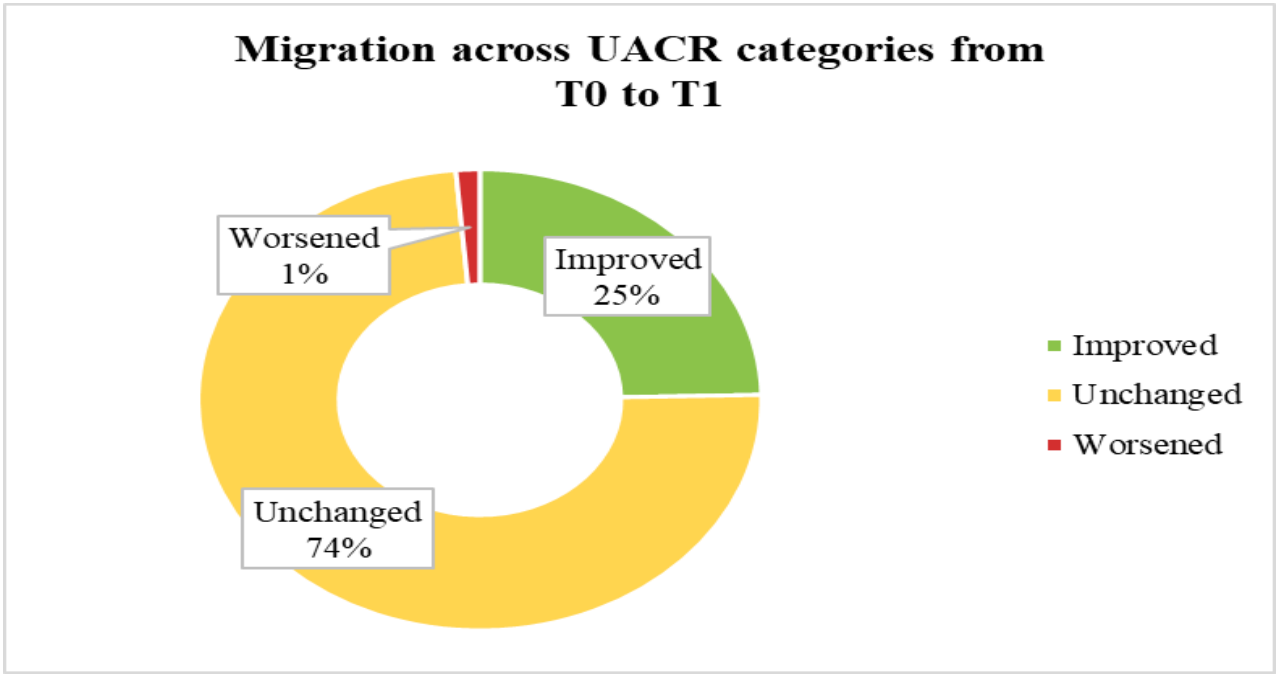
Table 4: Migration of UACR categories between baseline (T0) and follow-up (T1).

		UACR T1			
		A1	**A2**	**A3**	**Total**
UACR T0	**A1**	21	0	0	21
	A2	11	17	1	29
	A3	0	7	16	23
	Total	32	24	17	73

Reduction of UACR category was observed in approximately one-quarter of patients, with minimal progression. Improvement occurred predominantly among patients with moderate to severe baseline albuminuria. Notably, no patient in the A1 category progressed to a higher albuminuria stage.

Overall, 25% of patients improved their UACR category, 74.0% remained stable, and only 1.% experienced worsening between T0 and T1.

Figure 2: Changes in UACR categories from baseline (T0) to follow-up (T1).



Association between KDIGO Risk and UACR Changes

The relationship between KDIGO risk migration and changes in UACR is presented in Table 5.

Table 5: Association between KDIGO risk category migration and changes in UACR between baseline (T0) and follow-up (T1).

ΔRisk \ ΔUACR	**UACR worsened**	**UACR unchanged**	**UACR improved**	**Total**
Risk worsened	0	7	0	7
Risk same	1	36	4	41
Risk improved	0	10	9	19
Risk improved ≥2	0	1	5	6
Total	1	54	18	73

Cross-tabulation analysis showed that more than half of patients who improved their KDIGO risk category also exhibited a reduction in UACR. In contrast, risk worsening was not associated with progression of albuminuria, suggesting that other factors contributed to deterioration in risk classification.

Among patients who experienced KDIGO risk migration (n = 32), changes in albuminuria category contributed to 43.8% of transitions, whereas 56.2% occurred without UACR modification, suggesting that risk reclassification was predominantly driven by changes in eGFR (Table 6).

Table 6: Contribution of UACR category changes to KDIGO risk migration.

Indicator	N	%
KDIGO migration total	32	100%
+ UACR migration	14	43.8%
Without UACR change	18	56.2%

Association between KDIGO Risk and eGFR Changes

The association between KDIGO risk migration and changes in eGFR categories is presented in Table 7.

Table 7: Association between KDIGO risk migration and changes in eGFR category.

ΔCKD_Risk (T0-T1) * ΔeGFR_cat (T0-T1) Crosstabulation

		ΔeGFR_cat (T0-T1)					
		-2.00	-1.00	.00	1.00	2.00	Total
ΔCKD_Risk (T0-T1)	-1	0	7	0	0	0	7
	0	2	6	30	3	0	41
	1	0	1	9	9	0	19
	2	0	0	0	5	1	6
Total		2	14	39	17	1	73

Cross-tabulation analysis demonstrated that KDIGO risk migration was predominantly associated with changes in eGFR stage. Among patients who experienced risk category changes, 72% also showed a shift in eGFR stage, highlighting glomerular filtration dynamics as a major determinant of global risk classification.

Changes in eGFR stage represented the primary driver of KDIGO risk migration, while changes in albuminuria category contributed to a lesser extent (Table 8).

Table 8: Drivers of KDIGO global risk reclassification.

Driver	Contribution to risk migration
eGFR change	72%
UACR change	56%

eGFR Category Transitions

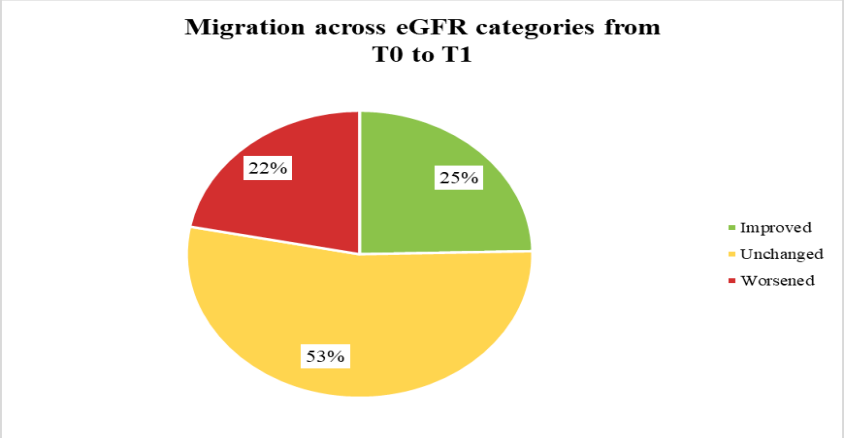
Transitions across eGFR stages between baseline and follow-up are presented in Table 9 and Figure 3.

Table 9: Transitions across eGFR stages between baseline (T0) and follow-up (T1).

		eGFR_cat_T1						Total
		G1	G2	G3a	G3b	G4	G5	
eGFR_cat_T0	G1	3	1	0	0	0	0	4
	G2	1	6	2	0	0	0	9
	G3a	0	5	12	7	2	0	26
	G3b	0	0	9	11	3	0	23
	G4	0	0	1	2	7	1	11
Total		4	12	24	20	12	1	73

Analysis of eGFR stage transitions showed heterogeneous changes across categories. Most patients remained within the same stage, while a smaller proportion improved or worsened their eGFR staging over time.

Figure 3: Changes in eGFR categories from baseline (T0) to follow-up (T1).



Overall, 53% of patients remained in the same eGFR stage, 25% showed improvement in their eGFR category, and 22% experienced worsening between T0 and T1.

Integrated Analysis of Renal Risk Indicators

Comparative migration across KDIGO risk, albuminuria (UACR), and eGFR categories is summarized in Table 10.

Table 10: Comparative migration across KDIGO risk, albuminuria (UACR), and eGFR categories between baseline (T0) and follow-up

Indicator	Improved	Stable	Worsened
KDIGO risk	34%	56%	10%
Albuminuria	25%	74%	1%
eGFR	25%	53%	22%

Proportion of patients demonstrating improvement, stability, or worsening across three renal risk indicators (KDIGO risk category, UACR category, and eGFR stage) between baseline (T0) and follow-up (T1). Overall, according to KDIGO, risk showed the highest proportion of improvement, while albuminuria remained largely stable, and eGFR demonstrated the greatest bidirectional variability.

Overall, the analysis of renal parameters and category migration patterns indicates that combined SGLT2i and RAASi therapy was associated with a predominantly stable or favorable renal trajectory over the six-month follow-up period

Improvements were most evident in albuminuria-related parameters, with a significant reduction in UACR and a borderline decrease in 24-hour urinary albumin levels in a subset of patients. Migration analysis also demonstrated that one-third of patients improved their KDIGO risk category, while the majority remained stable. Changes in overall KDIGO risk classification were mainly driven by changes in eGFR stage (eGFR), although reductions in albuminuria/24 h also contributed to risk reclassification in a subset of patients. Taken together, these findings suggest that dual therapy may contribute to the stabilization of renal function and partial regression of renal risk markers in patients with CKD.

DISCUSSION

Inhibitor and RAAS inhibitor therapy in patients with CKD over a six-month follow-up. Overall, the results indicate a mostly positive renal profile, marked by a significant reduction in UACR and a borderline decrease in albuminuria in some patients. Renal filtration markers remained largely unchanged, with no significant differences in eGFR or serum creatinine. Migration analyses further revealed that one-third of patients improved their KDIGO global risk category, while the majority stayed the same. Changes in risk classification were mainly due to shifts in eGFR stage, although reductions in albuminuria also played a role in risk improvement for some patients.

Clinical studies have shown that inhibitors of the RAAS decrease proteinuria, reduce renal fibrosis, and slow the decline of kidney function, thereby protecting the kidneys in both early and advanced stages of CKD [15]. SGLT2i were first approved by the U.S. Food and Drug Administration (FDA) for treating T2D. SGLT2 is mainly expressed in the kidneys, especially on the apical membrane of the S1 and S2 segments of the proximal tubule. By blocking sodium and glucose reabsorption in this area, SGLT2i cause glycosuria and natriuresis, leading to improved blood sugar control and mild to moderate weight loss in patients with T2D [34].

The renoprotective effects of SGLT2i are achieved through multiple mechanisms. First, they indirectly protect renal function by reducing glucose reabsorption, which helps improve metabolic control and promotes weight loss. Second, they directly influence renal hemodynamics by lowering intraglomerular pressure, decreasing diabetes-related hyperfiltration and tubular hypertrophy. These drugs have also been shown to decrease albuminuria and serum uric acid levels without causing significant potassium imbalances. Moreover, mild natriuresis lowers blood pressure, especially systolic pressure, through mechanisms such as afferent arteriolar vasoconstriction, osmotic diuresis, and weight loss. Importantly, the diuretic effect can increase hematocrit and erythropoietin levels by improving tubulointerstitial hypoxia and allowing renal fibroblasts to resume normal erythropoietin production, which contributes to renal protection [29].

Clinical trial evidence has demonstrated that SGLT2i significantly reduce albuminuria in patients with CKD. For example, Oshima et al. reported that treatment with the SGLT2i Canagliflozin reduced UACR by 31% at week 26 and significantly increased the likelihood of

achieving a ≥30% reduction in UACR. In patients with T2D and CKD, canagliflozin therapy was associated with early and sustained reductions in albuminuria, which were independently linked to improved long-term renal and cardiovascular outcomes [35].

Similarly, Nakhleh et al. evaluated 354 participants with CKD without diabetes who received SGLT2i and were followed for a median of 527 days. Their results demonstrated a significant increase in eGFR following SGLT2i therapy ($p < 0.001$), suggesting that these agents may exert renoprotective effects even in non-diabetic populations [36].

Our findings align with these observations. In this study, UACR showed a statistically significant decrease ($p < 0.001$), while urinary albumin excretion (independent of UACR) experienced a marginal reduction ($p = 0.050$) after six months of combination therapy. Urinary protein levels (measured in a subset of patients) and serum creatinine also displayed decreasing trends, although these changes did not reach statistical significance. Additionally, eGFR showed a modest increase over the follow-up period, though it was not statistically significant (Tables 1 and 2).

Zhou et al. further demonstrated that SGLT2i can sustainably reduce UACR at multiple time points and delay progression to macroalbuminuria. Moreover, within the first 24 weeks of treatment, SGLT2i therapy may increase eGFR compared with control groups and reduce the risk of incident or worsening nephropathy, including a ≥50% decline in eGFR, doubling of serum creatinine, acute renal failure, and end-stage renal disease. Importantly, these renoprotective effects appear to be largely independent of glycemic control [29].

According to the KDIGO classification, after six months of dual therapy, 34% of patients improved their renal risk category, 56% remained stable, and only 10% experienced worsening, suggesting an overall favorable treatment effect (Table 3 and Figure 1). This improvement appeared to be largely driven by reductions in UACR, rather than by substantial changes in glomerular filtration rate.

The low rate of UACR progression, together with the proportion of patients showing improvement, indicates a beneficial nephroprotective effect of therapy even in the absence of major changes in overall KDIGO risk categories. Analysis of albuminuria stages (A1–A3) between T0 and T1 showed improvement in 25% of patients, stability in 74%, and worsening in only 1% (Table 4 and Figure 2).

Reduction in albuminuria is known to be associated with a lower risk of CKD progression, supporting its role as a key marker of renal injury. In several patients, UACR decreased without a formal shift in KDIGO risk category, highlighting the limitations of categorical thresholds in detecting early therapeutic benefits. Conversely, the absence of albuminuria progression in patients with worsening KDIGO risk suggests that deterioration in risk classification was mainly driven by reductions in eGFR (Table 5).

Further analysis indicated that composite KDIGO risk migration reflected multidimensional changes in renal parameters. Albuminuria (UACR) demonstrated greater stability and a very low rate of deterioration, whereas eGFR stages showed greater bidirectional variability, suggesting that glomerular filtration may be more sensitive to short-term clinical or therapeutic fluctuations. These findings indicate that UACR reduction may represent an earlier and more consistent marker of treatment response than changes in filtration parameters (Tables 6 and 10).

Regarding the relationship between KDIGO risk migration and eGFR category changes, cross-tabulation analysis showed that most patients remained in the same risk category, while a smaller proportion experienced improvement or worsening in eGFR stage (Table 7). Overall, changes in eGFR stage represented the primary driver of KDIGO risk shifts, accounting for approximately 72% of transitions, while reductions in albuminuria contributed to 56% of improvements (Table 8).

Migration analysis revealed heterogeneous patterns across the evaluated renal risk indicators. Overall, KDIGO risk improved in 34% of patients, remained stable in 56%, and worsened in 10%. Albuminuria categories were largely stable, with 74% of patients showing no change, 25% demonstrating improvement, and only 1% experiencing worsening (Table 10).

When assessing renal function based on eGFR, which was available for all patients included in the study, a higher proportion of worsening was observed compared with UACR and overall KDIGO risk categories (Table 10). For instance, among the 26 patients initially classified in stage G3a, seven progressed to stage G3b and two to stage G4. Similarly, among the 23 patients in stage G3b, three advanced to stage G4 (Table 9). Consequently, eGFR stages demonstrated the greatest variability, with 25% of patients improving, 22% worsening, and 53% remaining unchanged (Table 10).

The combination of RAASi with SGLT2i may exert synergistic renoprotective effects by enhancing antifibrotic and antiproteinuric mechanisms through complementary pharmacological pathways (Ksiazek SH). Results from randomized controlled trials suggest that treatment combining angiotensin-converting enzyme inhibitors or angiotensin receptor blockers with SGLT2i in patients with albuminuria CKD, even in the absence of diabetes, may significantly improve kidney failure–free survival [32].

A two-year longitudinal retrospective study by Ngai et al. compared the effects of angiotensin receptor blocker (ARB) monotherapy with those of SGLT2i therapy combined with angiotensin-converting enzyme inhibitors (ACEi) in patients with CKD and diabetes mellitus. The ARB group showed a modest increase in eGFR and a reduction in serum creatinine levels compared with the dual therapy group, while glycated hemoglobin (HbA1c), potassium levels, and blood pressure remained within normal ranges in both groups.

Albuminuria remained relatively stable over time, with 60.8% of ARB users and 73.1% of those receiving combined therapy consistently or usually testing negative. Despite the expected additional benefits of SGLT2i/ACEi therapy, ARB monotherapy was associated with slightly better renal function markers and a lower prevalence of severe albuminuria in this cohort [37].

Jongs et al. investigated adult patients with CKD, eGFR between 25 and 75 mL/min/1.73 m² and UACR between 200 and 5000 mg/g, with or without T2D, to evaluate the effects of the SGLT2i Dapagliflozin. Their results demonstrated a significant reduction in albuminuria among patients treated with SGLT2i, including those with preserved or mildly reduced renal function [38].

Another important aspect of SGLT2 inhibitory therapy is its modest impact on lipid metabolism, characterized by reductions in plasma triglyceride levels and increases in the HDL concentration [26,39,40]. SGLT2i may enhance fatty acid oxidation and ketogenesis, which can help reduce oxidative stress and offer additional kidney protection compared to other glucose-lowering treatments [41]. Yen et al. conducted a study comparing the risks of dialysis, cardiovascular events, and mortality between SGLT2i users and non-users among patients with T2D and stage 5 CKD. The authors reported that SGLT2i use was linked to lower risks of dialysis initiation, hospitalization for heart failure, acute myocardial infarction, diabetic ketoacidosis, and acute kidney injury, although no significant differences were observed in all-cause mortality [42]. Therefore, SGLT2i also affect several local and systemic pathways involved in the progression of CKD and cardiovascular disease, further supporting their kidney-protective effects [43].

Furthermore, systematic reviews and meta-analyses including multiple randomized trials in patients with heart failure, CKD, and T2D have demonstrated that SGLT2i slow the decline of eGFR over time and reduce the risk of sustained doubling of serum creatinine, confirming their beneficial impact on renal outcomes across diverse patient populations [44].

Anemia represents one of the most common complications of CKD and results from multiple mechanisms, including erythropoietin deficiency, iron dysregulation, chronic inflammation, bone marrow dysfunction, and nutritional deficiencies [45]. Previous studies have shown that increases in hemoglobin levels, particularly during SGLT2i therapy, are associated with improved outcomes in patients with heart failure and CKD [46]. In our cohort, mean hemoglobin levels increased from 12.76 g/dL at baseline to 13.19 g/dL after six months of dual therapy, although this change did not reach statistical significance (Table 1).

Study Limitations

Several limitations of this study should be acknowledged. First, the retrospective observational design may introduce selection bias and limit the ability to establish causal relationships between therapy and outcomes. Second, the study was conducted at a single center with a relatively small sample size, which may restrict the generalizability of the findings to broader CKD populations. In addition, some biochemical parameters, particularly albuminuria and proteinuria measurements, were available only for a subset of patients due to incomplete data collection. The relatively short follow-up period of six months may also limit the ability to fully evaluate long-term renal outcomes and disease progression. Finally, the absence of a control group receiving monotherapy prevents a direct comparison of treatment effects between dual therapy and standard RAAS inhibition alone. Despite these limitations, the study provides valuable real-world insights into the renal effects of combined SGLT2i and RAASi therapy in patients with CKD.

CONCLUSION

CKD remains a significant global health issue. In this study, patients with CKD who received combined RAASi and SGLT2i therapy for 6 months showed a notable decrease in UACR and urinary albumin excretion over 24h (measured in a subset of patients). Renal filtration markers remained mostly stable, with slight increases in eGFR and hemoglobin levels, and minor decreases in serum creatinine and proteinuria, although these changes did not reach statistical significance. Migration analysis revealed that only a small percentage of patients experienced worsening according to KDIGO risk (10%) or albuminuria category (1%), while a larger proportion stayed stable or improved. Overall, these results suggest that dual therapy with RAASi and SGLT2i may help stabilize renal function and reduce albuminuria-related risk markers in patients with CKD. Further prospective studies with larger groups and longer follow-up are needed to confirm these findings.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. This research received no external funding.

Authors' contribution

Conceptualization, I.V.; D.M.; C.S.; E.B.; and A.S.; methodology, I.V., D.R.; C.S.; F.T. and L.-F.F.; validation, I.V.; D.R.; F.T.; L.-F.T.; A.S.; C.S.; D.M.; A.B. and O.C.C.; formal analysis, A.S.; C.S.; D.M. and I.V.; investigation, I.V.; F.T.; L.-F.F.; A.S.; O.C.C.; and A.S.; resources, I.V.; A.B.; O.C.C.; and D.R.; data curation, I.V.; E.B.; and C.S.; writing—original draft preparation, I.V.; C.S. and A.S.; writing—review and editing, I.V.; D.M.; C.S.; D.R.; E.B.; A.B.; and A.S.; visualization, I.V.; E.B.; D.R.; F.T.; L.-F.T.; A.S.; C.S.; D.M.; A.B. and O.C.C.; supervision, E.B.; I.V.; C.S. and A.S.; project administration, I.V.; D.M.; and C.S

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the hospital Ethics Committee of Sf. Ioan Clinical Emergency Hospital, Bucharest, Romania (Approval No. 2023/14.02.2025).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Acknowledgments

No generative AI was used in the production of this article.

References

1. Swamy, S.; Noor, S.M.; Mathew, R.O. Cardiovascular disease in diabetes and chronic kidney disease. Journal of clinical medicine 2023, 12, 6984.

2. Mititelu, R.; Mitoi, A.; Mazilu, C.; Jinga, M.; Radu, F.I.; Bucurica, A.; Mititelu, T.; Bucurica, S. Advancements in hepatocellular carcinoma management: the role of 18F-FDG PET-CT in diagnosing portal vein tumor thrombosis. Nuclear Medicine Communications 2024, 45, 651-657.

3. Soerjomataram, I.; Bray, F. Planning for tomorrow: global cancer incidence and the role of prevention 2020–2070. Nature reviews Clinical oncology 2021, 18, 663-672.

4. Bizuayehu, H.M.; Ahmed, K.Y.; Kibret, G.D.; Dadi, A.F.; Belachew, S.A.; Bagade, T.; Tegegne, T.K.; Venchiarutti, R.L.; Kibret, K.T.; Hailegebireal, A.H. Global disparities of cancer and its projected burden in 2050. JAMA network open 2024, 7, e2443198.

5. Florescu, A.; Pucerea, S.; Floria, M.; Rusu, E.; Cuiban, E.; Jinga, M.; Dragoi Galrinho, R.; Stanciu, S. Targeting Heart Disease in Cardiovascular–Kidney–Metabolic Syndrome: A Review of Novel Therapeutic Approaches with Prognostic and Quality-of-Life Impact. Romanian Journal of 2025, 128, 554-565.

6. Gorecki, G.; Pleș, L.; Sima, R.; Coman, I.; Grigorean, V.; Novac, M.; Pantiș, C.; Costache, D.; Tomescu, D. New Insights in Microcirculation Research in Sepsis. Romanian Journal of 2025, 128, 409-428.

7. Ahmad, F.B.; Anderson, R.N. The leading causes of death in the US for 2020. Jama 2021, 325, 1829-1830.

8. Gansevoort, R.T.; Correa-Rotter, R.; Hemmelgarn, B.R.; Jafar, T.H.; Heerspink, H.J.L.; Mann, J.F.; Matsushita, K.; Wen, C.P. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. The Lancet 2013, 382, 339-352.

9. Kovesdy, C.P. Epidemiology of chronic kidney disease: an update 2022. Kidney international supplements 2022, 12, 7-11.

10. Collins, A.J.; Foley, R.N.; Chavers, B.; Gilbertson, D.; Herzog, C.; Johansen, K.; Kasiske, B.; Kutner, N.; Liu, J.; St Peter, W. US Renal Data System 2011 Annual Data Report. AMERICAN JOURNAL OF KIDNEY DISEASES 2012, 59, EVII-E418.

11. Zhong, W.; Wu, K.; Long, Z.; Zhou, X.; Zhong, C.; Wang, S.; Lai, H.; Guo, Y.; Lv, D.; Lu, J. Gut dysbiosis promotes prostate cancer progression and docetaxel resistance via activating NF-κB-IL6-STAT3 axis. Microbiome 2022, 10, 94.

12. Sarafidis, P.; Ferro, C.J.; Morales, E.; Ortiz, A.; Malyszko, J.; Hojs, R.; Khazim, K.; Ekart, R.; Valdivielso, J.; Fouque, D. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. Nephrology Dialysis Transplantation 2020, 35, 1825-1825.

13. Przezak, A.; Bielka, W.; Pawlik, A. Hypertension and type 2 diabetes—the novel treatment possibilities. International journal of molecular sciences 2022, 23, 6500.

14. Petrie, J.R.; Guzik, T.J.; Touyz, R.M. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Canadian Journal of Cardiology 2018, 34, 575-584.

15. Zhang, F.; Liu, H.; Liu, D.; Liu, Y.; Li, H.; Tan, X.; Liu, F.; Peng, Y.; Zhang, H. Effects of RAAS inhibitors in patients with kidney disease. Current hypertension reports 2017, 19, 72.

16. Akiyama, H.; Nishimura, A.; Morita, N.; Yajima, T. Evolution of sodium-glucose co-transporter 2 inhibitors from a glucose-lowering drug to a pivotal therapeutic agent for cardio-renal-metabolic syndrome. Frontiers in endocrinology 2023, 14, 1111984.

17. Chun, K.J.; Jung, H.H. SGLT2 inhibitors and kidney and cardiac outcomes according to estimated GFR and albuminuria levels: a meta-analysis of randomized controlled trials. Kidney Medicine 2021, 3, 732-744. e731.

18. Provenzano, M.; Puchades, M.J.; Garofalo, C.; Jongs, N.; D'Marco, L.; Andreucci, M.; De Nicola, L.; Gorriz, J.L. Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: a randomized crossover clinical trial. Journal of the American Society of Nephrology 2022, 33, 1569-1580.

19. Xu, L.; Li, Y.; Lang, J.; Xia, P.; Zhao, X.; Wang, L.; Yu, Y.; Chen, L. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibition on renal function and albuminuria in patients with type 2 diabetes: a systematic review and meta-analysis. PeerJ 2017, 5, e3405.

20. Chiriac, I.A.; Mititelu, R.M.; Mazilu, C.; Niculescu, O.; Lepuș, M.G. Scintigraphic evaluation of the kidney. Rom J Mil Med 2015, 118, 26-32.

21. Weir, M.R. Kidney Protection Options in 2025: Are Renin-Angiotensin System Inhibitors Still Needed? In Proceedings of the Seminars in Nephrology, 2026; p. 151688.

22. Zvâncă, M.; Petca, A.; Baltă, O.; Boț, M.; Mehedințu, C.; Măru, N.; Petca, R. Improving the outcomes for pregnancies in the context of kidney disease. Romanian Journal of 123, 46.

23. Diaconu, C.; Salmen, T.; Gaman, M.A.; Bratu, O.G.; Mischianu, D.; Marcu, R.D.; Suceveanu, A.I.; Costache, R.S.; Pantea Stoian, A. SGLT2 inhibition in patients with type 2 diabetes and cardiovascular diseases: Which are the benefits. Rom J Mil Med 2019, 122, 16-21.

24. Isshiki, M.; Sakuma, I.; Hayashino, Y.; Sumita, T.; Hara, K.; Takahashi, K.; Shiojima, I.; Satoh-Asahara, N.; Kitazato, H.; Ito, D. Effects of dapagliflozin on renin-angiotensin-aldosterone system under renin-angiotensin system inhibitor administration. Endocrine Journal 2020, 67, 1127-1138.

25. Ansary, T.M.; Nakano, D.; Nishiyama, A. Diuretic effects of sodium glucose cotransporter 2 inhibitors and their influence on the renin-angiotensin system. International journal of molecular sciences 2019, 20, 629.

26. Forouzanmehr, B.; Hedayati, A.H.; Gholami, E.; Hemmati, M.A.; Maleki, M.; Butler, A.E.; Jamialahmadi, T.; Kesharwani, P.; Yaribeygi, H.; Sahebkar, A. Sodium-glucose cotransporter 2 inhibitors and renin-angiotensin-aldosterone system, possible cellular interactions and benefits. Cellular Signalling

2024, 122, 111335.

27. Møller, A.L.; Thöni, S.; Keller, F.; Sharifli, S.; Rasmussen, D.G.K.; Genovese, F.; Karsdal, M.A.; Mayer, G. Combination Therapy of RAS Inhibition and SGLT2 Inhibitors Decreases Levels of Endotrophin in Persons with Type 2 Diabetes. Biomedicines 2023, 11, 3084.

28. Ishibashi, T.; Morita, S.; Furuta, H.; Nishi, M.; Matsuoka, T.-A. Renoprotective potential of concomittant medications with SGLT2 inhibitors and renin-angiotensin system inhibitors in diabetic nephropathy without albuminuria: a retrospective cohort study. Scientific Reports 2023, 13, 16373.

29. Zou, H.; Zhou, B.; Xu, G. SGLT2 inhibitors: a novel choice for the combination therapy in diabetic kidney disease. Cardiovascular Diabetology 2017, 16, 65.

30. Seidu, S.; Kunutsor, S.K.; Topsever, P.; Khunti, K. Benefits and harms of sodium-glucose co-transporter-2 inhibitors (SGLT2-I) and renin–angiotensin–aldosterone system inhibitors (RAAS-I) versus SGLT2-Is alone in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials. Endocrinology, diabetes & metabolism 2022, 5, e00303.

31. Halder, S.; Bhattacharyya, A.; Mukherjee, S.; Konar, B.; Halder, A. Assessment of effects of combination of SGLT2 inhibitors and renin–angiotensin–aldosterone system blockers on the renal functions of patients of diabetic kidney disease (SGRASS-DKD study). Journal of Diabetology 2024, 15, 79-85.

32. Vart, P.; Vaduganathan, M.; Jongs, N.; Remuzzi, G.; Wheeler, D.C.; Hou, F.F.; McCausland, F.; Chertow, G.M.; Heerspink, H.J. Estimated lifetime benefit of combined RAAS and SGLT2 inhibitor therapy in patients with albuminuric CKD without diabetes. Clinical Journal of the American Society of Nephrology 2022, 17, 1754-1762.

33. Heerspink, H.J.; Stefánsson, B.V.; Correa-Rotter, R.; Chertow, G.M.; Greene, T.; Hou, F.-F.; Mann, J.F.; McMurray, J.J.; Lindberg, M.; Rossing, P. Dapagliflozin in patients with chronic kidney disease. New England Journal of Medicine 2020, 383, 1436-1446.

34. Siddiqui, R.; Obi, Y.; Dossabhoy, N.R.; Shafi, T. Is there a role for SGLT2 inhibitors in patients with end-stage kidney disease? Current hypertension reports 2024, 26, 463-474.

35. Oshima, M.; Neuen, B.L.; Li, J.; Perkovic, V.; Charytan, D.M.; de Zeeuw, D.; Edwards, R.; Greene, T.; Levin, A.; Mahaffey, K.W. Early change in albuminuria with canagliflozin predicts kidney and cardiovascular outcomes: a posthoc analysis from the CREDENCE trial. Journal of the American Society of Nephrology 2020, 31, 2925-2936.

36. Nakhleh, A.; Abdul-Ghani, M.; Gazit, S.; Gross, A.; Livnat, I.; Greenbloom, M.; Yarden, A.; Khazim, K.; Shehadeh, N.; Melzer Cohen, C. Real-world effectiveness of sodium-glucose cotransporter-2 inhibitors on the progression of chronic kidney disease in patients without diabetes, with and without albuminuria. Diabetes, Obesity and Metabolism 2024, 26, 3058-3067.

37. Ngai, A.W.; Baig, A.; Zia, M.; Arca-Contreras, K.; Haque, N.U.; Livetsky, V.; Rokicki, M.; Sukhram, S.D. Comparative Evaluation of ARB Monotherapy and SGLT2/ACE Inhibitor Combination Therapy in the Renal Function of Diabetes Mellitus Patients: A Retrospective, Longitudinal Cohort Study. International Journal of Molecular Sciences 2025, 26, 7412.

38. Jongs, N.; Chertow, G.M.; Greene, T.; McMurray, J.J.; Langkilde, A.M.; Correa-Rotter, R.; Kashihara, N.; Rossing, P.; Sjöström, C.D.; Stefánsson, B.V. Correlates and consequences of an acute change in eGFR in response to the SGLT2 inhibitor dapagliflozin in patients with CKD. Journal of the American Society of Nephrology 2022, 33, 2094-2107.

39. Van Baar, M.J.; Van Ruiten, C.C.; Muskiet, M.H.; Van Bloemendaal, L.; IJzerman, R.G.; Van Raalte, D.H. SGLT2 inhibitors in combination therapy: from mechanisms to clinical considerations in type 2 diabetes management. Diabetes care 2018, 41, 1543-1556.

40. Li, J.; Li, C.; Feng, X.; Wei, X. SGLT2 inhibition, blood lipids, and cardiovascular disease: A Mendelian randomization study. ESC heart failure 2024, 11, 3960-3971.

41. Szekeres, Z.; Toth, K.; Szabados, E. The effects of SGLT2 inhibitors on lipid metabolism. Metabolites 2021, 11, 87.

42. Yen, F.-S.; Hwu, C.-M.; Liu, J.-S.; Wu, Y.-L.; Chong, K.; Hsu, C.-C. Sodium–glucose cotransporter-2 inhibitors and the risk for dialysis and cardiovascular disease in patients with stage 5 chronic kidney disease. Annals of internal medicine 2024, 177, 693-700.

43. Tuttle, K.R.; Brosius III, F.C.; Cavender, M.A.; Fioretto, P.; Fowler, K.J.; Heerspink, H.J.; Manley, T.; McGuire, D.K.; Molitch, M.E.; Mottl, A.K. SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a scientific workshop sponsored by the National Kidney Foundation. Diabetes 2021, 70, 1-16.

44. Siddiqi, T.J.; Cherney, D.; Siddiqui, H.F.; Jafar, T.H.; Januzzi, J.L.; Khan, M.S.; Levin, A.; Marx, N.; Rangaswami, J.; Testani, J. Effects of sodium-glucose cotransporter-2 inhibitors on kidney outcomes across baseline cardiovascular-kidney-metabolic conditions: a systematic review and meta-analyses. Journal of the American Society of Nephrology 2025, 36, 242-255.

45. Badura, K.; Janc, J.; Wąsik, J.; Gnitecki, S.; Skwira, S.; Młynarska, E.; Rysz, J.; Franczyk, B. Anemia of chronic kidney disease—a narrative review of its pathophysiology, diagnosis, and management. Biomedicines 2024, 12, 1191.

46. Marques Vidas, M.; Portolés, J.; Cobo, M.; Gorriz, J.L.; Nuñez, J.; Cases, A. Anemia management in the cardiorenal patient: a nephrological perspective. Journal of the American Heart Association 2025, 14, e037363.

https://doi.org/10.55453/rjmm.2026.129.3.6

REVIEW

Fine-Tuning Outcomes of Lymphedema Treatment Using Bioengineered Enzymatic Cocktails- A Narrative Review and Case Series

Anca Emilia Oprescu[1]

[1] Doctoral School, Ovidius University, Constanta, Romania

Corresponding Author: anca.oprescu@icloud.com (AEO)

Abstract: (1) Background and aim: Multimodal treatment is the current standard approach for managing lymphedema, with the goal of normalizing or reducing volume discrepancies, improving function, and enhancing appearance. However, following the reduction of the solid component and enhancement of lymph flow through physiological procedures involving supermicrosurgery, residual areas of fibrosis or lipodystrophy may persist, causing dissatisfaction for both the patient and the physician. (2) Methods: We present a three-case series of lymphedema, two affecting the upper limb and one affecting a lower limb, all previously treated with lymphaticovenular anastomosis (LVA) and/or debulking liposuction, which resulted in satisfactory overall volume reduction of the limbs, but with persistent swelling of the dorsum of the hand and forefoot, respectively. All patients were subsequently treated with a combination of bioengineered enzymatic cocktail (BEC). (3) Results: All three patients demonstrated stable reduction of swelling in the affected areas at one-month follow-up, with improved quality of life and function, which was maintained at six months follow-up. (4) Conclusion: These preliminary observations suggest that multi-enzyme cocktails warrant investigation as adjuncts for localized, post-surgical residual lymphedema, particularly for distal, anatomically challenging regions, such as the hand, foot, and digits, where surgical options are limited.

Keywords: Residual lymphedema; Lymphedema pharmaceutical treatment; Head and neck lymphedema; Hand and foot lymphedema; Microsurgery; Lymphedema treatment; Quality of life.

INTRODUCTION

Lymphedema treatment has significantly advanced in recent years, driven by technological innovations such as supermicrosurgery [1] and a deeper understanding of the disease's pathophysiology [2,3]. Existing treatment algorithms are continually being re-evaluated [4], as is the optimal sequence of treatment modalities. Lymphedema treatment requires a multimodal approach that must primarily consider patient-related factors, including etiology, disease stage, individual anatomy, and medical history, as well as the experience of the treating physician and the technology available [2].

Patients with lymphedema strive for normalcy, and even compliant patients seek to minimize the time and effort required for compression therapy [5,6]. This is especially pertinent for highly functional areas, such as fingers, toes, hands, feet, and the head and neck, where treating the solid component of the disease poses considerable challenges [7].

PB Serum Medium is a synthetic bioengineered enzymatic mixture comprising three enzymes: lipase PB500, collagenase PB220, and lyase PB72K, produced by Proteos Biotech in Madrid, Spain. It has been utilized for treating lipodystrophic, scarred tissues, and localized, resistant adipose deposits.

Citation: Oprescu AE. Fine-Tuning Outcomes of Lymphedema Treatment Using Bioengineered Enzymatic Cocktails- A Narrative Review and Case Series. R. J. Mil. Med. 2026, CXXIX(3): 276-284 https://doi.org/10.55453/rjmm.2029.129.3.6

Academic Editor: Clara Ursescu

Received: 19 July 2025
Revised: 27 February 2026
Accepted: 09 April 2026
Published: 24 February 2024

NARRATIVE LITERATURE REVIEW

Lymphedema is a progressive condition characterized not only by lymphatic fluid accumulation but also by structural tissue remodeling, including chronic inflammation, adipose deposition, and fibrosis. As the disease evolves, the relative contribution of this "solid component" increases, rendering the condition less responsive to therapies aimed solely at improving lymphatic drainage. This phenomenon is particularly evident in distal anatomical regions such as the hands,

feet, and digits, where dense fibrotic changes and limited lymphatic reserve contribute to persistent deformity despite otherwise successful treatment.

Current management strategies follow a multimodal paradigm, combining complete decongestive therapy, physiologic microsurgical procedures such as lymphaticovenular anastomosis and vascularized lymph node transfer [1,3], and excisional approaches including liposuction. While these interventions are effective in reducing global limb volume, their ability to address localized, distal manifestations remains limited. Residual fibrosis and lipodystrophy in anatomically constrained regions continue to represent a significant therapeutic challenge and are frequently associated with persistent functional impairment and reduced patient satisfaction [4,8].

Pharmacologic and injectable therapies for lymphedema remain largely investigational, with no standardized or widely accepted agents available for clinical use [8, 9]. Among enzymatic approaches, hyaluronidase has demonstrated the capacity to degrade extracellular matrix glycosaminoglycans, thereby reducing interstitial resistance and facilitating fluid mobilization. In preclinical models, repeated hyaluronidase administration has also been associated with enhanced lymphangiogenesis in the context of vascularized lymph node transfer, suggesting a potential adjunctive role in lymphatic regeneration [10]. However, clinical translation remains limited, and its effects appear primarily directed toward the fluid component of lymphedema rather than established fibrosis or adipose tissue deposition.

Earlier investigations into systemic enzyme therapy provide indirect support for enzymatic modulation as a therapeutic strategy. Oral proteolytic combinations, including trypsin, chymotrypsin, bromelain, and papain, have demonstrated statistically significant reductions in limb volume in post-mastectomy lymphedema when compared to diuretic therapy [11]. Nevertheless, these studies predate contemporary multimodal treatment algorithms, lack anatomical specificity, and do not address localized, treatment-resistant disease. Furthermore, systemic administration limits the ability to achieve targeted effects within fibrotic or adipose-rich tissues.

Recent advances in lymphatic biology and regenerative medicine further support the rationale for localized therapeutic interventions. Experimental approaches such as nanofibrillar collagen scaffolds have shown the capacity to guide lymphatic regeneration [12], while molecular therapies involving VEGF-C and apelin signaling pathways have demonstrated reversal of established lymphedema in preclinical models [13]. Despite these promising developments, such strategies remain largely experimental and are not yet applicable in routine clinical practice. As a result, a therapeutic gap persists between established surgical techniques and emerging regenerative therapies, particularly in small, anatomically complex regions that are not amenable to further surgical intervention.

Within this context, locally administered, bioengineered enzymatic combinations represent a novel and mechanistically plausible approach. A multi-enzyme formulation combining lipase, collagenase, and lyase offers the potential to simultaneously target adipose hypertrophy and fibrotic extracellular matrix, the principal components of the solid phase of lymphedema. By promoting localized tissue remodeling, such an approach may improve compliance, reduce residual volume, and enhance functional outcomes in areas where conventional therapies have limited efficacy.

To our knowledge, no prior clinical reports have described the use of multi-enzyme injectable cocktails specifically for the treatment of localized, distal lymphedema. The present case series aims to address this gap by providing initial clinical observations on the feasibility and short-term outcomes of this targeted approach in patients with persistent, post-surgical residual disease.

MATERIALS AND METHODS

Study Design

This retrospective case series included three patients with extremity lymphedema who demonstrated persistent, localized distal swelling following standard surgical management. All treatments described were delivered as part of routine clinical care. No modifications to technique, dosing, or timing were implemented for research purposes.

Patient Selection

Patients were eligible for inclusion if they met all of the following criteria:

1. Diagnosis: Secondary upper- or lower-limb lymphedema, confirmed clinically and by lymphographic evaluation.

2. Disease Stage: ISL Stage 1-2 for upper-limb lymphedema or ISL Stage 1 for lower-limb lymphedema, characterized by persistent pitting edema with or without partial reversibility with elevation.

3. Prior Surgical Management: Completion of at least one physiological or debulking intervention—lymphaticovenous anastomosis (LVA), liposuction, or MITESE (minimally invasive tissue excision plus or minus skin excision)—with satisfactory global limb volume reduction.

4. Residual Localized Problem: Persistent swelling in functionally critical distal regions (dorsum of hand/foot, fingers, toes) refractory to compression therapy and physiotherapy.

5. Postoperative Stability: Stable postoperative status for at least 3 months before enzymatic treatment.

6. Clinical Indication: Patient-reported functional impairment (e.g., difficulty with footwear, hygiene, dexterity) attributable to localized swelling.

Exclusion criteria were acute cellulitis, uncontrolled systemic comorbidities, pregnancy, anticoagulation therapy, active dermatologic pathology at the planned injection site, prior enzymatic therapy in the affected region, and inability to comply with follow-up.

Treatment Protocol

Enzymatic Preparation and Reconstitution

PB Serum Medium (Proteos Biotech, Madrid, Spain) contains lipase PB500, collagenase PB220, and lyase PB72K. For each session, a full 20-mL kit was reconstituted according to manufacturer instructions. To reduce injection discomfort, 2 mL of 1% lidocaine was added; no further dilution was performed, yielding a final volume of 22 mL per session.

Injection Mapping and Technique

All procedures were performed in a minor procedure room under sterile conditions.

1. A 1-cm grid was marked over the treatment area to standardize injection distribution.
2. The skin was cleansed with 70% ethanol and allowed to air dry.
3. All injections were administered using a 30-gauge, 9-mm sterile needle.
4. Each grid square received 1.0 mL of solution delivered as:

o 0.5 mL subdermal (just beneath the dermis) targeting fibrotic tissue, and

o 0.5 mL superficial subcutaneous to address localized lipodystrophic components.

5. Needle depth did not exceed 9 mm; aspiration preceded each injection to avoid inadvertent intravascular delivery.
6. Injections were evenly spaced across the grid, with additional points added over palpably fibrotic or resistant areas.
7. No oral or injectable analgesia was required; all patients tolerated the procedure without interruption.

Treatment Schedule

Each patient received three treatment sessions, administered at 2-week intervals. No deviations from standard clinical practice occurred in the cases included in this review.

Compression Protocol

All patients continued their existing complete decongestive therapy, including the use of flat-knit 30–40 mmHg compression garments, without interruption. Daily wear was maintained as per the pre-treatment routine. Patients were instructed in local hygiene at the injection sites, and adherence to compression was reviewed at each visit.

Adverse Event Monitoring

At each follow-up, patients were assessed for pain (numeric rating scale, 0–10), erythema, ecchymosis, warmth,

paresthesia, skin breakdown, ulceration, and signs of infection or cellulitis. No laboratory testing was performed, as the treatment was local, conducted within routine clinical practice, and not expected to generate systemic effects.

Outcome Assessment

Primary Endpoints

1. Clinical reduction of localized swelling at 1-month follow-up, assessed using standardized clinical photography and Stemmer sign.
2. Patient-reported improvement in functional capacity and comfort, assessed via structured (non-validated) interviews.

Secondary Endpoints

1. Durability of clinical response at 6 months.

2. Absence of injection-related complications.

Objective volumetric measurements (water displacement, perometry, bioimpedance) were not feasible owing to the small magnitude and highly localized nature of distal hand and foot deformities. This limitation is acknowledged.

Functional and quality-of-life outcomes were assessed through non-validated patient-reported impressions obtained during structured interviews and routine communication. Validated PROM instruments were not used.

Photography Protocol

As this is a retrospective case series, clinical photographs and patient-reported outcomes were collected as part of routine clinical care. Some photographs were taken by patients themselves and vary in distance, angle, and lighting; all images were time-stamped and correspond to the documented treatment timepoints (pre-treatment, 1 month, and 6 months post-final session). Clinical photographs were obtained retrospectively as part of routine care. Because some images were patient-provided, standardized positioning, lighting, and camera distance could not be ensured. As a result, image quality and comparability vary.

Patient-reported outcomes were recorded via direct communication and messaging applications, reflecting perceived functional improvement and swelling reduction. In a prospective study, a standardized photography protocol and validated outcome instruments would have been employed; however, the current approach provides a descriptive record consistent with routine practice.

Ethical considerations

All enzymatic procedures represented standard-of-care management, and the retrospective analysis met institutional criteria for exemption from formal ethics committee review. All patients provided written informed consent for off-label use of PB Serum Medium, retrospective use of their clinical data, and publication of de-identified clinical images.

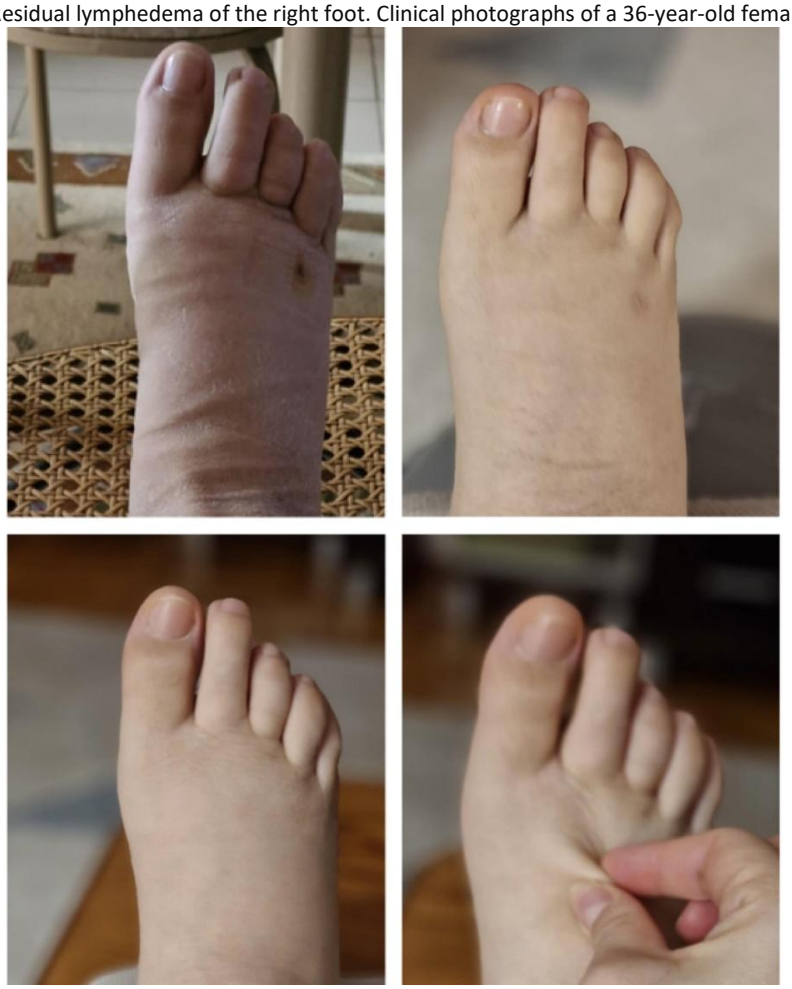
RESULTS

Case 1

A 36-year-old female patient, BMI 20.07kg/m2, otherwise healthy, without chronic treatment, presented with secondary lymphedema, stage III (lymphography) / Stage 1 ISL (pitting oedema that improves with elevation) of the right lower limb, with a more pronounced volume discrepancy in the leg compared to the thigh, following trauma in early childhood. The patient's history included a right femoral fracture, followed by a right ankle sprain. Initially, the patient underwent decongestive therapy [14], until LVA [15, 16] was performed in April 2023. Although good results were achieved initially, a relapse occurred, necessitating debulking liposuction [17] in May 2024. The volume discrepancy recorded prior to surgery was 900 cc, and the volume of aspirate removed was 700 cc. Although the debulking led to temporary relief, persistent swelling in the foot area remained problematic for the patient.

The patient subsequently received three sessions of PB Serum injections administered to the foot area. At one month post-treatment, the patient continued to experience episodic leg swelling but reported no residual swelling in the distal part of the foot (Figure 1). The results were maintained at six months, based on patient report, with supple skin, negative Stemmer sign, and requested further treatment of a small swelling around the ankle, an area outside of the initial treatment.

Figure 1: Residual lymphedema of the right foot. Clinical photographs of a 36-year-old female patient



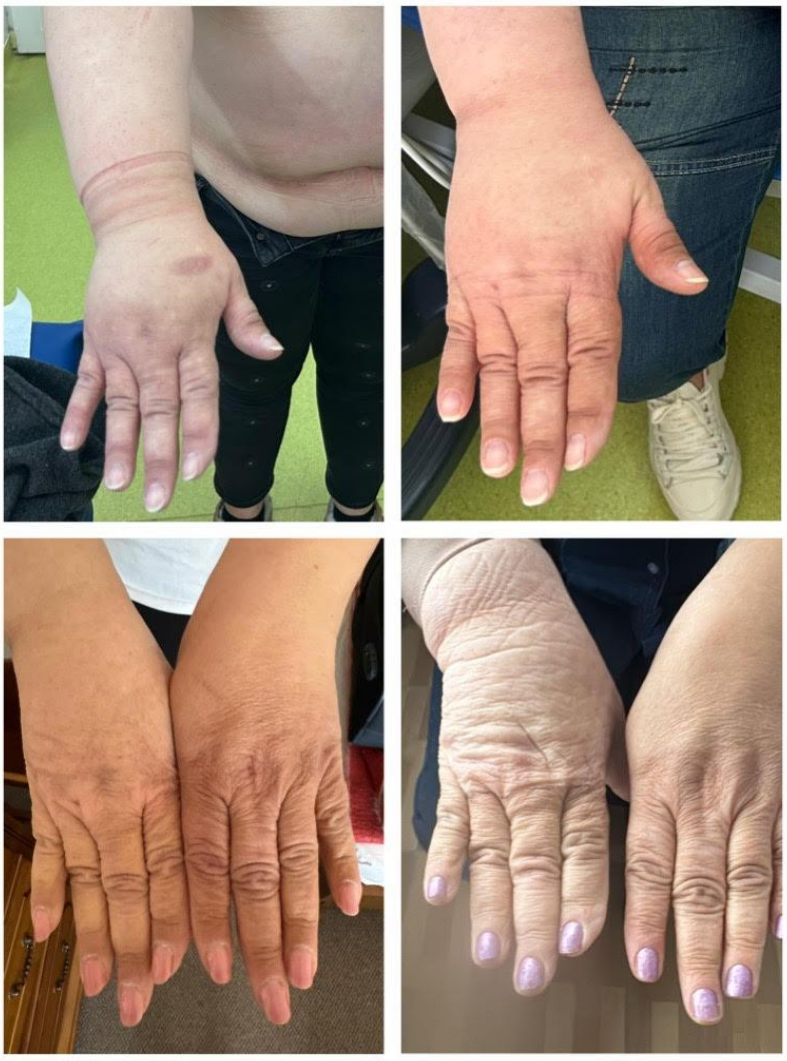
. Above: Left: Pretreatment image showing swollen toes and forefoot following previous lymphaticovenular anastomosis and debulking procedures. Right. Post-treatment appearance at one month following bioengineered enzymatic cocktail (BEC) injections, showing reduced volume and crease formation. Below: Post-treatment appearance after 6 months, showing results maintained with a negative Stemmer sign.

Case 2

A 57-year-old female, BMI-29.72kg/m2, otherwise healthy, without chronic treatment, who underwent radical right mastectomy and right axillary lymphadenectomy in 2020, followed by radio and chemotherapy, presented with secondary lymphedema of the right upper limb, stage IV (lymphography)/ stage 1 ISL (pitting edema that improves with elevation). The patient had previously undergone LVA [15, 18] in 2023, at another clinic, with no significant improvement in limb volume discrepancy. We offered debulking surgery [17], in March 2024, which resulted in the removal of approximately 1500 cc of aspirate (the initial volume difference was 1700 cc). The patient was satisfied with the results; however, compliance with compression in the hand and finger areas was low due to difficulties in maintaining hand hygiene [7].

The patient subsequently received the same PB Serum injection regimen, involving three sessions administered to the dorsum of the right hand, spaced at two-week intervals. One month after treatment, follow-up indicated a significant reduction in swelling, localized to the treated area (Figure 2). Results are maintained at six months after treatment, based on patient report, with supple skin and a negative Stemmer sign.

Figure 2: Residual lymphedema in the right hand and fingers. Clinical photographs of a 57-year-old female patient with post-mastectomy lymphedema.



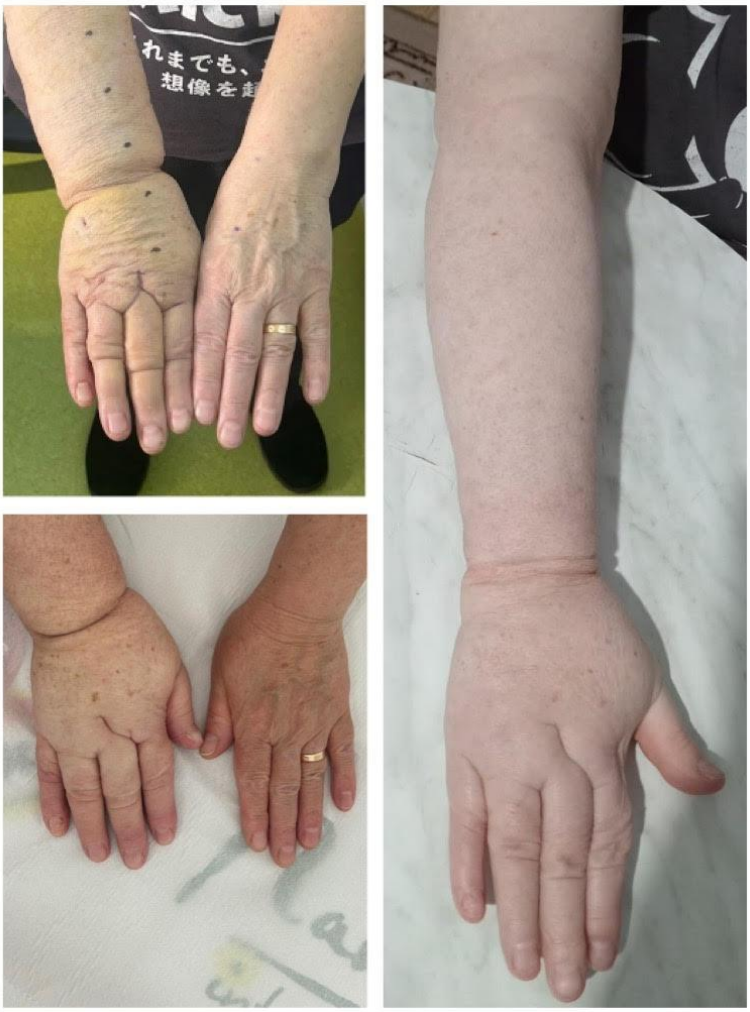
Left upper quadrant: Hand appearance before debulking procedure. Right upper quadrant: Affected right hand after debulking and before BEC treatment. Left lower quadrant: Reduced finger and dorsum swelling after BEC treatment, comparable with the left healthy hand, at one month after BEC treatment, and right lower quadrant: appearance after 6 months, showing results maintained and soft, supple, wrinkled skin.

Case 3

A 62-year-old female, BMI-30.12kg/m2, also known with osteoporosis and vertigo, who underwent right radical mastectomy and right axillary lymphadenectomy in 1993, followed by radio and chemotherapy, developed upper right limb lymphedema 20 years after surgery. At presentation, she is staged with stage IV upper right limb lymphedema (lymphography)/ stage 2 ISL (pitting edema that does not resolve with elevation). She underwent MITESE (minimal invasive tissue excision and skin excision) of the right upper arm [3], with significant volume reduction in 2025. A volume of 2300 ml of fat was aspirated in one session, followed by excision of redundant skin. The patient proved extremely compliant and followed thoroughly the postoperative compression regimen [14]. Still, volume excess was present in the dorsum of the right hand and fingers.

Three sessions of PB Serum Medium were administered at two-week intervals, and results at one month after treatment ended showed marked volume reduction at the injection site, especially around interphalangeal joints, and improvement of hand function (Figure 3). At six months follow-up, the improvement was maintained, based on patient report, with supple skin and a negative Stemmer sign.

Figure 3: Residual lymphedema in the right hand and fingers. Clinical photographs of a 62-year-old female patient with post-mastectomy lymphedema.



Left upper picture: Pretreatment swelling of fingers and deep creases around interphalangeal joints. Left lower picture: Decreased swelling and creases following BEC treatment after one month. Right picture: appearance of the hand at 6 months after BEC treatment, with soft, supple skin, without creases around interphalangeal joints.

DISCUSSION

This manuscript reports preliminary clinical observations of an off-label enzymatic adjunct used for residual, localized lymphedema after standard surgical management, and situates these observations within the limited available literature on pharmacologic and injectable approaches to lymphedema. While debulking procedures achieved >80% excess volume reduction across cases, functionally limiting distal residual fibrosis persisted despite compression therapy compliance. These observations suggest that multi-enzyme cocktails may address a specific clinical niche currently underserved by existing modalities [3,5,17]. These three cases illustrate that patient satisfaction is not solely dependent on volume reduction [15].

One major limitation of this report is the selection of the enzymatic cocktail, which was based on prior experience with localized adipose tissue rather than on comparative testing of the three available enzymatic cocktails for lymphedema treatment—specifically, those targeting adipose tissue. Quality of life improvements were assessed through anecdotal and spontaneous patient reports, and the assessment of changes in the treated area was based on photographs and patient self-reporting [6], rather than objective measurements. Validated patient-reported outcome measures were not administered, which limits quantitative assessment of perceived functional benefit.

A key limitation of this case series is the lack of standardized photography. Several follow-up images were provided by patients, preventing strict control over lighting, angle, and distance. Future prospective studies should incorporate a standardized imaging protocol.

Our observations suggest that adding a new tool for addressing small but sensitive areas may significantly improve perceived quality of life. The dorsum of the foot or hand, toes, fingers, face, head and neck, and children's extremities might benefit from injectable treatments rather than liposuction. Given that a compound targeting both fibrotic (collagenase) and adipose (lipase) tissue is already available on the market, investigating the role of enzymatic treatment within the lymphedema treatment algorithm [4] is warranted. Identifying the optimal enzymatic combination may also prove valuable if pathology examinations of the aspirate can determine whether fibrosis or adipose tissue is predominant. The potential benefit of this adjunct treatment, alongside physiological microsurgical approaches [19,20,21], merits further investigation.

An additional patient with sleep apnea and a heavy neck (lymphedema not formally diagnosed), treated in a similar manner, except no surgical procedure was performed initially, reported subjective improvement in breathing and sleep quality and returned for 2 more sessions for further improvement. This case signals a possible research field for head and neck lymphedema, where liposuction in fibrotic/ irradiated tissue might become problematic [3].

CONCLUSION

The initial clinical observations presented in the current article demonstrate the feasibility and consistent short-term improvement using an off-label multi-enzyme cocktail for distal lymphedema residuals refractory to standard care. While hypothesis-generating only, these findings support formal evaluation of injectable enzymatic therapy within contemporary lymphedema algorithms, particularly for anatomically challenging regions poorly addressed by surgery or compression. Future prospective studies with standardized imaging and validated patient-reported outcomes are warranted.

Conflicts of interest and sources of funding

The author declares no conflicts of interest related to this study. No financial grants or funding were received for this research. The author has no industrial links, affiliations, or financial interests in any of the products, devices, or therapeutic substances mentioned in this manuscript, including PB Serum Medium (Proteos Biotech, Madrid, Spain). This study did not involve clinical trials or commercial devices requiring additional conflict declarations.

Acknowledgments

The author acknowledges the patients who provided informed consent for the publication of their clinical information and photographs for scientific and educational purposes. The author also acknowledges the clinical staff at Alexandru Gafencu Military Emergency Hospital for their support in patient care and data collection.

Ethics approval and consent to participate

All patients signed consent forms for the release of their clinical information, including photographs, for publication in a scientific journal or presentation at a meeting.

Patient consent for publication

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

References

1. Koshima I, Yamamoto T, Narushima M, Mihara M, Iida T, Koshima Y. Fundamental and essential techniques for supermicrosurgical lymphaticovenular anastomosis: the art of Isao Koshima's supermicrosurgery. Microsurgery. 2021;41(6):568-574.

2. Lymphedema Framework. Best Practice for the Management of Lymphoedema. International consensus. London: MEP Ltd; 2006.

3. Schaverien MV, Coroneos CJ. Surgical Treatment of Lymphedema. Plast Reconstr Surg. 2019;144(3):738-758. doi: 10.1097/PRS.0000000000005993.

4. Executive Committee of the International Society of Lymphology. The diagnosis and treatment of peripheral lymphedema: 2020 Consensus Document of the International Society of Lymphology. Lymphology. 2020;53(1):3-19.

5. Pusic AL, Cemal Y, Albornoz C, Klassen A, Cano S, Sulimanoff I, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. J Cancer Surviv. 2013;7(1):83-92. doi: 10.1007/s11764-012-0247-5.

6. Keeley V. Quality of life assessment tools in chronic oedema. Br J Community Nurs. 2008;13(10):S22-7. doi: 10.12968/bjcn.2008.13.Sup5.31193.

7. Borman P, Yaman A, Yasrebi S, Özdemir O. The Importance of Awareness and Education in Patients with Breast Cancer-Related Lymphedema. J Cancer Educ. 2017;32(3):629-633. doi: 10.1007/s13187-016-1026-1.

8. Walker J, Tanna S, Roake J, Lyons O. A systematic review of pharmacologic and cell-based therapies for treatment of lymphedema (2010-2021). J Vasc Surg Venous Lymphat Disord. 2022;10(4):966-975.e1. https://doi.org/10.1016/j.jvsv.2021.09.004.

9. Brown S, Campbell AC, Kuonqui K, Sarker A, Park HJ, Shin J, Kataru RP, Coriddi M, Dayan JH, Mehrara BJ. The Future of Lymphedema: Potential Therapeutic Targets for Treatment. Curr Breast Cancer Rep. 2023:1-9. doi: 10.1007/s12609-023-00491-5.

10. Cheon H, Chen L, Kim SA, Gelvosa MN, Hong JP, Jeon JY, Suh HP. Improved lymphangiogenesis around vascularized lymph node flaps by periodic injection of hyaluronidase in a rodent model. Sci Rep. 2024;14(1):24430. https://doi.org/10.1038/s41598-024-74414-4.

11. Korpan MI, Fialka V. Wobenzym und Diuretikatherapie beim Lymphödem nach Mammaoperation. Wien Med Wochenschr. 1996;146(4):67-72.

12. Nguyen DH, Zhou A, Posternak V, Rochlin DH. Nanofibrillar Collagen Scaffold Enhances Edema Reduction and Formation of New Lymphatic Collectors after Lymphedema Surgery. Plast Reconstr Surg. 2021 Dec 1;148(6):1382-1393. doi: 10.1097/PRS.0000000000008590.

13. Creff J, Lamaa A, Benuzzi E, Balzan E, Pujol F, Draia-Nicolau T, et al. Apelin-VEGF-C mRNA delivery as therapeutic for the treatment of secondary lymphedema. EMBO Mol Med. 2024;16(2):386-415. doi: 10.1038/s44321-023-00017-7.

14. Vignes S, Porcher R, Arrault M, Dupuy A. Long-term management of breast cancer-related lymphedema after intensive decongestive physiotherapy. Breast Cancer Res Treat. 2007;101(3):285-90. doi: 10.1007/s10549-006-9297-6.

15. Chang DW, Suami H, Skoracki R. A prospective analysis of 100 consecutive lymphovenous bypass cases for treatment of extremity lymphedema. Plast Reconstr Surg. 2013;132(5):1305-1314. doi: 10.1097/PRS.0b013e3182a4d626.

16. Damstra RJ, Voesten HG, van Schelven WD, van der Lei B. Lymphatic venous anastomosis (LVA) for treatment of secondary arm lymphedema. A prospective study of 11 LVA procedures in 10 patients with breast cancer related lymphedema and a critical review of the literature. Breast Cancer Res Treat. 2009;113(2):199-206. doi: 10.1007/s10549-008-9932-5.

17. Brorson H. Liposuction in Lymphedema Treatment. J Reconstr Microsurg. 2016;32(1):56-65. doi: 10.1055/s-0035-1549158.

18. Torrisi JS, Joseph WJ, Ghanta S, Cuzzone DA, Albano NJ, Savetsky IL, et al. Lymphaticovenous bypass decreases pathologic skin changes in upper extremity breast cancer-related lymphedema. Lymphat Res Biol. 2015;13(1):46-53. doi: 10.1089/lrb.2014.0022.

19. Campisi C, Bellini C, Campisi C, Accogli S, Bonioli E, Boccardo F. Microsurgery for lymphedema: clinical research and long-term results. Microsurgery. 2010;30(4):256-60. doi: 10.1002/micr.20737.

20. Mihara M, Hara H, Araki J, Kikuchi K, Narushima M, Yamamoto T, Iida T, Yoshimatsu H, Murai N, Mitsui K, Okitsu T, Koshima I. Indocyanine green (ICG) lymphography is superior to lymphoscintigraphy for diagnostic imaging of early lymphedema of the upper limbs. PLoS One. 2012;7(6):e38182. doi: 10.1371/journal.pone.0038182.

21. Boccardo F, Casabona F, De Cian F, Friedman D, Villa G, Bogliolo S, Ferrero S, Murelli F, Campisi C. Lymphedema microsurgical preventive healing approach: a new technique for primary prevention of arm lymphedema after mastectomy. Ann Surg Oncol. 2009;16(3):703-8. doi: 10.1245/s10434-008-0270-y.

https://doi.org/10.55453/rjmm.2026.129.3.7

REVIEW

Digital Technologies in Cardiology: From Continuous Monitoring to Predictive Medicine

Simona Steliana Tudor[1], Ionela Daniela Ferțu[1], Caterina Nela Dumitru[1,2], Bogdan-Viorel Vîlceleanu[3,4*], Alexandru Mihai Popescu[3,4], Silviu Ionel Dumitrescu[4,5], Alice Elena Munteanu[4,5]

[1] Faculty of Medicine and Pharmacy. Medical-Pharmaceutical Research Center, "Dunarea de Jos" University of Galati, 800008 Galati, Romania; steliana.tudor@ugal.ro, ionela.fertu@ugal.ro, caterina.dumitru@ugal.ro
[2] Clinical Hospital of Infectious Diseases "St. Venerable Parascheva", 800179 Galați, Romania; caterina.dumitru@ugal.ro
[3] Carol Davila University of Medicine and Pharmacy, Doctoral School, 020022, Bucharest, Romania; Bogdan-viorel.vilceleanu@drd.umfcd.ro
[4] Carol Davila Central Emergency Universitary Military Hospital of Bucharest, 060011, Bucharest, Romania; Bogdan-viorel.vilceleanu@drd.umfcd.ro, silviudumius@yahoo.com, dralicemunteanu@gmail.com
[5] Titu Maiorescu University – Faculty of Medicine; silviudumius@yahoo.com, dralicemunteanu@gmail.com

*Correspondence: B-V.V. Bogdan-viorel.vilceleanu@drd.umfcd.ro

Abstract: Background: Digital transformation in cardiology is reshaping diagnosis, monitoring, and therapy through connected devices, digital biomarkers, telemedicine, and artificial intelligence. This paper synthesizes recent advances and emphasizes the shift from episodic assessment to continuous surveillance and personalized predictive care. Methods: The article included 81 studies published between 2015 and 2026, identified in PubMed, Google Scholar, and ScienceDirect, encompassing clinical trials, meta-analyses, observational studies, and reviews focused upon continuous cardiovascular monitoring, remote care, and AI-supported analysis. According to the selection criteria, studies with weak methodology or limited clinical relevance were removed. Results: Continuous monitoring enables early detection of physiological changes, improves individualized prevention, reduces hospitalizations, and supports cost efficiency and the expansion of remote services. Artificial intelligence and multimodal analytics facilitate dynamic risk stratification, clinical decision support, and the development of cardiovascular digital twin models for precision medicine. Implementation remains constrained by requirements for robust validation, potential algorithmic bias, data protection and cybersecurity concerns, and regulatory or acceptance barriers. Conclusions: Digital cardiology enables anticipatory, patient-centered healthcare based on continuous monitoring and AI as core clinical tools, promoting integrated patient–hospital–home ecosystems, real-time therapeutic guidance, and sustained cardiovascular prevention. The priorities defined by these directions are subjects for further research and healthcare development worldwide in the next decades.

Keywords: digital health; cardiology; wearable devices; digital biomarkers; biometric sensors; artificial intelligence; telemonitoring; telemedicine platforms; predictive medicine.

INTRODUCTION

Cardiovascular diseases (CVDs) represent the leading cause of morbidity and mortality worldwide, generating a significant burden on healthcare systems. Traditional cardiology is confronted with significant limitations, such as delayed diagnosis, intermittent monitoring, and a predominantly reactive therapeutic approach. In this context, the emergence and integration of digital health technologies mark the transition toward predictive, personalized, and prevention-oriented cardiology. The aim of this article is to analyze the transformation of cardiology through the lens of digital technologies and their impact on the prevention, diagnosis, and management of cardiovascular diseases. Although the evolution of digital technologies in cardiovascular research is relatively recent, their clinical use has demonstrated relevant progress in morbidity and mortality among patients with CVD. From a research perspective, it is essential to understand the emergence of these technologies, their development pace, current themes of interest, and the field's temporal evolution [1].

Citation: Tudor SS, Ferțu ID, Dumitru CN, Vîlceleanu BV, Popescu AM, Dumitrescu SI, Munteanu AE. *Digital technologies in cardiology: From continuous monitoring to predictive medicine*. R. J. Mil. Med. 2026, CXXIX(3): 285-300
https://doi.org/10.55453/rjmm.2029.129.3.7

Academic Editor: Octavian Vasiliu

Received: 24 February 2026
Revised: 02 April 2026
Accepted: 10 April 2026

Technological advances in the diagnosis of cardiovascular diseases also represent a major public health strategy. Integrating these solutions into clinical practice enables

early detection and the initiation of personalized treatments, with the potential to significantly reduce CVD-associated morbidity and mortality. In addition, the use of telemedicine and telemonitoring contributes to resource optimization and improved access to high-quality medical care, representing an essential step in reducing the global burden of cardiovascular diseases [2]. The development of machine learning (ML) and digital health technologies is redefining the future of cardiovascular prevention. The ability of ML to extract meaningful information from complex medical datasets helps guide clinical decisions; however, this aspect must be balanced against challenges related to privacy, safety, equity, and clinical interpretability [3].

In the future era of digital health, the complex interplay among preventive medicine, primary, secondary, and tertiary prevention will be supported by genomics, artificial intelligence, bioengineering, wearable devices, and telemedicine. Combining these technologies supports a considerable potential of improving medical outcomes and the efficiency of healthcare systems [4]. Artificial intelligence in cardiology must progress beyond simple task automation and should focus on augmenting human clinical expertise, facilitating proactive cardiovascular care based on precision medicine. By leveraging computational advantages while managing its limitations, cardiology is advancing toward an era of transformative innovation beyond the limits of traditional diagnostic and therapeutic paradigms [5]. Systematic literature analyses show that current machine learning methods for diagnosing heart diseases face various challenges, for example, data imbalance, thus limiting their clinical applicability. Nevertheless, these approaches contribute to improving data-driven decision-making processes [6]. Other studies emphasize the critical role of artificial intelligence in rethinking diagnostic and treatment methods to improve patient outcomes [7], as well as emerging trends in supervised prediction algorithms that increase diagnostic accuracy and guide future research directions [8]. In the field of arrhythmia monitoring, long-term continuous ambulatory ECG monitors and external loop recorders have proven more effective than 24-hour Holter monitoring in detecting arrhythmic symptoms, with no significant differences between the two technologies [9]. Moreover, remote patient monitoring interventions can reduce the use of acute care services when designed according to patient characteristics, provider factors, and implementation context [10].

MATERIALS AND METHODS

Study design

The objective of this article is to examine the digital transformation of cardiology, a process that redefines traditional paradigms of diagnosis, monitoring, and treatment through the integration of connected devices, digital biomarkers, telemedicine, and artificial intelligence. The article included studies published between 2015 and 2026 that investigated: the global burden of cardiovascular diseases; the limitations of traditional cardiology (late diagnosis, discontinuous monitoring, reactive treatment); and the emergence and impact of digital health technologies.

Data sources and search strategy

Searches were performed in databases relevant to cardiology and digital technologies applied in cardiology: PubMed, ScienceDirect, and Google Scholar. Search strategies were adapted for each database and included combinations of frequently used field-specific terms connected by Boolean operators (AND, OR): digital health, cardiology, wearable devices, digital biomarkers, artificial intelligence, predictive medicine. Examples of search expressions used: “digital health AND cardiology”, “wearable devices AND cardiovascular disease”, “artificial intelligence AND cardiac diagnosis”, “digital biomarkers AND heart disease”.

Eligibility criteria

Studies were included if they met at least one of the following criteria: clinical, observational, meta-analytical, or review studies relevant to digital health in cardiology; studies evaluating wearable devices, telemedicine, digital biomarkers, or artificial intelligence applications in the prevention, diagnosis, or management of cardiovascular diseases; articles published in English or Romanian between 2015 and 2026. Excluded were: articles without full-text availability; studies not relevant to digital cardiology; duplicate publications or studies with insufficient data.

Study selection

Study selection was conducted in two stages, i.e., screening of titles and abstracts to assess relevance, then an eligibility assessment based on full-text review. Duplicates were removed prior to full-text analysis. A total of 81 studies were ultimately included. The selected studies were analyzed and thematically organized into the main domains of digital health applied in cardiology: wearable devices and continuous monitoring; digital biomarkers; telemedicine and remote management; artificial intelligence and predictive medicine.

RESULTS

1. Wearable devices

We analyze the role of these devices in the screening and remote diagnosis of common cardiovascular diseases, such as arrhythmias, as well as in the management of patients with existing cardiovascular conditions, for example, heart failure. Recent literature provides

a comprehensive overview of wearable devices (Table 1). To date, challenges such as device accuracy, clinical validity, the lack of standardized regulatory policies, and concerns regarding patient data privacy continue to limit the widespread adoption of smart wearable technologies in clinical practice. Recommendations for addressing these challenges are presented, along with a simple and practical "ABCD"-type guide tailored to physicians' specific needs, aimed at accelerating the integration of these devices into clinical workflows to optimize patient care [11].

This review synthesizes the characteristics of wearable devices and the associated machine learning techniques. Relevant research studies illustrating the role of these devices in the screening and management of cardiovascular conditions are described, while directions for future research are also identified. Finally, the challenges limiting the widespread use of wearable devices in cardiovascular medicine are highlighted, and short- and long-term solutions are proposed to facilitate their integration into clinical practice [12].

Wearable technology lies at the intersection of precision cardiovascular medicine, providing continuous, non-invasive, evidence-based data on patients' health status. The convergence of AI, the Internet of Medical Things (IoMT), and real-world data integration positions wearable devices as essential tools for risk stratification and remote management. Future directions should prioritize standardized validation frameworks, strengthened cybersecurity, and equitable global access to maximize clinical and population-level impact [13]. Recent data suggest that wearable electrocardiograms perform comparably to conventional monitoring devices and may help reduce healthcare costs. However, challenges related to accessibility, data privacy, and the need to improve accuracy persist. Additional studies are required to critically evaluate existing limitations, given the significant potential of these devices to improve cardiovascular and overall health [14].

Heart failure is a progressive condition associated with increased morbidity and mortality. Early diagnosis and treatment can reduce hospitalizations and readmissions and improve quality of life. Current developments in wearable technology have transformed heart failure management, but their clinical integration requires careful evaluation of technical, clinical, and ethical challenges, including performance, regulation, and data protection [15].

The literature indicates that when integrated with telemonitoring, wearable devices can increase physical activity participation, improving peak oxygen consumption (VO_2peak) and quality of life in patients with coronary artery disease; physical function and quality of life in patients with heart failure; and walking capacity in patients with peripheral artery disease. These devices can detect atrial fibrillation, guide exercise timing, and safely monitor exercise intensity in patients with implantable cardiac devices. Real-time feedback enhances motivation and adherence, amplifying the benefits of cardiovascular rehabilitation programs [16].

Devices such as Apple Watch Series 9, Fitbit Charge 6, Garmin vívosmart 5, and Oura Ring Gen3 have proven suitable for monitoring cardiovascular function in community-dwelling adults. The systematic selection approach can also be extended to other physiological and behavioral variables [17].

Algorithms based on smartwatches show a strong correlation with atrial fibrillation burden determined by implantable cardiac monitoring and high clinical sensitivity for detecting recurrences, outperforming conventional non-invasive strategies. These findings support their use as a scalable alternative for rhythm monitoring after ablation [18].

Available data indicate excellent diagnostic accuracy, suggesting that these devices may represent an appropriate and accessible option for patients [19]. They demonstrate high diagnostic performance for atrial fibrillation and ST-segment abnormalities, especially in supervised settings. However, inconclusive recordings and algorithmic limitations remain important barriers, requiring real-world validation and algorithm optimization [20].

Compared with traditional methods, smartwatches enable more efficient detection of recurrences, characterization of arrhythmic burden, symptom–rhythm correlation, and increased patient engagement. Nevertheless, limitations such as motion artifacts, false-positive alerts, dependence on adherence, and issues related to regulation, interoperability, and privacy persist. Integrating these technologies into evidence-guided care pathways could allow more proactive and personalized management of atrial fibrillation [21].

The integration of wearable technology into healthcare systems can be helpful in facilitating early diagnosis, patient engagement, and continuous monitoring of cardiac health. Despite ethical considerations and inequalities in access, the potential benefits outweigh the challenges. Increased awareness, interdisciplinary collaboration, and further research are needed to optimize accuracy and support the widespread adoption of these technologies [22].

Table 1: Scientific articles presenting studies on digital health in cardiology – Wearable devices

Focus / Application	Year	Author	Conclusions
Smart wearable devices in cardiovascular care (screening, remote diagnosis, management)	2021	Bayoumy K. [11]	Wearable devices can support remote detection and diagnosis of cardiovascular diseases, including arrhythmias, and monitoring of patients with existing cardiovascular disease, such as heart failure. Widespread adoption is limited by accuracy, clinical validity, uneven regulation, and privacy risks; structured integration into clinical workflows is needed.
Wearable devices in cardiovascular medicine (features, data analysis, research directions)	2023	Hughes A. [12]	Wearables, together with advanced data analytics and machine learning, have potential in cardiovascular screening and management. Barriers to large-scale use remain, including validation, interoperability, and digital equity, requiring both short- and long-term solutions.
Wearable technology for cardiovascular health monitoring and disease management (precision medicine)	2025	Nazir A. [13]	Wearable technology can provide continuous, noninvasive, clinically useful data, especially when combined with artificial intelligence, the medical Internet of Things, and real-world data. Standardized validation frameworks, improved cybersecurity, and equitable global access are required.
Wearable technology in cardiology: advances, applications, and perspectives	2025	Jena N. [14]	Electrocardiograms obtained with wearable devices may achieve performance comparable to conventional monitoring and reduce costs. Challenges persist in accessibility, privacy, and the need for improved accuracy; further critical evaluations are required to confirm benefits and define limitations.
Wearable devices for monitoring and management of heart failure	2024	Odeh V.A. [15]	Wearable technology may improve early diagnosis and management of heart failure, with potential to reduce hospitalizations and improve quality of life. Clinical integration requires addressing technical performance, regulatory requirements, and data privacy.
Wearable devices for exercise prescription and physical activity monitoring in patients with cardiovascular disease	2025	Terada T. [16]	Wearables, especially when combined with telemonitoring, can increase participation in physical activity and improve functional capacity and quality of life across multiple cardiovascular conditions. They may also help differentiate atrial fibrillation from sinus rhythm and safely monitor exercise intensity; effectiveness depends on consistent use and integration into care.
Practical guide for selecting wearable devices measuring cardiovascular functions in the general population	2025	Lu J.K. [17]	A systematic device-selection process, illustrated with commercial models, can identify suitable options for measuring cardiovascular function in community-dwelling adults. The method can be extended to other physiological and lifestyle variables.
Detection and estimation of atrial fibrillation burden after ablation using smartwatches compared with continuous implantable monitoring	2025	Aguilar M. [18]	Smartwatch algorithms may correlate well with atrial fibrillation burden measured by continuous implantable monitoring and detect recurrences with good clinical sensitivity. Findings support their use as a scalable alternative for post-ablation rhythm monitoring.
Accuracy of smartwatches in detecting atrial fibrillation (systematic review and diagnostic meta-analysis)	2025	Barrera N. [19]	Smartwatches may show very good diagnostic accuracy for atrial fibrillation detection and represent a suitable option for screening and monitoring, provided correct use and clinical confirmation when necessary.
Diagnostic accuracy of wearable electrocardiography for atrial fibrillation and ST-segment changes (systematic review)	2025	Sîngeap M.S. [20]	Wearable ECG devices can effectively detect atrial fibrillation and ST-segment abnormalities, especially in supervised settings. Inconclusive recordings and algorithm limitations remain barriers; real-world validation and algorithm improvements are needed.
Monitoring atrial fibrillation through wearable digital technologies: the role of smartwatches	2025	Stachteas P. [21]	Smartwatch monitoring may improve recurrence detection, AF burden estimation, symptom–rhythm correlation, and patient engagement. Limitations include motion artifacts, false-positive alerts, short recordings, reliance on adherence and digital literacy, access inequities, and regulatory, interoperability, and privacy issues; promising as a complement to established methods.
Applications of smartwatches in atrial fibrillation detection: present and future directions	2024	Vyas R. [22]	Integration of wearable technology may enable earlier diagnosis, better engagement, and improved cardiac monitoring. Institutional collaboration, accuracy optimization, and implementation support are required, with attention to ethical considerations and disparities.

2. Digital biomarkers

Heart rate variability (HRV) indicates autonomic regulation and has become a digital biomarker with improtant applications in both clinical care and operational performance. Recent literature provides a comprehensive overview of digital biomarkers (Table 2). Considering HRV as a dual-use tool enables the connection between the medical field and operational human performance: the same cardiac data that can anticipate clinical events in patients may also signal the risk of exhaustion or overload in high-stress professional contexts. However, optimal use of this biomarker requires continuous data collection, validated artificial intelligence algorithms, privacy protection, and clear usage guidelines. Under these conditions, HRV becomes not only a monitoring tool but also a practical and ethical support for decision-making in clinical and operational environments [23].

The coefficient of variation of heart rate variability (HRV-CV) serves as an indicator of daily cardiac autonomic fluctuations and has potential as a scalable digital biomarker for behavioral monitoring and health risk stratification. Measuring HRV-CV during sleep provides a robust estimate of daily HRV variability; an analysis of nearly two million recordings from more than 21,000 individuals demonstrated that five nights of monitoring are sufficient for reliable seven-day estimates. Higher HRV-CV values are associated with greater alcohol consumption, lower physical activity levels, reduced sleep duration and regularity, older age, and increased body mass index (BMI). These findings provide the first large-scale characterization of HRV-CV and support its utility for behavioral monitoring and risk stratification [24].

In recent years, clinical evidence regarding digital biomarkers has been systematically evaluated across a variety of populations, interventions, devices, and sensor technologies, with a predominance of physical activity measurements and cardiac monitoring. The classification of behavioral and physiological data using the World Health Organization's ICF framework has proven applicable for organizing the wide range of identified digital biomarkers. Determining the true clinical value of these biomarkers requires systematic assessment of the quality and consistency of evidence regarding their impact on health outcomes [25].

Telemetry units are useful for providing continuous monitoring of vital signs and electrocardiographic data, parameters that function as digital signatures of physiological status and may facilitate the detection of anomalies preceding cardiac arrest. The available data suggest that dynamic changes in vital signs may contribute to the prediction of in-hospital cardiac arrest. However, there is still no consensus regarding the optimal methods for analyzing these digital biomarkers, and large prospective studies are needed to validate their predictive value in clinical practice [26].

Table 2: Scientific articles presenting studies on digital health in cardiology – Digital biomarkers

Focus / Application	Year	Author	Conclusions
Heart rate variability as a dual-use digital biomarker (clinical and operational)	2026	Burlacu A. [23]	Heart rate variability reflects autonomic regulation and can function as a digital biomarker in both clinical care and the assessment of performance and resilience. Responsible use requires consistent data collection, trustworthy AI-based analysis, protection of privacy, and clear rules for ethical implementation.
Coefficient of variation of heart rate variability during sleep as a behavior-associated digital biomarker	2026	Grosicki G.J. [24]	The coefficient of variation of heart rate variability during sleep may be a scalable digital biomarker for monitoring behaviors and risk stratification. A small number of nights can provide reliable estimates, and higher values are associated with increased alcohol consumption, lower physical activity, shorter and less consistent sleep, older age, and higher body mass index.
Studies based on digital biomarkers: synthesis of systematic analyses (scoping review)	2022	Motahari-Nezhad H. [25]	Evidence on digital biomarkers is extensive and includes diverse populations, interventions, and sensors, with predominance of physical activity monitoring and cardiac parameters. Standardized data classification helps structure the field, but clinical value requires systematic evaluation of evidence quality and impact on health outcomes.
Prediction of cardiorespiratory arrest using digital biomarkers (systematic review)	2023	De Sario Velásquez G.D. [26]	Continuous monitoring of vital signs and electrocardiography can identify changes preceding cardiac arrest, suggesting predictive utility. There is no consensus on optimal analytical methods; rigorous large-scale prospective studies are needed to confirm predictive value.

3. Biometric sensors

Recent literature provides a comprehensive overview of biometric sensors (Table 3). CVDs are still among the leading causes of mortality worldwide, tehrefore long-term and real-time monitoring of cardiovascular parameters is essential for the early identification of abnormalities and the initiation of interventions at the optimal moment. In this context, research interest has shifted toward developing flexible, wearable, or implantable sensors capable of continuously recording relevant physiological indicators. Among the available categories, mechanical sensors can directly reflect pressure fluctuations in the heart and blood vessels, offering high sensitivity and versatility. Four major classes of mechanical sensors—capacitive, piezoresistive, piezoelectric, and triboelectric—are described as recent developments for cardiovascular monitoring. Relevant biomechanical phenomena (e.g., arterial and endocardial pressure, pulse wave, and heart rhythm) and associated monitoring methods are also presented. Finally, the usefulness of continuous monitoring in the management of vascular diseases and the barriers to its translation into clinical practice are discussed [27].

Continuous monitoring of cardiovascular parameters can facilitate early detection of clinical deterioration and timely intervention. The development of flexible wearable/implantable sensors has accelerated, and mechanical sensors have emerged due to their ability to capture pressure variations within the cardiovascular system, combining high sensitivity with adequate flexibility for prolonged use. The paper synthesizes recent advances in sensors based on capacitive, piezoresistive, piezoelectric, and triboelectric principles, as well as the physical-mechanical mechanisms that can be monitored (pulse wave, blood pressure, heart rhythm, endocardial pressure). Challenges related to clinical implementation and the importance of real-time monitoring in the treatment of cardiovascular diseases are also highlighted [28].

Continuous blood pressure (BP) monitoring is highly relevant for real-time surveillance and early prevention of cardiovascular diseases. Wearable devices intended for BP monitoring have advanced significantly through adaptations to long-term wearability and improved comfort, but their development remains constrained by challenges such as motion artifacts and insufficient dynamic response. Methods based on pulse transit time, which combine photoplethysmographic (PPG) signals with electrocardiography (ECG), have attracted attention due to their potential for high accuracy and superior dynamic response [29].

Table 3: Scientific articles presenting studies on digital health in cardiology – Biometric sensors

Focus/application	Year	Author	Conclusions
Biomechanical detection systems for monitoring cardiac activity	2022	Owida H.A. [27]	Flexible wearable or implantable sensors can enable continuous, real-time cardiovascular monitoring, such as pressure, pulse wave, and heart rate, with potential for early intervention. There are advantages in accuracy and versatility, but translation into clinical practice remains difficult due to technical and implementation challenges.
Mechanical sensors for cardiovascular monitoring: from battery-powered to self-powered	2022	Tang C. [28]	Flexible mechanical sensors can directly reflect pressure fluctuations in the cardiovascular system and support long-term monitoring. Self-powered solutions are promising; however, challenges remain for clinical use and integration into real-time physiological monitoring.
Continuous wearable blood pressure monitoring based on pulse transit time and pulse arrival time (review)	2023	Zhou Z.B. [29]	Continuous blood pressure monitoring with wearable devices is advancing, and methods combining photoplethysmographic signals with electrocardiography can provide good dynamic response and accuracy. Nevertheless, motion noise and response limitations remain major issues; improvements are needed for reliable daily use.

4. Telemonitoring and telemedicine platforms

Telemedicine can facilitate the timely delivery of preventive interventions, potentially reducing cardiovascular morbidity and mortality. Recent literature provides a comprehensive overview of telemonitoring and telemedicine platforms (Table 4). The virtual implementation of prevention may help reduce pressure on hospitals by decreasing the incidence of acute cardiovascular events and limiting unnecessary presentations to medical facilities. Telemedicine platforms enable periodic check-ups, monitoring, and early interventions, supporting the prevention of acute events and slowing the progression of cardiovascular diseases [30]. The use of telehealth is increasing at multiple levels of healthcare systems; however, integration into primary care remains uneven. The paper synthesizes the characteristics, approaches, and dimensions of telehealth in this context, highlighting that it can support a wide range of activities through broadly accessible communication channels. Due to the opportunistic use of existing devices and platforms, telehealth can be scaled nationally and internationally. Nevertheless, technical, organizational, and human barriers persist; in particular, digital equity (access to technology and digital health literacy) is critical for extending services to underserved populations [31].

Telemedicine, defined as the provision of clinical services at a distance through digital technologies, is an important direction of research in contemporary cardiology. Follow-up consultations conducted via health applications can improve efficiency and adherence, reducing missed appointments and facilitating monitoring. Implementation requires adequate infrastructure (high-quality audio-video, document management, and payment solutions), as well as patient engagement in transmitting relevant information. However, telemedicine complements rather than replaces the physical consultation. Its usefulness has been highlighted especially in contexts with limited access to services, including during public health crises [32]. The use of telehealth for hypertension and cardiovascular diseases has increased, particularly during the COVID-19 pandemic [33]. The analyzed interventions targeted patients with hypertension, heart failure, and stroke and frequently employed team-based care models (physicians, nurses, pharmacists, and other professionals). Results suggest that telemedicine is generally comparable to traditional face-to-face care for blood pressure control and cardiovascular disease management, functioning as an extension of care for certain patient groups. It may also support communication, engagement, and monitoring outside the clinical setting [34].

Heart failure remains a major public health issue, and remote monitoring and telemedicine can support personalized interventions, including through the integration of artificial intelligence and machine learning. The need for continuous innovation, interdisciplinary collaboration, and strategic investment is emphasized to harness the transformative potential of these solutions toward patient-centered care and efficient resource use [35].

Evidence from randomized trials and meta-analyses indicates that telemedicine can improve the implementation of guideline-directed therapy, reduce hospitalizations, increase patient engagement, and, in some contexts, reduce mortality. Remote monitoring of vital signs, symptoms, and treatment adherence can enable early detection of clinical deterioration and intervention before decompensation, but barriers must also be considered, e.g., technological limitations, reimbursement challenges, gaps in digital literacy, and integration into clinical workflows. Future directions in this field must be focused on standardized guidelines, patient-centered design, and hybrid models (virtual plus face-to-face) [36]. Internet-based remote monitoring systems can facilitate rapid responses to emergencies, reduce resource utilization, and improve clinical outcomes in the management of chronic diseases. Strategies that combine automated data collection, patient self-reporting, and personalized communication are recommended to overcome obstacles to sustained behavioral change and quality-of-life improvement [37].

Analyses indicate improvements in outcomes, access, and patient satisfaction—especially in chronic disease management—through reduced geographic barriers and increased engagement, and, similarly, comprehensive evaluations show a favorable impact on clinical outcomes, cost savings, and higher satisfaction levels, suggesting transformative potential for healthcare delivery [38,39]. Telemedicine may be able to improve the accessibility of specialized cardiology care, including in rural and underserved areas, facilitating cardiac rehabilitation and reducing health disparities [40]. As technology advances, the role of telemedicine in cardiology is expected to grow, influencing efficiency, costs, and patient management; at the same time, implementation and regulatory challenges remain relevant [40]. Digital health tools can improve access to care and outcomes in rural populations through teleconsultations, remote monitoring, mobile applications, and wearable devices. Major barriers remain limited connectivity and low familiarity with digital technologies—issues that must be addressed to ensure equitable access and sustainable implementation [41].

Table 4: Scientific articles presenting studies on digital health in cardiology – Telemonitoring and telemedicine platforms

Focus / Application	Year	Author	Conclusions
Telemedicine in personalized prevention of cardiovascular diseases (systematic review)	2021	Battineni G. [30]	Telemedicine can facilitate cardiovascular prevention through timely interventions, with the potential to reduce morbidity and mortality and decrease pressure on hospitals. It can support regular check-ups and prevent disease progression, reducing unnecessary visits.
Telehealth in primary health care (scoping review)	2022	Beheshti L. [31]	Telehealth can be implemented in primary care using existing communication channels and can provide scalable services. Technical, organizational, and human barriers exist, and digital equity—through access and online health literacy—is essential for expansion to underserved populations.
Telemedicine: capabilities, characteristics, barriers, and applications	2021	Haleem A. [32]	Telemedicine can improve efficiency and continuity of care through audio-video consultations and management systems. It does not replace the physical consultation and remains a complementary tool, especially useful when access to medical services is limited, such as during epidemic contexts.
Telehealth for cardiovascular disease and hypertension (systematic review and meta-analysis, 2011–2021)	2023	Jackson T.N. [34]	Telehealth interventions for hypertension, heart failure, and stroke are often team-based and can be comparable to face-to-face care for blood pressure control. They may improve communication, patient engagement, and monitoring outside the clinic.
Remote monitoring and telemedicine in heart failure management	2024	Liu J.C. [35]	Heart failure management can benefit from remote monitoring and telemedicine, including personalized interventions supported by artificial intelligence and machine learning. Interdisciplinary

			collaboration and investment are required for integration into patient-centered care.
Telemedicine in heart failure treatment: evidence, limitations, and directions	2025	Choi D.J. [36]	Telemedicine interventions can improve guideline-directed therapy use, reduce hospitalizations, and increase patient engagement, with a possible mortality-reducing effect. Barriers include technological limitations, reimbursement, digital literacy, and workflow integration; hybrid models and standardized guidelines are recommended.
Internet-based remote monitoring for chronic diseases in Asia (systematic review)	2025	Emaliyawati E. [37]	Internet-based remote monitoring can reduce healthcare utilization and improve clinical outcomes in chronic diseases. For sustainable effects, combining automated data collection with patient reporting and personalized communication is important, addressing behavioral-change challenges.
Telemedicine: outcomes and access to care (systematic review)	2024	Ezeamii V.C. [38]	Telemedicine can increase access and patient satisfaction and improve outcomes in chronic diseases. Implementation should pursue equity and integration into patient-centered care.
Impact of telemedicine and remote patient monitoring on care delivery (comprehensive evaluation)	2024	Vudathaneni V.K.P. [39]	Improvements in patient outcomes, cost savings, and increased satisfaction are reported. Telemedicine and remote monitoring can transform care delivery if coherently integrated into health systems.
Telemedicine in cardiology: access to care and patient outcomes	2024	Tolu-Akinnawo O. [40]	Telemedicine can improve access to specialized cardiology care, including in rural settings, and can support cardiac rehabilitation, reducing disparities. Implementation and standardization challenges must be addressed.
Digital solutions for reducing care gaps in rural areas (scoping review)	2024	Maita K.C. [41]	Digital tools such as teleconsultations, remote monitoring, mobile applications, and wearable devices can improve access and outcomes in rural areas. Limited internet connectivity and low technological familiarity are major barriers that must be addressed to ensure equity.

5. Artificial Intelligence

Artificial intelligence and ML are increasingly influencing cardiovascular medicine by providing tools for predictive modeling, diagnosis, risk stratification, and decision support (Table 5). Relevant concepts in cardiology are discussed (e.g., feature selection and common methodological errors), along with supervised learning algorithms and their current applications, as well as the role of deep learning and unsupervised methods in analyzing complex data. Overall, AI is capable of contributing to precision cardiology and improved clinical outcomes, although integration into routine practice remains limited [42]. Despite advances in diagnosis and treatment, cardiovascular diseases remain a leading cause of morbidity and mortality. AI has the potential to transform cardiology practice, particularly in medical imaging and the interpretation of complex datasets, by supporting clinical decision-making and extracting clinically relevant information. Integration with digital communication technologies may enable home-based care models for elderly and chronically ill patients, reducing hospitalizations and improving quality of life. Reviews highlight the potential of AI in both imaging and clinical practice, as well as the need to address limitations and ethical considerations [43].

AI can support the prediction of cardiovascular outcomes, the noninvasive diagnosis of coronary artery disease, the detection of arrhythmias via wearable devices, and the optimization of heart failure management. The development of IoT and precision medicine is accelerating their integration. However, ethical and real-world implementation concerns remain, requiring robust governance frameworks and clinical validation [44]. AI is integrated into clinical decision support systems (CDSS) using either rule-based approaches or data-derived ML models. Techniques such as artificial neural networks and support vector machines have evolved, and increased computational power has enabled the development of deep neural networks (DNNs). Despite their promise, the current impact on clinical practice is still moderate; however, the rapid expansion of the literature suggests an increasingly important role in the field [45]. Methodological reviews describe AI workflows, common algorithms for regression and classification, and performance metrics. The role of explainable artificial intelligence (XAI) in enhancing model transparency and trust is emphasized. Applications in cardiology involving supervised learning, unsupervised learning, reinforcement learning, and natural language processing are reviewed, highlighting the need for legal, ethical, and methodological requirements for clinical implementation [46].

AI and ML can improve diagnostic accuracy, risk prediction, workflow efficiency, and resource utilization. Applications in imaging, major categories of cardiovascular diseases, clinical research, and outcome prediction are summarized, along with discussions of the algorithms and methodologies used. Nevertheless, limitations persist regarding generalizability, data quality, bias, interpretability, and integration into clinical processes [47]. In cardiovascular medicine, the main objectives of AI include optimizing care, increasing efficiency, and improving clinical outcomes in the context of expanding data sources and therapeutic advances. Editorials highlight research priorities and the need for concrete steps toward responsible clinical implementation [48].

Narrative syntheses show that AI models have been widely applied to ECG and imaging data (echocardiography, coronary angiography, cardiac CT, and cardiac MRI), targeting diagnosis and risk stratification for multiple pathologies (e.g., coronary artery

disease, cardiomyopathies, arrhythmias, and valvular diseases). Overall, the integration of AI promises significant advances in diagnosis and treatment, provided that clinical validation and ethical implementation are ensured [49].

Table 5: Scientific articles presenting studies on digital health in cardiology – Artificial intelligence

Focus / Application	Year	Author	Conclusions
Artificial intelligence in cardiology: framework for clinicians and applications	2018	Johnson K.W. [42]	Artificial intelligence and machine learning can influence prediction, diagnosis, and decision support in cardiology. Proper application requires solid predictive modeling principles, avoidance of methodological errors, and careful integration of advanced methods for precision cardiology.
Artificial intelligence and cardiovascular diseases: applications and role in practice	2020	Romiti S. [43]	Artificial intelligence can improve data interpretation and clinical decision-making, especially in imaging, by leveraging large data volumes. Digital technologies may support home care for elderly and chronically ill patients, reducing hospitalizations and improving quality of life.
Artificial intelligence in cardiology: current utility and perspectives	2022	Karatzia L. [44]	AI models can support outcome prediction, noninvasive diagnosis, arrhythmia detection via wearable devices, and heart failure management. Ethical dilemmas and real-world implementation challenges remain.
Artificial intelligence in cardiology: current status (narrative review)	2022	Koulaouzidis G. [45]	AI is important in clinical decision support systems and is rapidly advancing due to computational power and deep learning. Although routine clinical impact is still limited, applications are expanding and suggest increasing integration into cardiology.
Artificial intelligence technologies in cardiology: algorithms, evaluation, and explainable AI	2023	Ledziński Ł. [46]	Safe adoption requires understanding workflow, selecting appropriate algorithms, rigorous performance evaluation, and the use of explainable methods. Clear legal, ethical, and methodological requirements are needed for medical implementation.
Artificial intelligence in cardiovascular diseases: clinical applications, models, and limitations	2025	Chowdhury M.A. [47]	AI can increase diagnostic accuracy, disease prediction, workflow efficiency, and resource utilization in cardiovascular diseases. Real impact requires validation, clinical integration, and management of limitations to reduce errors and improve monitoring and decision-making.
Role of artificial intelligence in cardiology (editorial)	2023	Vidal-Pérez R. [48]	Major objectives include optimizing care, increasing efficiency, and improving clinical outcomes. The field benefits from large data volumes and technological advances, but implementation must be responsible and guided by clear research priorities.
Future horizons for artificial intelligence in cardiology (narrative review)	2024	Patrascanu O.S. [49]	AI models applied to electrocardiography, echocardiography, coronary angiography, computed tomography, and cardiac magnetic resonance can improve diagnosis and risk assessment for many cardiovascular diseases. Integration promises benefits, provided rigorous validation and safe implementation.

DISCUSSION

1. Continuous digital cardiovascular monitoring

The transition from episodic monitoring toward continuous, discreet surveillance is integrated into everyday life.

The digitalization of cardiovascular monitoring has accelerated a shift in the clinical paradigm—from point-in-time ("snapshot") assessments to longitudinal monitoring capable of capturing rare, intermittent, or asymptomatic events. In this context, wearable and implantable devices, along with contactless solutions, are shaping an "invisible" clinical surveillance infrastructure with the potential for early detection, dynamic risk stratification, and timely intervention.

Wearable devices and portable sensors

Electrocardiography (ECG) remains the reference tool for evaluating cardiac electrical activity, and the 12-lead ECG is the diagnostic standard for multiple non-arrhythmic pathologies. However, the technical complexity of acquisition and reliance on trained personnel limit its use outside medical settings. Portable ECG devices and remote monitoring solutions have sought to reduce this gap through simplified acquisition (typically single-lead), facilitating self-monitoring and extending surveillance into ambulatory environments.

An analysis of studies conducted on commercially available devices validated in adult populations and approved by the FDA indicates that reduced-lead ECG devices have significant potential for long-term monitoring, especially when combined with real-time alert mechanisms. Their clinical utility is particularly relevant for identifying abnormal rhythms, with evidence suggesting that certain remote devices may surpass conventional ECG in diagnosing specific arrhythmias, such as atrial fibrillation. Despite these advantages,

limitations persist regarding signal quality, device reliability, and the relatively small number of robust clinical studies evaluating their impact on therapeutic decision-making and clinical outcomes [50].

In parallel, smartwatches have evolved into multifunctional platforms with medical applications that can be grouped into three domains: monitoring, nudging, and prediction. Monitoring refers to the integration of data into medical management; nudging involves individual use aimed at behavior change; and prediction leverages aggregated data to train machine-learning algorithms to anticipate health outcomes. The literature highlights the potential of these devices within value-based medicine, while also emphasizing the need for more nuanced discussions regarding validation, clinical use, and the ethical implications of predictions generated from population-level data [51].

Implantable devices and ECG patches

Wireless transmission and ECG digitalization have facilitated the implementation of continuous monitoring strategies, with a major impact on the diagnosis and management of dysrhythmias. Implantable loop recorders (ILRs) represent a technologically mature option for long-term monitoring, with increasingly well-defined indications (e.g., unexplained syncope, suspected paroxysmal arrhythmias, post-event monitoring). Recent analyses highlight device progress and development directions, including optimization of detection algorithms and integration into clinical telemonitoring workflows [52].

In populations at risk of developing atrial fibrillation after specific interventions, ILR may overcome the limitations of prolonged external monitoring, which is often impractical. For example, in patients with atrial flutter undergoing cavotricuspid isthmus ablation, long-term ECG monitoring may reveal the onset of new atrial fibrillation, frequently within the first months after the procedure; ILR thus becomes a realistic solution for continuous surveillance, with implications for thromboembolic event prevention and therapy adjustment [53].

In cryptogenic stroke, underdiagnosed atrial fibrillation remains a major clinical issue. Evidence indicates that extended monitoring can increase detection rates, yet many studies present significant “gaps” in monitoring intervals, especially immediately after the index event. In addition to ILR, noninvasive strategies such as external loop recorders (ELR) and mobile cardiac outpatient telemetry (MCOT) are used; however, the relative role of wearable devices and “smart” monitoring in prevention remains insufficiently clarified. A synthesis of the evidence underscores the need for more precise recommendations regarding patient selection for each technology and for studies that reduce existing methodological gaps [54].

Contactless monitoring

Contactless monitoring, particularly during sleep, addresses a clinical and operational need: reducing the intrusiveness of polysomnography (PSG) and extending evaluation into non-hospital environments. A systematic review of contactless technologies describes a variety of sensors and systems (e.g., radar, temperature sensors, motion sensors, video cameras) capable of estimating cardiorespiratory parameters with minimal patient impact. Additionally, advantages and limitations related to accuracy, robustness to artifacts, and implementation conditions in clinical or home environments are identified [55].

Radars for vital sign detection offer distinct benefits: elimination of electrodes, freedom of movement, reduction of skin irritation, and facilitated patient access (particularly relevant in children and older adults). However, broad clinical acceptance depends on overcoming technical and validation barriers, especially regarding signal reliability under real-world conditions [56]. In the same direction, the use of IR-UWB radar for measuring multiscale cardiac motion proposes a contactless alternative for rapid and potentially accurate assessment, with promising applications in online monitoring and home care [57].

Video photoplethysmography (vPPG/rPPG/iPPG) represents another emerging direction. However, blood pressure estimation via vPPG is limited by low signal-to-noise ratio and variability in the correlation between pulse transit time and blood pressure, with performance dependent on method and analyzed region of interest (e.g., facial regions vs. hand) [58]. By comparison, evaluation of pulse frequency characteristics and variability through iPPG indicates that certain methods (such as POS and CHROM) may be more robust to motion and illumination artifacts, supporting the clinical potential of these systems for assessing autonomic nervous system dynamics, including through derived indicators (e.g., Poincaré maps) [59].

Continuous cardiovascular monitoring is emerging as a next-generation clinical infrastructure, but its large-scale implementation requires standardization, real-world validation, interoperability, and responsible integration into clinical workflows.

2. Artificial Intelligence in Cardiology

Cardiology is becoming anticipatory, personalized, and decision-oriented, not merely diagnostic.

AI is transforming cardiology through its ability to integrate large volumes of data (ECG, imaging, clinical data, sensors) and generate inferences that support clinical decisions. Beyond algorithmic performance, the critical challenges remain interpretability, generalization across diverse populations, bias control, and evaluation of real clinical impact.

ECG analysis through Deep Learning

Advances from 2017–2023 show a substantial increase in performance in arrhythmia detection and classification, with deep learning models frequently outperforming classical ML approaches. Various architectures are used (CNNs, RNNs, transformers, hybrid models), and the literature highlights both improved accuracy and the need for methodological guidelines regarding comparability, dataset selection, and external validation [60–62].

Recent directions include computationally efficient models adapted to resource-limited devices such as wearable monitors. For example, a lightweight 1D architecture based on ConvNeXtV2 demonstrated high performance in detecting atrial fibrillation and atrial flutter from single-lead ECG, while maintaining low computational cost and offering interpretability elements through Grad-CAM visualizations (attention to P-wave morphology and RR irregularities) [63].

AI in cardiac imaging

AI is increasingly applied in cardiovascular CT and MRI, with reported benefits for workflow (acquisition/post-processing time), image quality, and diagnostic accuracy. Applications include automated calcium scoring, stenosis quantification, plaque analysis, segmentation, and volumetric quantification, as well as myocardial tissue characterization [64,65].

In low- and middle-income countries, AI may facilitate task-shifting to less experienced operators; however, implementation depends on dataset diversity, infrastructure, governance, and ethical frameworks. Available reviews emphasize the need for multicenter data sharing, training, and interoperability standards [66]. A complementary direction is explainable AI (XAI), necessary to increase trust and clinical integration; however, XAI evaluation remains predominantly qualitative and insufficiently standardized [67].

Fusion modeling (clinical data + imaging) indicates prognostic improvements compared with traditional scores, but requires automated feature extraction from electronic health records and images—using CNNs and NLP—to become feasible in practice [68].

Clinical decision support systems

AI-based clinical decision support systems (CDSS) are considered a major direction for improving decision quality and patient outcomes. The literature highlights both applications (assisted diagnosis, personalized therapeutic recommendations, risk prediction, clinical documentation) and barriers: interpretability, bias, workflow integration, accountability, and medico-legal aspects [69].

Proof-of-concept studies show the possibility of predicting ischemic events over short time windows with accuracies >80% and potential for proactive intervention; however, translation into clinical implementation requires external validation, assessment of clinical benefit, and error analysis [70]. An important conceptual shift is the transition from “prediction” to patient-centered decision intelligence through multimodal integration (clinical notes, wearables, social determinants, environmental factors) and the provision of actionable, explainable, and context-sensitive recommendations [71].

3. From digital medicine to predictive medicine

Cardiology is evolving toward an anticipatory and personalized model based on dynamic risk and multimodal data.

Personalized risk models

Risk models increasingly guide clinical decisions, including in heart failure and cardiomyopathies. For example, in heart failure with preserved ejection fraction, a model using widely available variables can identify patients at high risk of sudden cardiac death, supporting stratification and differentiated monitoring [72].

In primary cardiomyopathies, risk assessment requires a multiparametric, stepwise approach that integrates clinical evaluation, ECG monitoring, multimodal imaging, genetics, and electroanatomical mapping, with implications for ablation and ICD indication [73,74]. In addition, the limitations of static models and surrogate criteria (e.g., appropriate ICD therapy), which may overestimate “true” risk and lead to unnecessary interventions, are emphasized; thus, dynamic models and disease-specific endpoints are needed [74,75]. The integration of machine learning in predicting mode of death and risk stratification, including in advanced imaging contexts, supports the shift toward individualized assessment; however, robustness, transparency, and clinical validation remain essential conditions [74,76].

Digital biomarkers and precision cardiology

Digital biomarkers (derived from sensors, wearables, and implantable devices) extend clinical observation beyond the hospital and may support therapeutic decisions. A synthesis of meta-analyses indicates evidence of variable quality: some interventions based on digital biomarkers are associated with meaningful improvements (including arrhythmia detection and reduced stroke incidence in certain contexts), yet reporting quality is often low. Rigorous use of AMSTAR-2 and GRADE tools is recommended to strengthen the evidence base [77].

Scoping reviews show rapid expansion of the field but also a lack of uniform operational definitions and standards for integrating digital biomarkers into practice, highlighting the need to map evidence across clinical domains and identify gaps [25]. Heart rate

variability (HRV) is an example of a digital biomarker with clinical and operational utility, but effective implementation depends on standardized acquisition, context-dependent interpretation, and environment-specific validation [23].

The cardiovascular digital twin

The concept of the cardiac digital twin promises a personalized in silico representation, dynamically updated with clinical and monitoring data, capable of simulating disease progression and treatment response. In precision cardiology, cardiac digital twins are explored, especially in rhythm disorders, with potential support for procedural planning and individualized predictions [78].

Integration of multimodal data into mechanistic and statistical models, amplified by the development of AI (including generative AI), may enable more dynamic simulations and real-time recommendations. However, major challenges remain regarding model personalization, clinical validation, computational resources, interoperability, and ethical governance [79,80].

In atrial fibrillation, atrial digital twins (particularly of the left atrium) can integrate structural, electrophysiological, and hemodynamic data to simulate arrhythmia behavior, therapeutic response, and thromboembolic risk. Applications include stroke risk prediction through computational fluid dynamics, in silico testing of antiarrhythmics, and virtual ablation planning. Nevertheless, scalability and prospective validation remain prerequisites for clinical translation [81]. Along the same line, virtual testing of amiodarone guided by a digital twin suggests the possibility of pre-estimating efficacy in high-risk post-ablation patients, opening a promising direction for precision therapy [82].

Overall, the discussed data support a convergent transition toward predictive cardiology, in which continuous monitoring (wearable, implantable, contactless), digital biomarkers, and AI are integrated into secure clinical ecosystems. However, large-scale translation depends on: (1) prospective validation in real-world conditions, (2) methodological standardization, (3) interoperability and integration into clinical workflows, (4) data explainability and ethical governance, and (5) digital equity, ensuring that benefits are distributed without amplifying disparities.

Clinical benefits and impact on the healthcare system

The integration of digital technologies in cardiology generates significant clinical benefits, with a direct impact on patient outcomes and the organization of healthcare systems. Continuous monitoring of physiological parameters enables early diagnosis and timely identification of clinical deterioration, facilitating rapid intervention and reducing the risk of severe complications. At the same time, longitudinal analysis of individual data supports personalized prevention through dynamic risk stratification and adaptation of therapeutic interventions to each patient's profile. The implementation of remote monitoring and early warning systems contributes to the reduction of hospitalizations and readmissions, particularly in heart failure, where early interventions can prevent decompensation. Moreover, telemedicine and remote care expand access to specialized services, improve continuity of care, and optimize interdisciplinary coordination. From a systemic perspective, these transformations may lead to economic efficiency by decreasing costs associated with avoidable hospital admissions and reallocating resources toward high-risk patients.

4. Limitations, risks, and ethical challenges

Despite its transformative potential, digital cardiology faces important limitations. A major concern is the insufficient clinical validation of some artificial intelligence algorithms, often developed on limited or non-representative datasets, which raises questions about the generalizability of results. At the same time, algorithmic bias may amplify existing inequalities among different population groups, highlighting the need for explicit equity strategies and performance auditing. Data protection and cybersecurity become essential in a context characterized by the continuous collection of sensitive information. Massive data flows may also generate informational overload for clinicians, increasing the risk of alarm fatigue and reducing decision-making efficiency. At the institutional level, regulatory and clinical responsibility challenges persist, including approval processes by authorities such as the FDA and EMA. Finally, patient acceptance—shaped by digital literacy, trust, and privacy concerns—remains a critical determinant of real-world implementation.

5. Future directions

The evolution of digital cardiology indicates a transition toward deeply integrated and predictive models of care. The development of continuous AI-guided cardiovascular prevention is emerging, based on dynamic, real-time risk assessment. In parallel, the integration of the digital twin concept promises personalized simulation of disease progression and treatment response, opening new perspectives for precision medicine. Another emerging field is real-time algorithm-guided therapies supported by continuous monitoring and adaptive predictive models. In interventional cardiology, augmented reality may improve procedural precision and the planning of complex interventions. At the macro-systemic level, the future belongs to integrated digital ecosystems linking patient–hospital–home, characterized by interoperability, data continuity, and hybrid models of care.

CONCLUSION

Digital cardiology is undergoing a profound transformation driven by the convergence of connected devices, digital biomarkers, telemedicine, and artificial intelligence. This evolution marks the shift from episodic monitoring to predictive and personalized medicine, with major potential to improve early diagnosis, prevention, and the efficiency of healthcare systems. However, sustainable implementation requires rigorous clinical validation, clear regulatory frameworks, ethical data governance, and true integration into clinical workflows. In this context, technology does not replace medical judgment but becomes the central infrastructure of the cardiology of the future—an anticipatory, connected, and deeply patient-centered cardiology.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

This research received no external funding.

Authors' contribution

Conceptualization, S.S.T, I.D.F. ; methodology, I.D.F., C.N.D. ; resources, B-V.V., C.N.D.; writing—original draft preparation, S.S.T, I.D.F., B-V.V.; writing—review and editing, S.I.D., A.E.M. ; supervision, S.I.D., A.E.M.. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

Generative AI was used for grammar revision and stylistic polishing, as the authors are non-native English speakers.

Ethics approval and consent to participate

Not applicable.

References

1. Zwack CC, Haghani M, Hollings M, Zhang L, Gauci S, Gallagher R, Redfern J. The evolution of digital health technologies in cardiovascular disease research. NPJ Digit Med. 2023;6(1):1. doi:10.1038/s41746-022-00734-2.

2. Restrepo Tique M, Araque O, Sánchez-Echeverri LA. Technological Advances in the Diagnosis of Cardiovascular Disease: A Public Health Strategy. Int J Environ Res Public Health. 2024;21(8):1083. doi: 10.3390/ijerph21081083.

3. Javaid A, Zghyer F, Kim C, Spaulding EM, Isakadze N, Ding J, Kargillis D, Gao Y, Rahman F, Brown DE, Saria S, Martin SS, Kramer CM, Blumenthal RS, Marvel FA. Medicine 2032: The future of cardiovascular disease prevention with machine learning and digital health technology. Am J Prev Cardiol. 2022;12:100379. doi: 10.1016/j.ajpc.2022.

4. De la Torre K, Min S, Lee H, Kang D. The Application of Preventive Medicine in the Future Digital Health Era. J Med Internet Res. 2025;27:e59165. doi: 10.2196/59165.

5. Pantelidis P, Dilaveris P, Ruipérez-Campillo S, Goliopoulou A, Giannakodimos A, Theofilis P, De Lucia R, Katsarou O, Zisimos K, Kalogeras K, Oikonomou E, Siasos G. Hearts, Data, and Artificial Intelligence Wizardry: From Imitation to Innovation in Cardiovascular Care. Biomedicines. 2025;13(5):1019. doi: 10.3390/biomedicines13051019.

6. Ahsan MM, Siddique Z. Machine learning-based heart disease diagnosis: A systematic literature review. Artif Intell Med. 2022;128:102289. doi: 10.1016/j.artmed.2022.102289.

7. Gunjal A, Judgi T. A comprehensive survey of artificial intelligence methods for cardiovascular disease detection: Recent advances and future challenges. MethodsX. 2025;15:103678. doi: 10.1016/j.mex.2025.103678.

8. Mao Y, Jimma BL, Mihretie TB. Machine learning algorithms for heart disease diagnosis: A systematic review. Curr Probl Cardiol. 2025;50(8):103082. doi: 10.1016/j.cpcardiol.2025.103082.

9. Health Quality Ontario. Long-Term Continuous Ambulatory ECG Monitors and External Cardiac Loop Recorders for Cardiac Arrhythmia: A Health Technology Assessment. Ont Health Technol Assess Ser. 2017;17(1):1-56.

10. Thomas EE, Taylor ML, Banbury A, Snoswell CL, Haydon HM, Gallegos Rejas VM, Smith AC, Caffery LJ. Factors influencing the effectiveness of remote patient monitoring interventions: a realist review. BMJ Open. 2021;11(8):e051844. doi: 10.1136/bmjopen-2021-051844.

11. Bayoumy K, Gaber M, Elshafeey A, Mhaimeed O, Dineen EH, Marvel FA, Martin SS, Muse ED, Turakhia MP, Tarakji KG, Elshazly MB. Smart wearable devices in cardiovascular care: where we are and how to move forward. Nat Rev Cardiol. 2021;18(8):581-599. doi: 10.1038/s41569-021-00522-7.

12. Hughes A, Shandhi MMH, Master H, Dunn J, Brittain E. Wearable Devices in Cardiovascular Medicine. Circ Res. 2023;132(5):652-670. doi: 10.1161/CIRCRESAHA.122.322389.

13. Nazir A, Nazir A, Shah Wali Jamal M, Sadiq SUR, Aman S, Mustapha MJ, Lawal SO, AbdulKareem MO, Bamigbola MF. Wearable Technology and Its Potential Role in Cardiovascular Health Monitoring and Disease Management. Health Sci Rep. 2025;8(11):e71486. doi: 10.1002/hsr2.71486.

14. Jena N, Singh P, Chandramohan D, Garapati HN, Gummadi J, Mylavarapu M, Shaik BF, Nanjundappa A, Apala DR, Toquica C, Lapsiwala B, Simhadri PK. Wearable Technology in Cardiology: Advancements, Applications, and Future Prospects. Rev Cardiovasc Med. 2025;26(6):39025. doi: 10.31083/RCM39025.

15. Odeh VA, Chen Y, Wang W, Ding X. Recent Advances in the Wearable Devices for Monitoring and Management of Heart Failure. Rev Cardiovasc Med. 2024;25(10):386. doi: 10.31083/j.rcm2510386.

16. Terada T, Hausen M, Way KL, O'Neill CD, Marçal IR, Dorian P, Reed JL. Wearable Devices for Exercise Prescription and Physical Activity Monitoring

in Patients with Various Cardiovascular Conditions. CJC Open. 2025;7(5):695-706. doi: 10.1016/j.cjco.2025.02.017.

17. Lu JK, Wang W, Goh J, Maier AB. Selecting Wearable Devices to Measure Cardiovascular Functions in Community-Dwelling Adults: Application of a Practical Guide for Device Selection. Mayo Clin Proc Digit Health. 2025;3(2):100202. doi: 10.1016/j.mcpdig.2025.100202.

18. Aguilar M, Macle L, Chamieh R, Khairy P, Deyell MW, Bennett RG, Andrade JG. Wearable Smartwatches for Atrial Fibrillation Detection and Burden Estimation After Ablation: Comparison With Continuous Monitoring. Europace. 2025:euaf280. doi: 10.1093/europace/euaf280.

19. Barrera N, Solorzano M, Jimenez Y, Kushnir Y, Gallegos-Koyner F, Dagostin de Carvalho G. Accuracy of Smartwatches in the Detection of Atrial Fibrillation: A Systematic Review and Diagnostic Meta-Analysis. JACC Adv. 2025;4(11 Pt 1):102133. doi: 10.1016/j.jacadv.2025.

20. Sîngeap MS, Corneanu LE, Prodaniuc A, Șova IA, Coșovanu EO, Petriș OR. Diagnostic Accuracy of Wearable ECG Devices for Atrial Fibrillation and ST-Segment Changes: A Systematic Review. Diagnostics (Basel). 2025;15(24):3162. doi: 10.3390/diagnostics15243162.

21. Stachteas P, Bantidos MG, Papoutsidakis N, Nasoufidou A, Karakasis P, Sidiropoulos G, Kofos C, Patoulias D, Ediaroglou V, Stavropoulos G, Karagiannidis E, Fyntanidou B, Tsalikakis D, Smyrnakis E, Kassimis G, Papadopoulos CE, Fragakis N. Monitoring Atrial Fibrillation Using Wearable Digital Technologies: The Emerging Role of Smartwatches. J Clin Med. 2025;15(1):14. doi: 10.3390/jcm15010014.

22. Vyas R, Jain S, Thakre A, Thotamgari SR, Raina S, Brar V, Sengupta P, Agrawal P. Smart watch applications in atrial fibrillation detection: Current state and future directions. J Cardiovasc Electrophysiol. 2024;35(12):2474-2482. doi: 10.1111/jce.16451.

23. Burlacu A, Brinza C, Geman O, Karppa M, Hemanth DJ. Heart rate variability as a dual-use digital biomarker: integrating clinical, AI, and operational perspectives on human performance and resilience. BMC Cardiovasc Disord. 2026;26(1):87. doi: 10.1186/s12872-026-05543-z.

24. Grosicki GJ, Carter JR, Laursen PB, Plews DJ, Altini M, Galpin AJ, Fielding F, Hippel WV, Chapman C, Jasinski SR, Beattie UK, Holmes KE. Heart rate variability coefficient of variation during sleep as a digital biomarker that reflects behavior and varies by age and sex. Am J Physiol Heart Circ Physiol. 2026;330(1):H187-H199. doi: 10.1152/ajpheart.00738.2025.

25. Motahari-Nezhad H, Fgaier M, Mahdi Abid M, Péntek M, Gulácsi L, Zrubka Z. Digital Biomarker-Based Studies: Scoping Review of Systematic Reviews. JMIR Mhealth Uhealth. 2022;10(10):e35722. doi: 10.2196/35722.

26. De Sario Velasquez GD, Forte AJ, McLeod CJ, Bruce CJ, Pacheco-Spann LM, Maita KC, Avila FR, Torres-Guzman RA, Garcia JP, Borna S, Felton CL, Carter RE, Haider CR. Predicting Cardiopulmonary Arrest with Digital Biomarkers: A Systematic Review. J Clin Med. 2023;12(23):7430. doi: 10.3390/jcm12237430.

27. Owida HA. Biomechanical Sensing Systems for Cardiac Activity Monitoring. Int J Biomater. 2022;2022:8312564. doi: 10.1155/2022/8312564.

28. Tang C, Liu Z, Li L. Mechanical Sensors for Cardiovascular Monitoring: From Battery-Powered to Self-Powered. Biosensors (Basel). 2022;12(8):651. doi: 10.3390/bios12080651.

29. Zhou ZB, Cui TR, Li D, Jian JM, Li Z, Ji SR, Li X, Xu JD, Liu HF, Yang Y, Ren TL. Wearable Continuous Blood Pressure Monitoring Devices Based on Pulse Wave Transit Time and Pulse Arrival Time: A Review. Materials (Basel). 2023;16(6):2133. doi: 10.3390/ma16062133.

30. Battineni G, Sagaro GG, Chintalapudi N, Amenta F. The Benefits of Telemedicine in Personalized Prevention of Cardiovascular Diseases (CVD): A Systematic Review. J Pers Med. 2021;11(7):658. doi: 10.3390/jpm11070658.

31. Beheshti L, Kalankesh LR, Doshmangir L, Farahbakhsh M. Telehealth in Primary Health Care: A Scoping Review of the Literature. Perspect Health Inf Manag. 2022;19(1):1n.

32. Haleem A, Javaid M, Singh RP, Suman R. Telemedicine for healthcare: Capabilities, features, barriers, and applications. Sens Int. 2021;2:100117. doi: 10.1016/j.sintl.2021.100117.

33. Chivu CD, Crăciun MD, Pițigoi D, Aramă V, Luminos ML, Jugulete G, et al. The Dynamic Risk of COVID-19-Related Events in Vaccinated Healthcare Workers (HCWs) from a Tertiary Hospital in Bucharest, Romania: A Study Based on Active Surveillance Data. Vaccines (Basel). 2024;12(2):182. doi: 10.3390/vaccines12020182.

34. Jackson TN, Sreedhara M, Bostic M, Spafford M, Popat S, Lowe Beasley K, Jordan J, Ahn R. Telehealth Use to Address Cardiovascular Disease and Hypertension in the United States: A Systematic Review and Meta-Analysis, 2011-2021. Telemed Rep. 2023;4(1):67-86. doi: 10.1089/tmr.2023.0011.

35. Liu JC, Cheng CY, Cheng TH, Liu CN, Chen JJ, Hao WR. Unveiling the Potential: Remote Monitoring and Telemedicine in Shaping the Future of Heart Failure Management. Life (Basel). 2024;14(8):936. doi: 10.3390/life14080936.

36. Choi DJ. The role and prospects of telemedicine in the treatment of heart failure patients: a narrative review. Ewha Med J. 2025;48(2):e26. doi: 10.12771/emj.2025.00360.

37. Emaliyawati E, Ibrahim K, Kurniawan T, Fitria N, Songwathana P. A Systematic Review of Internet-Based Remote Patient Monitoring Systems for Chronic Disease Management in Asian. Patient Prefer Adherence. 2025;19:2985-3000. doi: 10.2147/PPA.S544351.

38. Ezeamii VC, Okobi OE, Wambai-Sani H, Perera GS, Zaynieva S, Okonkwo CC, Ohaiba MM, William-Enemali PC, Obodo OR, Obiefuna NG. Revolutionizing Healthcare: How Telemedicine Is Improving Patient Outcomes and Expanding Access to Care. Cureus. 2024;16(7):e63881. doi: 10.7759/cureus.63881.

39. Vudathaneni VKP, Lanke RB, Mudaliyar MC, Movva KV, Mounika Kalluri L, Boyapati R. The Impact of Telemedicine and Remote Patient Monitoring on Healthcare Delivery: A Comprehensive Evaluation. Cureus. 2024 Mar 4;16(3):e55534. doi: 10.7759/cureus.55534.

40. Tolu-Akinnawo O, Ezekwueme F, Awoyemi T. Telemedicine in Cardiology: Enhancing Access to Care and Improving Patient Outcomes. Cureus. 2024;16(6):e62852. doi: 10.7759/cureus.62852.

41. Maita KC, Maniaci MJ, Haider CR, Avila FR, Torres-Guzman RA, Borna S, Lunde JJ, Coffey JD, Demaerschalk BM, Forte AJ. The Impact of Digital Health Solutions on Bridging the Health Care Gap in Rural Areas: A Scoping Review. Perm J. 2024;28(3):130-143. doi: 10.7812/TPP/23.134.

42. Johnson KW, Torres Soto J, Glicksberg BS, Shameer K, Miotto R, Ali M, Ashley E, Dudley JT. Artificial Intelligence in Cardiology. J Am Coll Cardiol. 2018;71(23):2668-2679. doi: 10.1016/j.jacc.2018.03.521.

43. Romiti S, Vinciguerra M, Saade W, Anso Cortajarena I, Greco E. Artificial Intelligence (AI) and Cardiovascular Diseases: An Unexpected Alliance. Cardiol Res Pract. 2020;2020:4972346. doi: 10.1155/2020/4972346.

44. Karatzia L, Aung N, Aksentijevic D. Artificial intelligence in cardiology: Hope for the future and power for the present. Front Cardiovasc Med. 2022;9:945726. doi: 10.3389/fcvm.2022.945726.

45. Koulaouzidis G, Jadczyk T, Iakovidis DK, Koulaouzidis A, Bisnaire M, Charisopoulou D. Artificial Intelligence in Cardiology-A Narrative Review of Current Status. J Clin Med. 2022;11(13):3910. doi: 10.3390/jcm11133910.

46. Ledziński Ł, Grześk G. Artificial Intelligence Technologies in Cardiology. J Cardiovasc Dev Dis. 2023;10(5):202. doi: 10.3390/jcdd10050202.

47. Chowdhury MA, Rizk R, Chiu C, Zhang JJ, Scholl JL, Bosch TJ, Singh A, Baugh LA, McGough JS, Santosh KC, Chen WCW. The Heart of Transformation: Exploring Artificial Intelligence in Cardiovascular Disease. Biomedicines. 2025;13(2):427. doi: 10.3390/biomedicines13020427.

48. Vidal-Perez R, Vazquez-Rodriguez JM. Role of artificial intelligence in cardiology. World J Cardiol. 2023;15(4):116-118. doi: 10.4330/wjc.v15.i4.116.

49. Patrascanu OS, Tutunaru D, Musat CL, Dragostin OM, Fulga A, Nechita L, Ciubara AB, Piraianu AI, Stamate E, Poalelungi DG, Dragostin I, Iancu DC, Ciubara A, Fulga I. Future Horizons: The Potential Role of Artificial Intelligence in Cardiology. J Pers Med. 2024;14(6):656. doi: 10.3390/jpm14060656.

50. Bouzid Z, Al-Zaiti SS, Bond R, Sejdić E. Remote and wearable ECG devices with diagnostic abilities in adults: A state-of-the-science scoping review. Heart Rhythm. 2022;19(7):1192-1201. doi: 10.1016/j.hrthm.2022.02.030.

51. Köhler C, Bartschke A, Fürstenau D, Schaaf T, Salgado-Baez E. The Value of Smartwatches in the Health Care Sector for Monitoring, Nudging, and Predicting: Viewpoint on 25 Years of Research. J Med Internet Res. 2024;26:e58936. doi: 10.2196/58936.

52. Akella K, Murtaza G, Della Rocca DG, Kodwani N, Gopinathannair R, Natale A, Lakkireddy D. Implantable loop recorders for cardiac dysrhythmia monitoring. Future Cardiol. 2020;16(6):725-733. doi: 10.2217/fca-2020-0035.

53. Mittal S, Pokushalov E, Romanov A, Ferrara M, Arshad A, Musat D, Preminger M, Sichrovsky T, Steinberg JS. Long-term ECG monitoring using an implantable loop recorder for the detection of atrial fibrillation after cavotricuspid isthmus ablation in patients with atrial flutter. Heart Rhythm. 2013;10(11):1598-604. doi: 10.1016/j.hrthm.2013.07.044.

54. Pezawas T. ECG Smart Monitoring versus Implantable Loop Recorders for Atrial Fibrillation Detection after Cryptogenic Stroke-An Overview for Decision Making. J Cardiovasc Dev Dis. 2023;10(7):306. doi: 10.3390/jcdd10070306.

55. Boiko A, Martínez Madrid N, Seepold R. Contactless Technologies, Sensors, and Systems for Cardiac and Respiratory Measurement during Sleep: A Systematic Review. Sensors (Basel). 2023;23(11):5038. doi: 10.3390/s23115038.

56. Kebe M, Gadhafi R, Mohammad B, Sanduleanu M, Saleh H, Al-Qutayri M. Human Vital Signs Detection Methods and Potential Using Radars: A Review. Sensors (Basel). 2020;20(5):1454. doi: 10.3390/s20051454.

57. Qiao JH, Qi FG, Liang FL, Ma J, Lv H, Yu X, Xue HJ, An Q, Yan KD, Shi D, Qiao YH, Wang JQ, Zhang Y. Contactless multiscale measurement of cardiac motion using biomedical radar sensor. Front Cardiovasc Med. 2022;9:1057195. doi: 10.3389/fcvm.2022.1057195.

58. Shirbani F, Moriarty A, Hui N, Cox J, Tan I, Avolio AP, Butlin M. Contactless video-based photoplethysmography technique comparison investigating pulse transit time estimation of arterial blood pressure. Annu Int Conf IEEE Eng Med Biol Soc. 2021;2021:5650-5653. doi: 10.1109/EMBC46164.2021.9629489.

59. van Es VAA, Lopata RGP, Scilingo EP, Nardelli M. Contactless Cardiovascular Assessment by Imaging Photoplethysmography: A Comparison with Wearable Monitoring. Sensors (Basel). 2023;23(3):1505. doi: 10.3390/s23031505.

60. Ansari Y, Mourad O, Qaraqe K, Serpedin E. Deep learning for ECG Arrhythmia detection and classification: an overview of progress for period 2017-2023. Front Physiol. 2023;14:1246746. doi: 10.3389/fphys.2023.1246746.

61. Katal N, Gupta S, Verma P, Sharma B. Deep-Learning-Based Arrhythmia Detection Using ECG Signals: A Comparative Study and Performance Evaluation. Diagnostics (Basel). 2023;13(24):3605. doi: 10.3390/diagnostics13243605.

62. Reshad AI, Nino V, Valero M. Deep Learning-Based Detection of Arrhythmia Using ECG Signals - A Comprehensive Review. Vasc Health Risk Manag. 2025;21:685-703. doi: 10.2147/VHRM.S508620.

63. Kraft D, Rumm P. Atrial Fibrillation and Atrial Flutter Detection Using Deep Learning. Sensors (Basel). 2025;25(13):4109. doi: 10.3390/s25134109.

64. Lanzafame LRM, Bucolo GM, Muscogiuri G, Sironi S, Gaeta M, Ascenti G, Booz C, Vogl TJ, Blandino A, Mazziotti S, D'Angelo T. Artificial Intelligence in Cardiovascular CT and MR Imaging. Life (Basel). 2023;13(2):507. doi: 10.3390/life13020507.

65. Tolu-Akinnawo OZ, Ezekwueme F, Omolayo O, Batheja S, Awoyemi T. Advancements in Artificial Intelligence in Noninvasive Cardiac Imaging: A Comprehensive Review. Clin Cardiol. 2025;48(1):e70087. doi: 10.1002/clc.70087.

66. Marey A, Mehrtabar S, Afify A, Pal B, Trvalik A, Adeleke S, Umair M. From Echocardiography to CT/MRI: Lessons for AI Implementation in Cardiovascular Imaging in LMICs-A Systematic Review and Narrative Synthesis. Bioengineering (Basel). 2025;12(10):1038. doi: 10.3390/bioengineering12101038.

67. Haupt M, Maurer MH, Thomas RP. Explainable Artificial Intelligence in Radiological Cardiovascular Imaging-A Systematic Review. Diagnostics (Basel). 2025;15(11):1399. doi: 10.3390/diagnostics15111399.

68. van Assen M, Tariq A, Razavi AC, Yang C, Banerjee I, De Cecco CN. Fusion Modeling: Combining Clinical and Imaging Data to Advance Cardiac Care. Circ Cardiovasc Imaging. 2023;16(12):e014533. doi: 10.1161/CIRCIMAGING.122.014533.

69. Elhaddad M, Hamam S. AI-Driven Clinical Decision Support Systems: An Ongoing Pursuit of Potential. Cureus. 2024;16(4):e57728. doi: 10.7759/cureus.57728.

70. Elvas LB, Nunes M, Ferreira JC, Dias MS, Rosário LB. AI-Driven Decision Support for Early Detection of Cardiac Events: Unveiling Patterns and Predicting Myocardial Ischemia. J Pers Med. 2023;13(9):1421. doi: 10.3390/jpm13091421.

71. Subudhi G, Subudhi S, Garg S, Mehandru D. Artificial Intelligence in Medicine: Moving From "Prediction" to "Patient-Centric Decision Intelligence". Cureus. 2025;17(12):e100323. doi: 10.7759/cureus.100323.

72. Adabag S, Langsetmo L. Sudden cardiac death risk prediction in heart failure with preserved ejection fraction. Heart Rhythm. 2020;17(3):358-364. doi: 10.1016/j.hrthm.2019.12.009.

73. Lazzeroni D, Crocamo A, Ziveri V, Notarangelo MF, Rizzello D, Spoladori M, Donelli D, Cacciola G, Ardissino D, Niccoli G, Peretto G. Personalized Management of Sudden Death Risk in Primary Cardiomyopathies: From Clinical Evaluation and Multimodality Imaging to Ablation and Cardioverter-Defibrillator Implant. J Pers Med. 2023;13(5):877. doi: 10.3390/jpm13050877.

74. Werner RA, Derlin T, Bengel FM. Personalized prediction of mode of cardiac death in heart failure using supervised machine learning in the context of cardiac innervation imaging. J Nucl Cardiol. 2022;29(1):202-203. doi: 10.1007/s12350-020-02215-z.

75. van der Heide MYC, Verstraelen TE, Wilde AAM. Personalized sudden cardiac death risk prediction in genetic heart diseases: Beyond one-size-fits-all. Heart Rhythm. 2026;23(1):e62-e74. doi: 10.1016/j.hrthm.2025.07.041.

76. Singh M, Kumar A, Khanna NN, Laird JR, Nicolaides A, Faa G, Johri AM, Mantella LE, Fernandes JFE, Teji JS, Singh N, Fouda MM, Singh R, Sharma A, Kitas G, Rathore V, Singh IM, Tadepalli K, Al-Maini M, Isenovic ER, Chaturvedi S, Garg D, Paraskevas KI, Mikhailidis DP, Viswanathan V, Kalra MK, Ruzsa Z, Saba L, Laine AF, Bhatt DL, Suri JS. Artificial intelligence for cardiovascular disease risk assessment in personalised framework: a scoping review. EClinicalMedicine. 2024;73:102660. doi: 10.1016/j.eclinm.2024.102660.

77. Motahari-Nezhad H, Al-Abdulkarim H, Fgaier M, Abid MM, Péntek M, Gulácsi L, Zrubka Z. Digital Biomarker-Based Interventions: Systematic Review of Systematic Reviews. J Med Internet Res. 2022;24(12):e41042. doi: 10.2196/41042.

78. Trayanova NA, Prakosa A. Up digital and personal: How heart digital twins can transform heart patient care. Heart Rhythm. 2024 ;21(1):89-99. doi: 10.1016/j.hrthm.2023.10.019.

79. Thangaraj PM, Benson SH, Oikonomou EK, Asselbergs FW, Khera R. Cardiovascular care with digital twin technology in the era of generative artificial intelligence. Eur Heart J. 2024;45(45):4808-4821. doi: 10.1093/eurheartj/ehae619.

80. Skalidis I, Stalikas N, Collet C, Chatzizisis YS, Samant S, Apostolos A, Tsigkas G, Iglesias JF, Arroyo D, Garin D, Cook S, Salihu A, Meier D, Fournier S, Hovasse T, De Backer O, Garot P, Akodad M. Digital twins and simulations in transcatheter coronary and structural heart interventions. Eur Heart J Digit Health. 2025;7(2):ztaf129. doi: 10.1093/ehjdh/ztaf129.

81. Karakasis P, Antoniadis AP, Theofilis P, Vlachakis PK, Milaras N, Patoulias D, Karamitsos T, Fragakis N. Digital Twin Models in Atrial Fibrillation: Charting the Future of Precision Therapy? J Pers Med. 2025;15(6):256. doi: 10.3390/jpm15060256.

82. Hwang T, Lim B, Kwon OS, Kim MH, Kim D, Park JW, Yu HT, Kim TH, Uhm JS, Joung B, Lee MH, Hwang C, Pak HN. Clinical usefulness of digital twin guided virtual amiodarone test in patients with atrial fibrillation ablation. NPJ Digit Med. 2024;7(1):297. doi: 10.1038/s41746-024-01298-z.

https://doi.org/10.55453/rjmm.2026.129.3.8

REVIEW

Artificial Intelligence in Military Medicine: Clinical, Operational, and Educational Applications

Simona Steliana Tudor[1], Silviu Ionel Dumitrescu[2,3], Ionela Daniela Ferțu[1], Caterina Nela Dumitru[1,4], Bogdan-Viorel Vîlceleanu[3,5*], Iulia Theodora Ioniță[3,5], Alice Elena Munteanu[2,3]

[1] Faculty of Medicine and Pharmacy. Medical-Pharmaceutical Research Center, "Dunarea de Jos" University of Galati, 800008 Galati, Romania; steliana.tudor@ugal.ro, ionela.fertu@ugal.ro, caterina.dumitru@ugal.ro
[2] Titu Maiorescu University – Faculty of Medicine;
[3] Carol Davila Central Emergency University Military Hospital of Bucharest, 060011, Bucharest, Romania;
[4] Clinical Hospital of Infectious Diseases "St. Venerable Parascheva", 800179 Galați, Romania; caterina.dumitru@ugal.ro
[5] Carol Davila University of Medicine and Pharmacy, Doctoral School, 020022, Bucharest, Romania;

*Correspondence: B-V.V. Bogdan-viorel.vilceleanu@drd.umfcd.ro

Abstract: (1) Introduction: Artificial intelligence (AI) is transforming healthcare and has particular relevance in military medicine, where austere environments, uncertainty, and time-critical decisions are common; (2) Methods: A literature review was conducted in PubMed/MEDLINE, Scopus, and Web of Science, covering studies published between 2000 and 2026. Relevant articles on AI in military medicine were identified and grouped into three domains: clinical, operational, and educational; (3) Results: Forty-one studies were included. In the clinical domain, AI supports decision-making, trauma care, medical imaging, and mental health, including early detection of post-traumatic stress disorder (PTSD). Operational applications include physiological monitoring, triage optimization, and medical evacuation. In education, AI enhances medical simulation and adaptive learning. Key limitations include poor data quality and availability, algorithmic bias, and limited validation in real operational settings; (4) Conclusions: AI can substantially improve military medical practice by increasing diagnostic accuracy, supporting rapid decisions, and improving operational efficiency. However, implementation requires rigorous clinical validation, transparent and reliable systems, and careful attention to ethical and organizational issues. AI should be used as a complementary tool that supports, rather than replaces, clinical judgment.

Keywords: artificial intelligence; military medicine; clinical decision support; combat trauma; operational medicine; medical evacuation; mental health; post-traumatic stress disorder (PTSD); simulation-based training; machine learning.

INTRODUCTION

Artificial intelligence (AI) has become a central driver in the transformation of modern healthcare systems, offering new opportunities to improve diagnosis, treatment, and patient management. In the context of military medicine, these technologies are of particular relevance because of the unique features of the operational environment, including austere conditions, limited resources, high levels of uncertainty, and the need for rapid critical clinical decision-making [1–3].

Military medicine differs substantially from civilian medicine because of the complexity of the scenarios in which it is practiced. Military medical personnel are required to manage severe trauma, perform triage in combat settings, and make rapid decisions in the absence of standard medical infrastructure. In this context, AI provides tools capable of supporting clinicians through rapid data analysis, model-based prediction, and real-time decision support [4–6].

One of the major areas of AI application in military medicine is clinical decision support. AI-based systems can integrate large volumes of clinical and physiological data to guide therapeutic decisions, particularly in resource-limited environments where expert medical support is not always available [4,6]. In addition, predictive models developed using machine learning are increasingly being applied to

Citation Tudor SS, Dumitrescu SI, Fertu ID, Dumitru CN, Vilceleanu BV, Ionita IT, Munteanu AE. . *Artificial Intelligence in Military Medicine: Clinical, Operational, and Educational Applications*. R. J. Mil. Med. 2026, CXXIX(3): 301-311
https://doi.org/10.55453/rjmm.2026.129.3.8

Academic Editor: Octavian Vasiliu

Received: 21 March 2026
Revised: 12 April 2026
Accepted: 18 April 2026

anticipate patient outcomes, including the need for massive transfusion or the risk of death [7].

At the same time, AI plays an essential role in operational medicine. Continuous monitoring of physiological parameters through wearable sensors allows for the early detection of clinical deterioration, including internal hemorrhage, before overt symptoms become evident [8,9]. Furthermore, intelligent medical evacuation systems and triage algorithms can optimize resource allocation and improve the efficiency of interventions during large-scale combat operations [10,11].

Another area of major impact is military mental health. AI is being used for the early detection of psychiatric disorders, including PTSD, through the analysis of behavioral and physiological data. Machine learning models may support diagnosis, monitoring, and intervention, providing additional assistance to medical personnel in the management of these complex conditions [12–14].

In addition, AI is profoundly reshaping military medical education. The integration of digital simulations, virtual patients, and adaptive learning technologies enables the development of clinical competencies in a controlled and safe environment. These tools help prepare medical personnel for real combat situations, reduce training risks, and improve professional performance [15,16].

Nevertheless, the implementation of AI in military medicine is not without challenges. Limitations related to data quality, algorithmic bias, lack of validation under real-world conditions, and ethical concerns associated with the use of AI in critical settings raise important questions regarding safety and accountability in decision-making [5,6,17]. Moreover, integrating these technologies into complex military infrastructures requires solutions that are robust from both technical and organizational perspectives.

The aim of this article is to systematically examine the applications of artificial intelligence in military medicine across three main domains: clinical, operational, and educational. In addition, the benefits, limitations, and future directions of research are discussed, with particular emphasis on the safe and effective integration of AI into military medical practice.

MATERIALS AND METHODS

Study Design

The present study was conducted as a review aimed at synthesizing the existing literature on the applications of artificial intelligence in military medicine. The analysis focused on three principal domains: clinical, operational, and educational applications. This approach was chosen because of the heterogeneity of the available literature, which includes original studies, systematic reviews, experimental investigations, and expert perspectives. The methodology allows for an integrative analysis of emerging technologies and their implementation in the complex contexts specific to military healthcare systems.

Search Strategy

A systematic literature search was performed in the following electronic databases: PubMed/MEDLINE, Scopus, and Web of Science. The search strategy included relevant keywords and MeSH terms such as “artificial intelligence,” “machine learning,” “military medicine,” “combat casualty care,” “battlefield,” “decision support systems,” and “military training.” Boolean operators (AND, OR) were used to refine the search queries, and the strategy was adapted to each database in order to ensure an optimal balance between sensitivity and specificity.

Eligibility Criteria

Inclusion criteria: peer-reviewed scientific articles; studies addressing applications of artificial intelligence in military medicine or related operational contexts; publications covering clinical, operational, or educational domains; articles published in English; and studies published between 2000 and 2026. Exclusion criteria: studies not directly relevant to military medicine; publications without full-text availability; and duplicate studies or publications based on overlapping datasets.

Study Selection Process

Study selection was conducted in several successive stages. Initially, titles and abstracts were screened to identify potentially relevant publications. Eligible articles were then reviewed in full text according to the predefined criteria. Duplicate and redundant publications were removed, resulting in a final sample of 41 studies included in the analysis. The selection process was carried out manually based on thematic relevance and methodological quality.

Data Extraction and Synthesis

Data were systematically extracted from each included study. The following information was collected: authors and year of publication, study type, domain of application (clinical, operational, or educational), type of AI technology used, and the main findings and conclusions. The extracted data were synthesized qualitatively and organized into a summary table (Table 1), facilitating comparison across studies and the identification of major research directions.

Thematic Classification

The included studies were grouped into three principal domains: clinical applications (e.g., decision support, trauma management, diagnostic imaging, and mental health), operational applications (e.g., physiological monitoring, medical evacuation, and battlefield decision-making), and educational applications (e.g., simulation, AI-assisted training programs, and competency development technologies). This thematic classification enabled a coherent structure for the analysis and facilitated the organization of the Results and Discussion sections.

Methodological Limitations

The design of this study entails certain limitations, including the risk of selection bias and the inability to perform a quantitative synthesis. Furthermore, the included studies showed considerable methodological heterogeneity in terms of design, sample size, and validation context. In addition, many AI applications in military medicine are still in experimental or early implementation stages, with limited validation under real operational conditions. These factors may influence the generalizability of the findings.

RESULTS

1. Clinical Applications of Artificial Intelligence

Clinical Decision Support Systems

Artificial intelligence has become an essential tool in the development of clinical decision support systems (CDSS), owing to its ability to analyze large volumes of data and provide rapid, accurate recommendations in critical situations. In military medicine, where decisions often must be made under uncertainty and with limited resources, these systems contribute to greater diagnostic accuracy and more effective therapeutic interventions [4,6].

Machine learning-based models can integrate clinical, physiological, and contextual data to support medical decisions in real time. For example, AI-based decision support systems are being used for patient triage and intervention prioritization in austere environments, reducing reliance on limited local expertise [4]. However, the effectiveness of such systems is strongly influenced by data quality and their ability to generalize across contexts, both of which remain major challenges [6].

Trauma and Combat Medicine

Trauma management represents one of the most important challenges in military medicine, and AI offers innovative solutions to improve clinical outcomes. Predictive algorithms can anticipate patient deterioration and the need for critical interventions, such as massive transfusion, thereby enabling earlier and more personalized treatment [7].

In addition, the development of automated systems for battlefield trauma management demonstrates the potential of AI to support medical teams in highly complex situations. Automated trauma systems can integrate real-time data to guide therapeutic decisions and improve intervention coordination [18].

AI is also being applied to battlefield triage, where algorithms can prioritize patients according to injury severity and survival probability. This approach is essential in large-scale combat operations, where medical resources are limited and timely intervention is critical [6].

Medical Imaging and AI-Assisted Diagnosis

Applications of AI in medical imaging have developed rapidly and are increasingly used for the automated interpretation of radiographs and other imaging studies. In military medicine, these technologies are especially valuable in field hospitals, where access to specialists is often limited [19].

Deep learning algorithms can rapidly detect abnormalities on chest radiographs and other medical images, thereby contributing to the early diagnosis of critical conditions. The use of AI in military radiology may reduce diagnostic time and improve accuracy, particularly in settings with high patient volumes. [20].

Mental Health and Post-Traumatic Stress Disorder (PTSD)

Mental health is a fundamental component of military medicine, and AI provides innovative tools for diagnosis, monitoring, and intervention. Machine learning models can analyze behavioral and physiological data to identify early signs of PTSD and other psychiatric disorders [12].

In addition, AI-based digital systems may support continuous patient monitoring and facilitate personalized interventions. Recent studies suggest that AI can contribute to improved diagnosis and optimized treatment in military mental health settings [14]. The integration of AI into military behavioral health may enable the development of more effective prevention and intervention strategies, thereby reducing the psychological burden associated with exposure to conflict [21].

2. Operational Applications of Artificial Intelligence

Field Operational Medicine

In military operations, AI plays a crucial role in supporting real-time medical decision-making. Intelligent systems can integrate data from multiple sources, including physiological sensors and tactical information, to provide a comprehensive picture of both the patient's condition and the operational environment [22].

These technologies contribute to reducing response time and increasing the efficiency of medical interventions, and they are particularly valuable in environments where access to medical infrastructure is limited [3].

Intelligent Systems for Medical Evacuation (MEDEVAC)

Medical evacuation is a critical component of military medicine, and AI may help optimize this process through intelligent decision support systems. These systems can analyze patient parameters, environmental conditions, and resource availability in real time in order to determine the most effective evacuation strategy [10,11].

By integrating AI, the MEDEVAC process can become more efficient and safer, reducing transport times and improving patients' chances of survival [10].

Physiological Monitoring and Intelligent Sensors

Wearable sensors and continuous monitoring systems represent another important AI application in military medicine. These technologies allow the collection and analysis of physiological data in real time, facilitating the early detection of patient deterioration [8].

For example, compensatory reserve measurements can identify hemorrhage before overt clinical signs appear, offering a major advantage in trauma management [9]. In addition, continuous health monitoring contributes to the assessment of operational readiness ("combat readiness") [23].

Autonomous Systems and Combat Support

AI is also being used in the development of autonomous systems capable of supporting medical activities in conflict zones. These systems may include robotic platforms or algorithms able to provide real-time recommendations, thereby reducing the exposure of medical personnel to risk [24].

The integration of such technologies into military operations may improve efficiency and strengthen response capabilities in critical situations.

3. Educational and Training Applications

Integration of AI into Military Medical Education

Military medical education is undergoing rapid transformation through the integration of artificial intelligence. The inclusion of AI in medical curricula supports the development of digital competencies and prepares personnel for the use of emerging technologies [24].

There is also an increasing need for AI-related training among healthcare professionals so that these technologies can be used effectively and responsibly in clinical practice [14].

Medical Simulation and Virtual Learning

Medical simulation is an essential tool in military training, and AI contributes to the development of more realistic and interactive learning environments. The use of virtual patients and AI-based simulations allows medical personnel to train in scenarios that closely resemble real conditions, without placing actual patients at risk [16].

Gamification and virtual reality technologies are also being used to enhance learner engagement and performance, thereby facilitating the acquisition of competencies required for trauma management [25].

Technology-Assisted Procedural Training

AI and related technologies are also being applied to procedural training, including the use of medical devices and intervention techniques. For example, training in portable ultrasound and emergency device utilization can be enhanced through intelligent systems and automated feedback [26–28].

These approaches contribute to improved professional competence and reduced clinical error, and they are particularly relevant to the preparation of military medical personnel.

To synthesize the reviewed literature, the included studies were organized according to their domain of application, the type of AI technology employed, and the main reported findings. This structure highlights the principal directions of AI development in military medicine (Table 1).

Table 1: Summary of Included Studies on Artificial Intelligence Applications in Military Medicine (n = 41)

Reference	Domain	Subdomain	Type of AI application / technology	Main findings	Relevance to military medicine
Leone R.M. [1]	General	Military medicine	Conceptual AI analysis	AI transforms military medical practice	General strategic framework
Adirim T. [2]	General	Military health system	AI integration	Modernization of the Military Health System	Institutional implementation
Lurin I. [3]	Operational	Civilian/military medicine	Comparative analysis	AI useful in austere environments	Civil-military transfer
Umlauf L. [4]	Clinical	Decision support	AI-based CDSS	Supports decisions in resource-limited settings	Useful in field hospitals
Schwab J.H. [5]	Clinical	Decision support	AI medical decision support	Data quality concerns	Need for validation
Mathais Q. [6]	Clinical/ Operational	Triage	AI algorithms	Potential and limitations in the field	Combat triage
Lammers D. [7]	Clinical	Trauma	Predictive machine learning	Predicts transfusion/death	Early intervention
Convertino V.A. [8]	Operational	Monitoring	Compensatory reserve	Early hemorrhage detection	Field advantage
Cosic K. [9]	Mental/ Operational	War psychology	AI emotion analysis	Stress-war correlations	Mental monitoring
Krygier J. [10]	Operational	MEDEVAC	Intelligent system	Evacuation optimization	Increased survival
Lubkowski P. [11]	Operational	MEDEVAC	Evacuation DSS	Optimal resource selection	Logistics management
Bertl M. [12]	Clinical	PTSD	AI review	AI for PTSD screening	Mental health
Pellegrin G. [13]	Clinical	PTSD	Machine learning	PTSD pattern detection	Early diagnosis
Callcut R.A. [14]	Clinical	Imaging	AI radiography	Improved accuracy	Rapid diagnosis
Peacock J.G. [15]	Educational	Medical training	Digital transformation	Educational modernization	Military curriculum
Stathakarou N. [16]	Educational	Simulation	Gamification	Improved performance	Trauma training
Cruz-Gonzalez P. [17]	Clinical	Mental health	Systematic review	Benefits and risks of AI	Responsible use
Baker J.B. [18]	Clinical	Trauma	Automated system	Real-time trauma management	Decision support
Cloran F.J. [19]	Clinical	Radiology	AI imaging	Rapid diagnosis	Useful in theaters
Ozmen, M.M. [20]	Clinical/ Operational	Surgery	AI + robotics	Surgical digitalization	Future autonomy
Shore H.J. [21]	Clinical	Mental health	Digital technology	PTSD monitoring	Reduced psychological burden
Russell B.C. [22]	Operational	Sensors	AI-enabled sensors	Real-time data	Decision support
de Vries H.J. [23]	Operational	Readiness	Real-time monitoring	Assessment of soldier status	Preventive medicine

Spirnak J.R. [24]	Educational	Curriculum	AI training	Need for AI education	Personnel preparation
Stathakarou N. [25]	Educational	Simulation	Game-based learning	Increased engagement	Efficient learning
Monti J.D. [26]	Educational	Procedures	eFAST training	Improved competencies	Rapid diagnosis
Gendron B. [27]	Educational	Procedures	Device training	Improved performance	Emergency maneuvers
Meadows R.M. [28]	Clinical/ Educational	Ultrasound	Portable ultrasound	Pneumothorax detection	Useful in the field
Rakhilin N. [29]	Operational	Operational medicine	AI integration	Implementation challenges	Human factors
Favorov O. [30]	Operational	Wearable sensors	Wearable sensors	Detects motor deficits	Soldier monitoring
Savell S.C. [31]	Clinical	POCUS ultrasound	Rapid diagnosis	Field utility	Rapid assessment
Bornemann P. [32]	Clinical	Ultrasound	Portable devices	High acceptance	Useful in the field
Vučemilović A. [33]	Clinical	Clinical decision	Decision strategy	Lessons from conflict	Military context
Esfandiari E. [34]	Educational	AI acceptance	Perception study	Moderate acceptance	Need for training
Riggenbach Z.W. [35]	General	Military AI	Overview	Introduction of AI at the front	Education and strategy
Cole R. [36]	General	Medical warfare	AI warfare	Preparation of the medical system	Adaptation to the future
Patel N.C. [37]	Operational	Health system	AI defence	AI optimizes the system	Public policy relevance
Bhakar R. [38]	Educational	Surgical education	AI training	Improves training	Surgical competencies
McConnon A.D. [39]	Clinical	Mental health	AI behavioral health	Psychological monitoring	PTSD prevention
Meyer N. [40]	General	Military medicine	Review of AI applications	Multiple AI applications	Domain synthesis
Caffery S.J. [41]	Educational	Simulation	Medical simulations	Realistic training	Military preparedness

Abbreviations: AI = artificial intelligence; PTSD = post-traumatic stress disorder; MEDEVAC = medical evacuation; CDSS = clinical decision support system; eFAST = extended Focused Assessment with Sonography for Trauma.

DISCUSSION

1. Synergy Between Clinical and Operational Applications

A central finding of this review is the interdependence between the clinical and operational applications of AI. Clinical decision support systems developed to optimize diagnosis and treatment become even more valuable when integrated into the broader military operational ecosystem. In settings where medical decisions are influenced by tactical and logistical factors, AI enables an integrated approach in which clinical data are correlated with information about the environment and available resources [3,4,22].

For example, algorithms used for patient triage or for predicting trauma outcomes do not function in isolation; rather, they are incorporated into more complex systems involving medical evacuation and resource allocation. This integration supports global optimization of interventions and may improve survival rates in combat scenarios [7,10,11].

The Role of AI in Emergency Medicine and Military Trauma

The findings reviewed here indicate that military trauma care is one of the most promising fields for AI application. Machine learning-based predictive models allow earlier identification of patients who require critical interventions, such as massive transfusion or urgent surgery [7].

At the same time, the development of automated trauma management systems and triage algorithms for large-scale combat operations suggests a clear trend toward partial automation of decision-making processes [6,18]. However, these advances also raise important questions regarding algorithm reliability under real-world conditions and the need for validation across diverse operational settings.

Importance of Continuous Monitoring and Real-Time Data

Another major finding is the importance of continuous physiological monitoring in military medicine. Wearable sensors and AI-based monitoring systems enable real-time data collection and provide a dynamic picture of patient status [8,23]. These technologies have the potential to shift military medicine from a reactive model to a proactive one, in which clinical deterioration may be anticipated and prevented. For instance, the early detection of hemorrhage through compensatory reserve analysis illustrates how AI may contribute to earlier intervention and reduced mortality [9]. However, reliance on continuous data streams also raises concerns about data security, infrastructure stability, and system interoperability, all of which are critical in military contexts.

AI and the Transformation of Military Mental Health

The integration of AI into military mental health represents a significant advance, especially given the high prevalence of PTSD. Machine learning models can support early identification of symptoms and longitudinal monitoring, thereby creating opportunities for more personalized interventions [12,14].

However, the application of AI in this field is accompanied by specific challenges, including the complexity of psychological data and the risk of misinterpretation. In addition, acceptance by both patients and healthcare professionals remains a key determinant of successful implementation [21].

Impact of AI on Military Medical Education

The results suggest that AI has a major impact on military medical education and training by supporting the transition to more modern learning methods. Medical simulations, virtual patients, and gamification technologies make it possible to develop competencies in controlled environments while increasing the preparedness of medical personnel [16,25].

The integration of AI into educational curricula also contributes to the development of digital competencies and prepares professionals to work with emerging technologies. Nevertheless, the implementation of such programs requires substantial resources and adaptation of existing educational systems [14,24].

Balancing Automation and Human Decision-Making

A critical issue highlighted in the literature is the need to maintain a balance between the automation enabled by AI and the decision-making role of the clinician. Although AI can offer valuable support, final decisions must remain under the responsibility of medical personnel, particularly in situations with major ethical implications [6,17].

Excessive reliance on algorithms may lead to reduced clinical autonomy and potential errors if systems fail or perform inadequately. Accordingly, AI should be understood as a complementary tool rather than a substitute for human expertise.

Limitations of the Literature and Implications for Research

The reviewed literature reveals important limitations, including a lack of prospective studies and limited validation under real combat conditions. Most studies have been conducted in controlled environments or on restricted datasets, which may reduce the applicability of their findings [6].

Furthermore, methodological variability and lack of standardized datasets hinder cross-study comparison and the development of generalizable models. These limitations underscore the need for future research assessing AI effectiveness under real operational conditions.

Practical Implications for Military Medicine

From a practical perspective, the implementation of AI in military medicine requires a multidisciplinary approach involving specialists in medicine, engineering, and data science. The development of regulatory frameworks and standardized protocols for the use of these technologies is also essential.

The adoption of AI may improve the resilience of military healthcare systems and strengthen their capacity to respond in crisis situations. However, successful implementation depends on effective integration into existing workflows and user acceptance.

Summary

Overall, this review highlights the transformative potential of AI in military medicine by offering innovative solutions to clinical, operational, and educational challenges. At the same time, realizing this potential requires careful attention to the associated

limitations and risks, as well as the development of implementation strategies tailored to the specific characteristics of the military environment.

2. Benefits of Artificial Intelligence in Military Medicine

The integration of artificial intelligence into military medicine offers significant benefits across clinical, operational, and educational domains, contributing to improved efficiency and better medical outcomes under complex conditions.

Improved Clinical Decision-Making

One of the principal advantages of AI lies in its ability to support clinical decisions through the rapid analysis of large volumes of data. AI-based decision support systems can identify subtle patterns and generate real-time therapeutic recommendations, thereby reducing variability in decision-making and the risk of human error [4,6]. This is particularly important in military medicine, where decisions are frequently made under pressure and uncertainty.

Greater Operational Efficiency

AI contributes to the optimization of operational workflows by automating selected processes and facilitating the coordination of medical interventions. For example, intelligent medical evacuation systems and triage algorithms enable more efficient use of resources and shorter response times [10,11]. In addition, the integration of AI into operational medicine improves planning capacity and adaptability in dynamic situations [3].

Reduced Response Time

In emergency situations, the time to intervention is a critical determinant of patient survival. AI enables rapid analysis of data and the delivery of immediate recommendations, thereby reducing the time required for diagnosis and treatment [7]. This capability is essential in the context of severe trauma and battlefield interventions.

Continuous Monitoring and Early Detection

The use of wearable sensors and AI-based monitoring systems allows continuous assessment of the physiological status of military personnel. These technologies can identify early deterioration, including internal hemorrhage, before overt clinical signs appear [9]. As a result, AI may help prevent complications and support the timely initiation of treatment.

Optimization of Training and Competency Development

In the educational domain, AI facilitates the development of innovative training approaches such as medical simulations and virtual patients. These tools enable medical personnel to train in realistic settings without risk to actual patients and may improve professional performance [16,25]. In addition, AI-based adaptive learning allows greater personalization of the educational process.

3. Limitations, Risks, and Challenges

Despite its substantial benefits, the implementation of AI in military medicine is associated with multiple challenges that must be addressed to ensure its safe and effective use.

Technical Limitations

One of the principal obstacles is the quality and availability of data. AI models depend on large, well-annotated datasets, and the absence of such data may impair algorithm performance [6].

Moreover, algorithmic bias and limited generalizability across different operational environments may result in inaccurate outputs or suboptimal decisions.

Operational Challenges

The implementation of AI in military settings involves challenges related to infrastructure, connectivity, and interoperability. In conflict zones, access to stable networks and technological resources may be limited, thereby affecting the operation of AI-based systems [3]. In addition, integrating these technologies into existing systems often requires substantial adaptation.

Human Factors and Technology Acceptance

Adoption of AI depends largely on acceptance by medical personnel. Limited trust in algorithms, insufficient training, and resistance to change may restrict effective use of these technologies [29]. There is also a risk of overreliance on AI, which could reduce independent decision-making capacity.

Ethical and Medico-Legal Considerations

The use of AI in military medicine raises complex ethical issues, including accountability for decisions, algorithm transparency, and the protection of personal data. In military operations, these concerns are amplified by the potential consequences for patient safety and survival [19]. Furthermore, the use of AI in automated triage or other critical decisions requires clear ethical frameworks and appropriate regulatory oversight.

Even if AI-facilitated triage can reduce variability between users, it is difficult to use it in order to outperform humans due to ethical reasons regarding AI autonomy in medical setting decision making, but if it is supported by large datasets and appropriately trained, it can be used to enhance consistency and increase the productivity of humans already working on the specific task [6].

4. Future Research Directions

The continued development and implementation of AI in military medicine require sustained research and innovation efforts aimed at overcoming current limitations and maximizing the potential of these technologies.

Clinical Validation in Real-World Environments

A key priority is the validation of AI systems under real military operational conditions. Prospective studies and field evaluations are needed to demonstrate the safety and effectiveness of these technologies [6].

Development of Explainable AI

Greater algorithmic transparency is essential for the acceptance and use of AI in clinical practice. Explainable AI allows users to understand how recommendations are generated, thereby increasing trust in these systems [5].

Multimodal Data Integration

Future AI systems should integrate data from multiple sources, including clinical, imaging, and physiological data. Such a multimodal approach may improve predictive accuracy and decision relevance [25].

Development of Autonomous Systems

Advances in AI may lead to the development of autonomous systems capable of performing triage, monitoring, and even basic medical interventions in the absence of medical personnel. These technologies could have major implications for care delivery in conflict zones [24].

Personalization of Medical Training

AI also creates opportunities for the development of personalized educational programs adapted to the individual needs of learners. Such approaches may improve training efficiency and enhance the acquisition of competencies specific to military medicine [16].

CONCLUSION

Artificial intelligence is a transformative technology in military medicine, with broad applications across clinical, operational, and educational domains. Its ability to rapidly analyze complex data, support medical decisions, and optimize processes contributes substantially to improving the quality of care in military settings.

Clinical applications of AI, including decision support, trauma management, and AI-assisted diagnosis, demonstrate its potential to reduce mortality and improve patient outcomes. At the same time, AI in operational medicine may optimize resource utilization and enhance the efficiency of interventions in austere environments. In the educational field, AI is reshaping the training of medical personnel by providing innovative simulation- and adaptive learning-based solutions.

However, large-scale implementation remains constrained by technical, operational, and ethical challenges that require interdisciplinary approaches and appropriate regulation. The development of robust, transparent, and clinically validated systems is essential to ensure the safe and effective use of AI in military medicine.

Looking ahead, AI is unlikely to replace the military clinician; rather, it should be regarded as a complementary tool that expands decision-making capacity and improves the performance of military medical systems. The responsible integration of these technologies will play an essential role in the future development of military medicine and in strengthening the resilience of healthcare systems in conflict settings.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

This research received no external funding.

Authors' contribution

Conceptualization, S.S.T, I.D.F. ; methodology, I.D.F., C.N.D. ; resources, B-V.V., C.N.D.; writing—original draft preparation, S.S.T, I.D.F., B-V.V.; writing—review and editing, I.T.I, S.I.D., A.E.M. ; supervision, S.I.D., A.E.M.. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

References

1. Leone RM, Chambers JA, Donham BP, Junker CA. Artificial intelligence in military medicine. Mil Med. 2024;189(9-10):244-248. doi:10.1093/milmed/usae359.

2. Adirim T, Madsen C. Artificial intelligence in the U.S. Military Health System. Mil Med. 2025;190(7-8):199-202. doi:10.1093/milmed/usae428.

3. Lurin I, Gorobeiko M, Lovin A, et al. AI in civil and military medicine. Georgian Med News. 2024;(348):94-98.

4. Umlauf L, Remley M, Colombo C, Pamplin J. Artificial intelligence decision support systems in resource-limited environments. Mil Med. 2025;190(11-12):257-260. doi:10.1093/milmed/usaf010.

5. Schwab JH. AI-based medical decision support: exploring the data gap. J Bone Joint Surg Am. 2026;108(4):266-268. doi:10.2106/JBJS.25.01387.

6. Mathais Q, Cungi PJ, Lamblin A, et al. AI for battlefield triage: opportunities and limits. J Trauma Acute Care Surg. 2026. doi:10.1097/TA.0000000000004973.

7. Lammers D, Marenco C, Morte K, et al. Machine learning for military trauma. J Surg Res. 2022;270:369-375. doi:10.1016/j.jss.2021.09.017.

8. Convertino VA, Cardin S. Advanced medical monitoring for the battlefield: clinical applicability of compensatory reserve measurements. J Trauma Acute Care Surg. 2022;93(2 Suppl 1):S147-S154. doi:10.1097/TA.0000000000003595.

9. Cosic K, Kopilas V, Jovanovic T. War, emotions, mental health, and AI. Front Psychol. 2024;15:1394045. doi:10.3389/fpsyg.2024.1394045.

10. Krygier J, Lubkowski P, Maslanka K, et al. Smart medical evacuation support system for the military. Sensors (Basel). 2024;24(14):4581. doi:10.3390/s24144581.

11. Lubkowski P, Krygier J, Sondej T, et al. Decision support system for medical evacuations in military operations. Sensors (Basel). 2023;23(11):5144. doi:10.3390/s23115144.

12. Bertl M, Metsallik J, Ross P. AI-based decision support systems for PTSD: systematic review. Front Psychiatry. 2022;13:923613. doi:10.3389/fpsyt.2022.923613.

13. Pellegrin G, Ricka N, Fompeyrine DA, et al. PTSD assessment via machine learning. Sci Rep. 2025;15:7562. doi:10.1038/s41598-025-91916-x.

14. Callcut RA. Context matters: evaluating AI-assisted chest radiograph interpretation in military field hospitals. Trauma Surg Acute Care Open. 2025 Dec 10;10(4):e002112. doi: 10.1136/tsaco-2025-002112.

15. Peacock JG, Cole R, Duncan J, et al. Transforming military healthcare education and training. Mil Med. 2025;190(9-10):e1905-e1912. doi:10.1093/milmed/usaf169.

16. Stathakarou N, Kononowicz AA, Mattsson E, Karlgren K. Gamification in the Design of Virtual Patients for Swedish Military Medics to Support Trauma Training: Interaction Analysis and Semistructured Interview Study. JMIR Serious Games. 2024 Oct 22;12:e63390. doi: 10.2196/63390.

17. Cruz-Gonzalez P, He AW, Lam EP, Ng IMC, Li MW, Hou R, Chan JN, Sahni Y, Vinas Guasch N, Miller T, Lau BW, Sánchez Vidaña DI. Artificial intelligence in mental health care: a systematic review of diagnosis, monitoring, and intervention applications. Psychol Med. 2025 Feb 6;55:e18. doi: 10.1017/S0033291724003295.

18. Baker JB, Blumhorst J, Strating SJ, Holub H, Perry M, Remondelli MH, Leone R, Shackelford SA, Gurney JM. Proof of concept of an Automated Battlefield Trauma System for large-scale combat operations. J Trauma Acute Care Surg. 2025 Aug 1;99(3S Suppl 1):S170-S174. doi: 10.1097/TA.0000000000004675.

19. Cloran FJ. Artificial Intelligence in Military Radiology-Clearing the Starting Gate: A Military Radiologist's Perspective. J Am Coll Radiol. 2023 Sep;20(9):857-858. doi: 10.1016/j.jacr.2023.06.012.

20. Ozmen, M.M., Ozmen, A., Koç, Ç.K. (2021). Artificial Intelligence for Next-Generation Medical Robotics. In: Atallah, S. (eds) Digital Surgery. Springer, Cham. doi: 10.1007/978-3-030-49100-0_3.

21. Shore JH, Synyahovskyy V, Hukovskyy O, Korostiy V, McVeigh F, Poropatich R. Technology in the Trenches: The Impact of evolving technologies on Combat Mental Health. Curr Psychiatry Rep. 2025 Feb;27(2):127-133. doi: 10.1007/s11920-024-01581-6.

22. Russell BK, McGeown J, Beard BL. Developing AI-enabled sensors and decision support for military operators. J Sci Med Sport. 2023;26(Suppl 1):S40-S45. doi:10.1016/j.jsams.2023.03.001.

23. de Vries HJ, van der Wal SJ, Delahaij R, Venrooij W, Kamphuis W. Real-time monitoring of military health and readiness: a perspective on future research. Front Digit Health. 2025;7:1542140. doi:10.3389/fdgth.2025.1542140.

24. Spirnak JR, Antani S. Need for AI curriculum in military medical education. Mil Med. 2024;189(5-6):954-958. doi:10.1093/milmed/usad412.

25. Stathakarou N, Kononowicz AA, Swain C, Karlgren K. Game Elements in the Design of Simulations in Military Trauma Management Training: Protocol for a Systematic Review. JMIR Res Protoc. 2023 Sep 8;12:e45969. doi: 10.2196/45969.

26. Monti JD, Perreault MD. Impact of a 4-hour Introductory eFAST Training Intervention Among Ultrasound-Naïve U.S. Military Medics. Mil Med. 2020 Jun 8;185(5-6):e601-e608. doi: 10.1093/milmed/usaa014.

27. Gendron B, Cronin A, Monti J, Brigg A. Military Medic Performance with Employment of a Commercial Intraosseous Infusion Device: A Randomized,

Crossover Study. Mil Med. 2018 May 1;183(5-6):e216-e222. doi: 10.1093/milmed/usx078.

28. Meadows RM, Monti JD, Umar MA, Van Arnem KA, Chin EJ, Mitchell CA, Love S. US Army Combat Medic Performance With Portable Ultrasound to Detect Sonographic Findings of Pneumothorax in a Cadaveric Model. J Spec Oper Med. 2020 Fall;20(3):71-75. doi: 10.55460/SOPZ-STAP.

29. Rakhilin N, Morris HD, Pham DL, et al. AI in operational medicine. Bioengineering (Basel). 2025;12(5):519. doi:10.3390/bioengineering12050519.

30. Favorov O, Kursun O, Challener T, Cecchini A, McCulloch KL. Wearable sensors detect movement differences in the Portable Warrior Test of Tactical Agility after mTBI in service members. Mil Med. 2023;188(3-4):e637-e645. doi:10.1093/milmed/usab361.

31. Savell SC, Baldwin DS, Blessing A, Medelllin KL, Savell CB, Maddry JK. Military Use of Point of Care Ultrasound (POCUS). J Spec Oper Med. 2021 Summer;21(2):35-42. doi: 10.55460/AJTO-LW17.

32. Bornemann P, Bornemann G. Military family physicians' perceptions of a pocket point-of-care ultrasound device. Mil Med. 2014;179(12):1474-1477. doi:10.7205/MILMED-D-14-00241.

33. Vučemilović A, Volf M. Clinical decision-making strategy illustrated by the Gulf War. Rev Environ Health. 2024;40(2):360-370. doi:10.1515/reveh-2024-0070.

34. Esfandiari E, Kalroozi F, Mehrabi N, Hosseini Y. Knowledge and acceptance of AI among military physicians. J Educ Health Promot. 2024;13:271. doi:10.4103/jehp.jehp_898_23.

35. Riggenbach ZW, Van Eaton J, Kelly AA, et al. AI on the front lines: a primer. Mil Med. 2025;190(9-10):e1851-e1857. doi:10.1093/milmed/usaf165.

36. Cole R, Simmons S, Duncan J, et al. Readying military medicine for AI-enabled warfare. Mil Med. 2025. doi:10.1093/milmed/usaf460.

37. Patel NC. AI and UK defence healthcare delivery. BMJ Mil Health. 2025;171(3):198-201. doi:10.1136/military-2024-002682.

38. Bhakar R, Miller J, Simenacz A. AI and surgical education. Cureus. 2025;17(12):e98231. doi:10.7759/cureus.98231.

39. McConnon AD, Nash AJ, Roberts JR, Juni SZ, Derenbecker A, Shanahan P, Waters AJ. Incorporating AI Into Military Behavioral Health: A Narrative Review. Mil Med. 2025 Sep 1;190(9-10):e1870-e1881. doi: 10.1093/milmed/usaf162.

40. Meyer N, Ullrich L, Goldsmith Z, et al. Applications of AI in military medicine and surgery. 2024. DOI: 10.5772/intechopen.115144.

41. Caffery SJ, Ferrari BD, Hackett MG. Military medical simulations. Military Medicine, Volume 190, Issue 3-4, March/April 2025, Pages e554–e560, DOI:10.1093/milmed/usae468.

https://doi.org/10.55453/rjmm.2026.129.3.9

ARTICLE

Association Between Rehabilitation Timing and Mobility Outcomes in COVID-19 ICU Survivors

Andra Pintilie[1], Elena Costescu[2,*] , Marius Popescu[3,*], Adrian Streinu-Cercel[4]

[1] "Carol Davila" University of Medicine and Pharmacy Bucharest, Doctoral School, Department of Rehabilitation Medicine, 37 Dionisie Lupu Street, area 2, Bucharest, 4192910; andra.pintilie@gmail.com
[2] "Apollonia" University of Iasi, Faculty of Medicine, 11 Pacurari Street, Iasi, 700511; naturaone@gmail.com
[3] "Carol Davila" University of Medicine and Pharmacy Bucharest, Doctoral School, Department of Rehabilitation Medicine, 37 Dionisie Lupu Street, area 2, Bucharest, 4192910; marius.popescu@umfcd.ro
[4] "Carol Davila" University of Medicine and Pharmacy Bucharest, 37 Dionisie Lupu Street, area 2, Bucharest, 4192910; astreinucercel@yahoo.com

*Correspondence: naturaone@gmail.com (EC), marius.popescu@umfcd.ro (MP)

Abstract: Background: Severe SARS-CoV-2 infection often results in prolonged immobilization and intensive care unit–acquired weakness (ICUAW), contributing to delayed functional recovery. Early physical and rehabilitation medicine (PRM) interventions may mitigate neuromuscular decline, yet real-world data integrating kinesitherapy with proprioceptive focal stimulation (PFS) remain limited. This study evaluated the functional impact of early rehabilitation and the role of timing in rehabilitation among critically ill COVID-19 patients. Methods: A transversal observational cohort study included 148 adults with confirmed COVID-19 admitted to the ICU of the National Institute for Infectious Diseases "Prof. Dr. Matei Balș" (June 2020–June 2022). Individualized rehabilitation (kinesitherapy ± PFS) was initiated after hemodynamic stabilization. Outcomes included the Medical Research Council score, the ICU Mobility Scale, the Manchester Mobility Score, and the Glasgow Coma Scale. Statistical analyses used the chi-square, Mann–Whitney U, and Spearman's rank correlation tests. Results: One hundred and eight patients (73.0%) required mechanical ventilation. Intubation was strongly associated with muscular atrophy ($p = 7.1\times10^{-10}$) and lower ICU mobility ($p = 1.56\times10^{-11}$). Delayed rehabilitation correlated moderately with poorer mobility at ICU discharge ($\rho = -0.397$). Conclusion: Early PRM is feasible and associated with better functional outcomes in severe COVID-19. Rehabilitation timing appears critical, particularly in mechanically ventilated patients.

Keywords: COVID-19; ICU-acquired weakness; early mobilization; physical and rehabilitation medicine; proprioceptive focal stimulation; ICU mobility

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has profoundly impacted intensive care practice worldwide, leading to an unprecedented number of critically ill patients requiring prolonged mechanical ventilation and complex multidisciplinary management. Although the acute respiratory manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection initially dominated clinical attention, it rapidly became evident that survivors frequently experience significant neuromuscular and functional impairments that extend well beyond the acute phase of illness [1,2].

Among the most clinically relevant complications in critically ill patients is intensive care unit-acquired weakness (ICUAW), a syndrome characterized by diffuse, symmetrical muscle weakness that develops during critical illness in the absence of other identifiable causes [3]. ICUAW encompasses critical illness polyneuropathy, critical illness myopathy, or their combination, and is associated with prolonged mechanical ventilation, extended ICU and hospital length of stay, increased mortality, and persistent long-term disability [4,5]. In the context of severe COVID-19, the risk of ICUAW appears to be amplified by multiple converging factors, including systemic inflammation, prolonged immobilization, deep sedation, hypoxemia, and frequent use of neuromuscular blocking agents [6].

Citation: Pintilie A, Costescu E, Popescu M, Streinu-Cercel A. *Association Between Rehabilitation Timing and Mobility Outcomes in COVID-19 ICU Survivors*. R. J. Mil. Med. 2026, CXXIX(3): 312-319
https://doi.org/10.55453/rjmm.2026.129.3.9

Academic Editor: Clara Ursescu

Received: 22 Januray 2026
Revised: 31 March 2026
Accepted: 06 April 2026

Post-intensive care syndrome (PICS) has further emphasized the multidimensional burden faced by ICU survivors, involving physical, cognitive, and psychological impairments that may persist for years after discharge [7]. From a rehabilitation perspective, the physical domain—particularly severe deconditioning and neuromuscular weakness—represents a major determinant of delayed functional recovery and reduced quality of life. Previous longitudinal studies in non-COVID acute respiratory distress syndrome (ARDS) survivors have demonstrated functional disability persisting up to five years post-ICU, underscoring the long-term consequences of critical illness [5].

Early mobilization and structured physical and rehabilitation medicine (PRM) interventions have emerged as key strategies to counteract ICU-related deconditioning. Current evidence suggests that initiating rehabilitation as soon as the patient achieves hemodynamic and respiratory stability can reduce muscle wasting, improve functional outcomes, shorten duration of mechanical ventilation, and decrease ICU length of stay [8,9]. However, during the COVID-19 pandemic, the implementation of early rehabilitation has faced substantial barriers, including infection control constraints, staff overload, patient instability, and limited availability of specialized rehabilitation teams [10].

In this context, innovative neurorehabilitation approaches that can be applied even in deeply impaired or non-cooperative patients are of particular interest. Proprioceptive focal stimulation (PFS) represents a modern therapeutic modality designed to preserve the functional interaction between sensory input and motor output by delivering patterned proprioceptive stimuli that mimic physiological gait-related afferent signals. Preliminary data suggest that such approaches may help maintain central motor programs and mitigate disuse-related neuromuscular decline, even when active movement is not yet feasible [11].

Despite the growing recognition of the importance of early rehabilitation in COVID-19 critical care, real-world clinical data integrating conventional kinesitherapy with advanced proprioceptive stimulation techniques remain limited, particularly in Eastern European ICU settings [12-15]. Moreover, the interaction between intubation status, timing of rehabilitation initiation, and functional outcomes in severe COVID-19 populations requires further clarification.

Aim of the study. The present study aimed to evaluate the clinical correlations and functional impact of early rehabilitation interventions—including kinesitherapy and proprioceptive focal stimulation—in critically ill patients with SARS-CoV-2 infection and ICU-acquired weakness, and to identify factors associated with unfavorable functional evolution during ICU stay.

MATERIALS AND METHODS

1. Study Design and Setting

The present research was designed as a retrospective observational cohort study conducted in the adult Intensive Care Unit (ICU) of the National Institute for Infectious Diseases “Prof. Dr. Matei Balș”, Bucharest, Romania. The study period extended from 9 June 2020 to 9 June 2022, corresponding to the major pandemic waves requiring intensive care support.

The study followed the principles of the Declaration of Helsinki and current recommendations for observational clinical research. All rehabilitation procedures were integrated into routine clinical care and adapted to the dynamic clinical status of critically ill patients.

2. Participants and Eligibility Criteria

A total of 148 patients with confirmed SARS-CoV-2 infection were included in the analysis.

Inclusion criteria:

- age ≥ 18 years;
- confirmed COVID-19 diagnosis by RT-PCR;
- admission to adult ICU;
- clinical indication for physical and rehabilitation medicine (PRM) intervention;
- hemodynamic stability sufficient to allow at least passive mobilization.

Exclusion criteria:

- pre-existing severe neuromuscular disorders;
- major limb amputation;
- unstable fractures that contraindicate mobilization;
- incomplete clinical data.

Patients were consecutively enrolled to minimize selection bias.

3. Multidisciplinary Rehabilitation Team

Rehabilitation management was delivered by a specialized multidisciplinary team coordinated by a physician in Physical and Rehabilitation Medicine and supported by physiotherapists/kinetotherapists, ICU physicians, nursing staff, when necessary, occupational therapists and speech therapists.

This integrated approach is consistent with modern ICU rehabilitation frameworks [9,16-19].

4. Rehabilitation Protocol

The rehabilitation program was individualized according to the patient's clinical status, respiratory support level, and neurological responsiveness. Interventions were progressively adapted from passive to active-assisted modalities. Of the total of 148 patients participating in the study, 98 (66.2%) received functional proprioceptive stimulation treatment through vibrations with the specific device, and the remaining 50 (33.8%) patients benefited from physiotherapy. The device was a multifunctional rehabilitation system integrating a central control unit with an interactive touchscreen display, combined with upper and lower limb support structures, proprioceptive stimulation modules, and adjustable positioning frames to facilitate motor recovery, balance training, and neuromuscular re-education in clinical settings.

4.1. Kinesitherapy

Kinesitherapy represented the core rehabilitation intervention and included passive mobilization of major joints, passive-active mobilization, low-, medium-, and high-resistance exercises when feasible, positioning and postural management, prevention of joint stiffness and pressure injuries. Session frequency and duration were tailored to patient tolerance and ICU constraints.

4.2. Proprioceptive Focal Stimulation (PFS)

Selected patients received adjunctive proprioceptive focal stimulation using a dedicated medical device designed to deliver patterned sensory inputs mimicking physiological gait-related afferent signals.

The system consisted of a central control and charging unit, wireless stimulators, limb orthoses and fixation straps, and a mobile support system for bedridden patients. The therapeutic rationale was to maintain sensorimotor loop activation and preserve central motor programs even in the absence of voluntary movement [11,20].

5. Outcome Measures

Functional and clinical assessment was performed using validated instruments widely employed in ICU rehabilitation research.

Primary functional measures: Medical Research Council (MRC) muscle strength score (0–5 grading), ICU Mobility Scale (IMS), Manchester Mobility Score, and Glasgow Coma Scale (GCS).

Secondary qualitative measures quality of movement sensation, motor response quality, and level of active participation. Evaluations were performed at rehabilitation initiation and at ICU discharge when clinically feasible.

6. Recorded Variables

The study database included both quantitative and qualitative variables.

Demographic and clinical variables include sex, age, intubation status, and days until initiation of rehabilitation.

Musculoskeletal variables include motor deficit severity, presence of muscular atrophy, and functional mobility scores.

Rehabilitation exposure variables include the number of kinesitherapy sessions, the number of PFS sessions, the total duration of rehabilitation, and the intensity level of exercises.

7. Statistical Analysis

Statistical processing was performed using IBM SPSS Statistics version 20. Descriptive statistics were used to characterize the study population.

Inferential analysis included Chi-square test and Fisher’s exact test for associations between categorical variables, Mann–Whitney U test and Kruskal–Wallis test for non-parametric comparisons, Spearman rank correlation (two-tailed) for relationships between quantitative variables.

Effect size indicators (Phi coefficient and odds ratio, where applicable) were calculated to estimate the strength of associations. Statistical significance was set at $p < 0.05$.

8. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the National Institute for Infectious Diseases "Prof. Dr. Matei Balş" (approval code: 3249).

Given the observational nature of the study and the use of standard-of-care rehabilitation procedures, informed consent was obtained according to institutional regulations.

RESULTS

1. Characteristics of the Study Group

The analyzed cohort included 148 patients admitted to the adult intensive care unit with confirmed SARS-CoV-2 infection. The demographic and clinical profile reflected a severely affected critical care population requiring complex multidisciplinary management.

Out of the total sample, 108 patients (73.0%) required endotracheal intubation and invasive mechanical ventilation, while 40 patients (27.0%) were managed without intubation. This distribution highlights the high severity burden of the studied ICU population.

Male patients were predominant in the severe clinical spectrum, consistent with previously reported sex-related differences in COVID-19 severity.

2. Association between Intubation Status and Musculoskeletal Complications

A highly significant association was identified between intubation status and the presence of muscular atrophy. The chi-square test demonstrated a very strong relationship between invasive ventilation and musculoskeletal deterioration (χ^2 test, $p = 7.1\times10^{-10}$).

From a clinical perspective, intubated patients showed a markedly higher prevalence of muscle atrophy compared with non-intubated patients, supporting the hypothesis that prolonged immobilization and mechanical ventilation substantially contribute to ICU-acquired weakness.

Similarly, motor deficit severity was more pronounced among intubated patients, reinforcing the central role of respiratory support duration in functional decline.

3. ICU Mobility Outcomes According to Intubation Status

Functional mobility at ICU discharge, assessed using the ICU Mobility Scale, differed significantly between the two groups.

The Mann–Whitney U test revealed that intubated patients had significantly lower mobility scores compared with non-intubated patients ($p = 1.56\times10^{-11}$). The magnitude of this difference indicates a clinically meaningful functional gap between the groups. These findings confirm that invasive mechanical ventilation is strongly associated not only with respiratory severity but also with impaired early functional recovery.

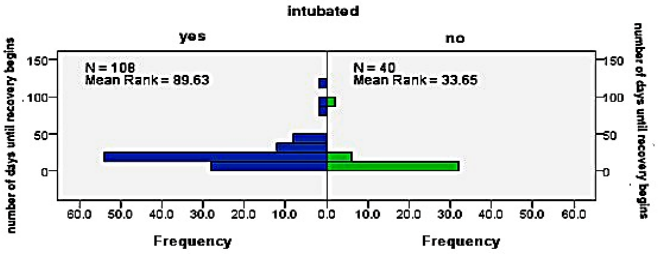
Table 1 summarizes the functional outcomes according to intubation status.

Table 1: Summary of the functional outcomes according to intubation status.

Parameter	Value
Total N	148
Mann-Whitney U	3794.000
Wilcoxon W	9680.000
Test statistic	3794.000
Standard Error	231.234
Standardized Test Statistic	7.066
Asymptotic Sig. (2-sided test)	.000

Figure 1 illustrates the distribution of ICU Mobility Scale scores in intubated versus non-intubated patients.

Figure 1: Distribution of ICU Mobility Scale scores in intubated versus non-intubated patients.



4. Timing of Rehabilitation Initiation and Functional Recovery

An important objective of the present study was to evaluate whether the delay in initiating the rehabilitation program influenced functional outcomes.

Spearman correlation analysis demonstrated a moderate negative correlation between the number of days until rehabilitation onset and the ICU Mobility Scale score at discharge ($\rho = -0.397$). This finding indicates that patients who started rehabilitation earlier tended to achieve better functional mobility.

From a clinical standpoint, this result strongly supports the concept of early mobilization as a key determinant of functional prognosis in critically ill COVID-19 patients.

5. Participation and Sensorimotor Response during Rehabilitation

Qualitative analysis of rehabilitation sessions showed that patients who were able to engage earlier in passive-active or assisted mobilization demonstrated improved quality of movement sensation, better motor response scores, and higher levels of active participation. Although variability existed depending on clinical stability, the overall trend favored early, progressively intensified rehabilitation exposure. At the end of the program, 39.2% (58 patients) were transferred to the ward.

6. Mortality and Severity Profile

Consistent with the observed functional impairments, intubated patients also exhibited a more severe overall clinical trajectory. At the end of the program, 60.8% (90 patients) died. The coexistence of muscular atrophy, severe motor deficit, and reduced mobility scores characterized the subgroup with the highest risk profile. These findings emphasize the tight interconnection between respiratory severity, immobilization burden, and neuromuscular deterioration in critically ill COVID-19 patients.

DISCUSSION

The present study provides additional real-world evidence regarding the functional burden associated with severe SARS-CoV-2 infection in critically ill patients and reinforces the central role of early physical and rehabilitation medicine (PRM) interventions in the intensive care setting. Several clinically relevant observations emerged from the analysis.

First, the very high proportion of intubated patients (73%) reflects the severity profile of the studied cohort and is consistent with reports from tertiary COVID-19 centers during peak pandemic waves [6,12]. More importantly, intubation status was strongly associated with muscular atrophy and impaired mobility outcomes. The highly significant relationship identified in our cohort ($p = 7.1\times10^{-10}$) supports the well-established pathophysiological link between prolonged mechanical ventilation, immobilization, systemic inflammation, and the development of ICU-acquired weakness (ICUAW) [3,4].

Our findings are in line with previous investigations demonstrating that patients requiring invasive mechanical ventilation are at markedly increased risk of critical illness polyneuropathy and myopathy [5,13]. The observed functional gap between intubated and non-intubated patients, as reflected by significantly lower ICU Mobility Scale scores ($p = 1.56\times10^{-11}$), further confirms that respiratory severity directly translates into early functional disability. From a clinical rehabilitation perspective, this emphasizes the need for proactive neuromuscular monitoring in mechanically ventilated COVID-19 patients.

A particularly important contribution of the present study is the demonstration of a moderate negative correlation between delayed initiation of rehabilitation and functional mobility at ICU discharge ($\rho = -0.397$). This finding strongly supports the concept that timing matters in ICU rehabilitation. Earlier studies in non-COVID critical care populations have shown that early mobilization is associated with shorter duration of delirium, improved muscle strength, and better functional independence at discharge [8,14]. Our data extend these observations specifically to the severe COVID-19 population, where implementation barriers were initially substantial.

From a mechanistic standpoint, early mobilization likely mitigates multiple pathways involved in the development of ICUAW, including muscle protein catabolism, mitochondrial dysfunction, impaired neuromuscular junction transmission, and central motor

deconditioning [3,15]. In the context of SARS-CoV-2 infection, these mechanisms may be further amplified by cytokine-mediated inflammation and prolonged hypoxemia, making timely rehabilitation even more critical.

Another relevant aspect of the present study is the integration of proprioceptive focal stimulation (PFS) within the rehabilitation protocol. Although the current analysis was not designed to isolate the independent effect of PFS, qualitative observations suggested improved sensorimotor engagement in patients exposed to structured proprioceptive input. The theoretical rationale for PFS is supported by neurophysiological principles indicating that patterned afferent stimulation can help preserve central pattern generator activity and maintain sensorimotor loop integrity even in conditions of limited voluntary movement [11,16]. This approach may be particularly valuable in deeply sedated or minimally responsive ICU patients, where conventional active mobilization is not yet feasible.

The multidimensional nature of post-intensive care syndrome (PICS) must also be considered when interpreting our results. Physical impairment rarely occurs in isolation and is frequently accompanied by cognitive and psychological sequelae [7]. Therefore, the benefits of early PRM involvement likely extend beyond pure motor recovery, potentially contributing to improved global functional trajectories. This supports current recommendations advocating for early, multidisciplinary rehabilitation pathways in critical care [9,16].

From a sex-related perspective, our observations of more severe functional profiles among male patients are consistent with epidemiological data showing higher COVID-19 severity and mortality in men [12]. Potential explanations include differences in immune response, hormonal modulation, comorbidity burden, and health-seeking behavior. While sex was not the primary focus of the present study, these findings suggest that male ICU patients may require particularly vigilant functional monitoring.

Clinical Implications

The present findings carry several practical implications for ICU teams, such as that early PRM consultation should be considered standard of care in severe COVID-19, mobilization protocols should begin as soon as hemodynamic stability allows, mechanically ventilated patients represent a high-risk subgroup for ICUAW, adjunctive modalities such as proprioceptive stimulation may be useful in low-responsiveness phases, continuity of rehabilitation after ICU discharge is essential.

In resource-constrained environments, even low-intensity early mobilization strategies may yield meaningful functional benefits.

Study Limitations

Several limitations must be acknowledged. First, the observational design precludes causal inference regarding the effectiveness of the rehabilitation interventions. Second, although the cohort reflects real-world ICU practice, potential confounding related to baseline disease severity and comorbidities cannot be fully excluded. Third, long-term post-discharge functional outcomes were not available, limiting conclusions regarding sustained recovery. Finally, the independent contribution of proprioceptive focal stimulation could not be isolated from the global rehabilitation program.

Future Directions

Future research should prioritize randomized controlled trials of early ICU rehabilitation in COVID-19, dose–response analyses of mobilization intensity, long-term functional follow-up, mechanistic studies of sensorimotor stimulation in ICUAW, and integration of digital and automated rehabilitation technologies. Such investigations may help refine personalized rehabilitation pathways for critically ill patients.

CONCLUSION

The present study confirms the substantial functional burden associated with severe SARS-CoV-2 infection in critically ill patients and highlights the pivotal role of early physical and rehabilitation medicine (PRM) interventions in the intensive care environment. In our cohort, invasive mechanical ventilation was strongly associated with muscular atrophy and significantly reduced functional mobility, emphasizing the close interplay between respiratory severity and neuromuscular deterioration.

An important finding of this research is the moderate negative correlation between delayed initiation of rehabilitation and functional mobility at ICU discharge, supporting the concept that early mobilization represents a key determinant of functional prognosis in severe COVID-19. Patients who benefited from earlier rehabilitation exposure demonstrated better sensorimotor engagement and higher levels of active participation.

The integration of conventional kinesitherapy with adjunctive proprioceptive focal stimulation appears feasible in the ICU setting and may contribute to preserving sensorimotor loop activity during phases of limited voluntary movement. Although further controlled studies are required to isolate the independent effect of this modality, the present data support its potential role within comprehensive ICU rehabilitation protocols.

From a clinical perspective, mechanically ventilated patients should be considered a high-risk subgroup for intensive care unit-acquired weakness and require proactive functional monitoring and early rehabilitation planning. Continuity of multidisciplinary rehabilitation after ICU discharge remains essential for optimizing long-term recovery trajectories.

Future research should focus on randomized controlled trials, standardized early mobilization algorithms, and long-term functional follow-up in post-COVID critical care survivors. The development of personalized, phase-adapted rehabilitation pathways may further improve outcomes in this vulnerable population.

The present study has several strengths that enhance its clinical relevance. First, it reflects real-world ICU practice during the COVID-19 pandemic, providing valuable insight into the functional evolution of critically ill patients managed in a high-complexity infectious diseases center. Second, the study integrates standardized functional assessment tools (MRC, ICU Mobility Scale, Manchester Mobility Score, Glasgow Coma Scale), allowing objective evaluation of neuromuscular status. Third, the analysis includes the timing of rehabilitation initiation, an important but often underreported determinant of functional recovery.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. This research received no external funding.

Acknowledgments

No generative AI was used by the authors in the production of this article.

Authors' contribution

Conceptualization, A.P. and E.C.; methodology, M.P.; software, E.C.; validation, C.U., M.P., and A.S.C.; formal analysis, C.U.; investigation, A.P.; resources, A.P.; data curation, A.P.; writing—original draft preparation, A.P.; writing—review and editing, E.C.; visualization, M.P.; supervision, A.S.C.; project administration, A.P.; funding acquisition, A.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 National Institute for Infectious Diseases "Prof. Dr. Matei Balș" Ethics Committee, protocol code 3249 for studies involving humans.

Patient consent for publication

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

References

1. Zhou C, Wu L, Ni F, Ji W, Wu J, Zhang H. Critical illness polyneuropathy and myopathy: a systematic review. Neural Regen Res. 2014;9(1):101–110. doi:10.4103/1673-5374.125337

2. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011;364(14):1293–1304. doi:10.1056/NEJMoa1011802

3. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness. Lancet Neurol. 2011;10(10):931–941. doi:10.1016/S1474-4422(11)70178-8

4. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing ICU-acquired weakness. Crit Care Med. 2009;37(10 Suppl):S299–S308. doi:10.1097/CCM.0b013e3181b6ef67

5. Moisey LL, Mourtzakis M, Cotton BA, et al. Skeletal muscle predicts ventilator-free days. Crit Care. 2013;17:R206. doi:10.1186/cc12901

6. Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after ICU discharge. Crit Care Med. 2012;40(2):502–509. doi:10.1097/CCM.0b013e318232da75

7. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. J Transl Int Med. 2017;5(2):90–92. doi:10.1515/jtim-2016-0016

8. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated patients. Lancet. 2009;373(9678):1874–1882. doi:10.1016/S0140-6736(09)60658-9

9. Hodgson CL, Stiller K, Needham DM, et al. Expert consensus on early rehabilitation in ICU. Intensive Care Med. 2014;40(12):1751–1763. doi:10.1007/s00134-014-3368-8

10. Curci C, Negrini F, Ferrillo M, et al. Functional outcome after inpatient rehabilitation in post-COVID-19 patients. Eur J Phys Rehabil Med. 2021;57(3):443–450. doi:10.23736/S1973-9087.21.06547-6

11. Zhou SA, Zhou L. Physical Medicine and Rehabilitation. In: Comprehensive Biomedical Physics. Elsevier; 2014.

12. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified as a risk factor for COVID-19 severity. Nat Commun. 2020;11:6317. doi:10.1038/s41467-020-19741-6

13. Tipping CJ, Harrold M, Holland A, et al. Early mobilization in ICU: systematic review. Crit Care. 2017;21:276. doi:10.1186/s13054-017-1836-2

14. Batt J, Dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness. Neurol Clin. 2014;32(3):613–628. doi:10.1016/j.ncl.2014.04.015

15. Hermans G, Van den Berghe G. Clinical review: intensive care unit-acquired weakness. Crit Care. 2015;19:274. doi:10.1186/s13054-015-0993-7

16. Spruit MA, Holland AE, Singh SJ, et al. COVID-19 rehabilitation recommendations. Eur Respir J. 2020;56:2002197. doi:10.1183/13993003.02197-

2020

17. Ursescu C, Costescu E, Popescu MN, Țabrean MC, Berteanu M. Modeling post-COVID respiratory rehabilitation with nonlinear dynamics and fractal metrics: beyond spirometry. Balneo PRM Res J. 2025;16(4). doi:10.12680/balneo.2025.901

18. Păduraru CS, Păduraru O, Costescu E, Duceac LD. Clinical and infrastructure risk management in an emergency hospital unit in Iași, Romania. Balneo PRM Res J. 2025;16(3). doi:10.12680/balneo.2025.834

19. Călin G, Costescu E, Damir DL, Mihai C, Grierosu C, Ciuhodaru T. Pluridisciplinary approaches in global postural rehabilitation. Balneo PRM Res J. 2024;15(2). doi:10.12680/balneo.2024.711

20. Mazzoleni S, Stampacchia G, Battini E, et al. Sensorimotor stimulation approaches in neurorehabilitation. Biomed Res Int. 2013;2013:613959. doi:10.1155/2013/613959

https://doi.org/10.55453/rjmm.2026.129.3.10

REVIEW

Analgesia in Military Mass-Casualty (MASCAL) Incidents: Evidence Synthesis and an Operational Triage-Linked Framework

Georgi Semovski[1,*], Ahmed Nedzhib[1,*], Dimo Dimov[1]

[1] Department of Disaster Medicine, Military Medical Academy, 3, St. Georgi Sofiyski Str., 1606 Sofia, Bulgaria

*Correspondence: mazoa94@gmail.com (GS); anedzhib@gmail.com

Abstract: Military mass-casualty (MASCAL) incidents impose severe constraints on analgesia delivery due to rapid triage, limited monitoring capacity, and heterogeneous provider qualifications. This review aimed to map current evidence on battlefield analgesics and identify options suitable for high-throughput MASCAL conditions. A scoping review was conducted following PRISMA-ScR methodology, including a systematic PubMed/MEDLINE search (2017-2023), dual-review screening, predefined eligibility criteria, and structured data extraction. Sixty-six articles met the inclusion criteria. Evidence indicates that transmucosal opioids – oral transmucosal fentanyl citrate (OTFC) and the sufentanil sublingual tablet (SST) – provide rapid, effective analgesia but require continuous observation, airway-rescue competence, and governance controls, which may limit their safe use in large-scale MASCAL operations. Ketamine demonstrates the most favorable operational profile, combining reliable analgesia with preserved airway reflexes, cardiovascular stability, flexible dosing routes, and minimal monitoring requirements. Cannabinoid preparations and α2-agonists lack sufficient evidence for acute trauma analgesia and present pharmacologic or safety limitations that preclude routine prehospital use. Based on these findings, we propose a triage-linked analgesia framework that aligns agent selection with provider level, monitoring capacity, and evacuation timelines. Overall, ketamine emerges as the primary analgesic option for MASCAL incidents, whereas transmucosal opioids should be reserved for trained personnel operating under protocolized oversight.

Keywords: Mass-casualty (MASCAL) events; Tactical Combat Casualty Care (TCCC); Oral transmucosal fentanyl citrate (OTFC); Sufentanil sublingual tablet (SST); Prehospital military medicine.

INTRODUCTION

Effective pain management is a critical component of combat casualty care, directly influencing survival, functional outcomes, and evacuation readiness. Pain is widely recognized as the fifth vital sign, and its timely, context-appropriate treatment becomes particularly challenging during military mass-casualty (MASCAL) incidents, where casualty volume exceeds medical capacity and constraints on personnel, monitoring, and time limit clinical decision-making [1]. For the purposes of this review, “prehospital” care includes all interventions from the point of injury to initial evacuation, and “analgesia” refers to pharmacologic strategies targeting acute pain and its physiologic consequences.

The development of Tactical Combat Casualty Care (TCCC) since 1996 has transformed battlefield medicine and substantially reduced preventable mortality during operations in Iraq and Afghanistan [2,3]. Current TCCC guidelines endorse a tiered analgesia strategy based on pain severity and provider qualification, including non-steroidal anti-inflammatory drugs (NSAIDs), ketamine, and oral transmucosal fentanyl citrate (OTFC). OTFC (800 µg) offers rapid, non-invasive analgesia without the need for intravenous access – an advantage of particular significance during MASCAL events characterized by accelerated triage and limited equipment availability [4,5].

However, OTFC – like all opioids – has a narrow therapeutic index and may cause respiratory depression, requiring airway-rescue capability and continuous observation. These risks are magnified in MASCAL conditions, where high casualty throughput and variable provider experience increase the likelihood of dosing or monitoring errors [6,7]. Concurrently, the broader global opioid crisis underscores the need for responsible opioid stewardship in operational environments [8-10],

Citation: Semovski G, Nedzhib A, Dimov D *Analgesia in military mass-casulaty (MASCAL) incidents: Evidence synthesis and an operational triage-linked framework* R. J. Mil. Med. 2026, CXXIX(3): 320-334 https://doi.org/10.55453/rjmm.2026.129.3.10

Academic Editor: Clara Ursescu

Received: 25 January 2025
Revised: 21 March 2026
Accepted: 28 March 2026

stimulating renewed interest in optimizing existing analgesics and evaluating potential adjuncts that could reduce opioid burden without compromising efficacy.

Military medicine, therefore, requires analgesic agents that are potent, fast-acting, logistically lightweight, and safe for use across multiple provider levels [3,11]. Because MASCAL scenarios differ fundamentally from routine battlefield care – particularly regarding triage prioritization, monitoring capability, and evacuation timelines – there is a need for an operationally grounded framework guiding analgesic selection during large-scale casualty surges. This review synthesizes current evidence on established and emerging analgesic modalities, evaluates their suitability for MASCAL environments, and proposes a triage-linked analgesia algorithm to support clinical decision-making during military mass-casualty incidents.

METHODS

This study was conducted as a scoping review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [12]. The objective was to map contemporary evidence on pharmacologic analgesia relevant to military prehospital care, with specific emphasis on mass-casualty (MASCAL) conditions where resource constraints, rapid triage, and variable provider qualifications affect therapeutic choices.

1. Conceptual framework and operational focus

Consistent with the definitions outlined in the Introduction, the review targeted studies applicable to:

- MASCAL environments, defined as incidents in which casualty volume exceeds available medical capacity [13].
- Prehospital military care, spanning the point of injury through the initial evacuation phases [3,14].
- Analgesia, referring to pharmacologic interventions for acute trauma pain with operational relevance [15].

The operational intent of the review was to support the development of a structured, triage-linked analgesia framework suitable for battlefield and MASCAL conditions [16,17].

2. Information sources

A structured literature search was performed in PubMed/MEDLINE, selected for its comprehensive indexing of military medicine, trauma, anesthesiology, emergency care, and pharmacology [18,19]. The search period spanned 1 January 2017 to 1 June 2023, reflecting recent developments in opioid stewardship, adjunct analgesia, and battlefield protocols [20,21].

Reference lists of eligible studies and pertinent reviews were also screened to identify additional sources [22].

3. Search strategy

The search combined Medical Subject Headings (MeSH) and free-text terms. Boolean operators were applied to optimize sensitivity [23]. The core strategy was:

("analgesia"[MeSH] OR "acute pain" OR "pain management") AND ("combat" OR "military" OR "battlefield" OR "prehospital") AND ("mass casualty" OR "MASCAL" OR "triage") AND ("opioids" OR "fentanyl" OR "sufentanil" OR "OTFC" OR "ketamine" OR "cannabinoids" OR "alpha-2 agonists").

The full list of search strings is provided in Appendix 1 (PRISMA-ScR Search Strategy) [24].

4. Eligibility criteria

Inclusion criteria:

- Studies examining acute pain management relevant to prehospital or battlefield settings [25];
- Evaluation of pharmacologic analgesics (opioids, ketamine, cannabinoid-based agents, α2-adrenergic agonists, or opioid-sparing strategies) [26];
- Findings with operational implications for military use or MASCAL environments [27];
- English-language publications, 2017-2023;
- Clinical, experimental, observational, or review methodologies applicable to austere decision-making contexts [28].

Exclusion criteria:

- Chronic pain studies;
- Non-trauma or elective surgery contexts;

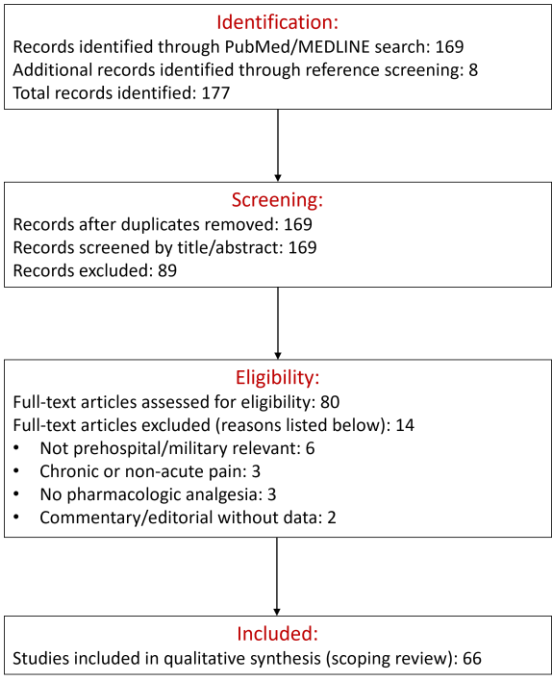
- Articles lacking prehospital or operational relevance;
- Narrative commentaries without substantive data;
- Non-English publications.

5. Selection of sources of evidence

Two reviewers independently screened titles and abstracts, followed by full-text review of potentially eligible studies [29]. Discrepancies were resolved through consensus. This dual-review approach ensured methodological rigor consistent with PRISMA-ScR recommendations [12].

The search yielded 169 records; after screening and full-text assessment, 66 studies met the inclusion criteria. The selection process is depicted in Figure 1 [30].

Figure 1: PRISMA-ScR flow diagram for study selection.



6. Data charting process

A standardized data-charting template was developed a priori [31]. Extracted variables included:

- Study characteristics and design;
- Population and operational context;
- Analgesic agent, dose, route, onset, and duration;
- Monitoring requirements;
- Adverse effects and operational risks;
- Applicability to MASCAL triage and resource limitations;
- Key findings and recommendations.

Two reviewers independently extracted data to ensure accuracy and completeness [32].

7. Synthesis of results

Due to heterogeneity across study designs and outcome measures, results were synthesized narratively [33]. Evidence was categorized into:

1. Opioid analgesics in battlefield and MASCAL settings;
2. Dissociative analgesia and ketamine-based regimens;
3. Opioid-sparing and adjunctive agents, including cannabinoids and α2-adrenergic agonists;
4. Governance and monitoring requirements across provider levels;
5. Operational implications for triage-linked decision-making in MASCAL environments.

These findings informed the development of:

- Table 1: Analgesic options and operational characteristics;
- Table 2: Triage-linked MASCAL analgesia workflow [34].

RESULTS

A total of 66 studies met the inclusion criteria and were analyzed. Evidence was organized into four domains relevant to analgesia in prehospital battlefield and mass-casualty (MASCAL) environments: (1) opioid analgesics, (2) dissociative analgesia with ketamine, (3) opioid-sparing adjuncts including cannabinoids and α_2-adrenergic agonists, and (4) operational considerations related to provider capabilities, monitoring, and governance.

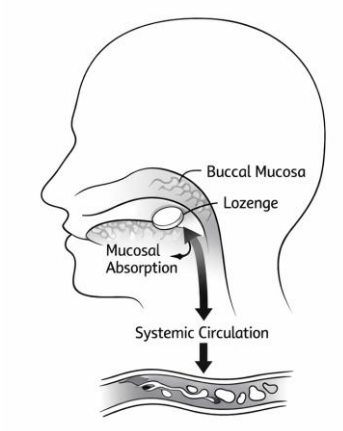
1. Opioid analgesics in battlefield and MASCAL Settings

1.1. Oral Transmucosal Fentanyl Citrate (OTFC)

OTFC 800 µg consistently demonstrated rapid analgesic onset (5-10 min) and operational advantages due to non-invasive buccal administration (Figure 2) [35,36]. Studies highlighted its suitability in settings where intravenous access is impractical, aligning with TCCC analgesia guidance [4,5,37]. Preliminary experience in civilian mass-casualty responses also supported its usefulness in resource-limited environments [38].

However, multiple studies emphasized OTFC's narrow therapeutic index and potential for respiratory depression, particularly in settings lacking sustained monitoring [6,39]. Case series and guideline analyses underscored the need for airway-rescue capability and close observation, with concerns about dosing control during high-throughput MASCAL conditions [7,40]. Data from Operation HERRICK further illustrated the practical challenges of opioid administration in austere combat environments [41].

Figure 2: Conceptual illustration of buccal (oral transmucosal) opioid administration.



Schematic representation of a solid transmucosal dosage form positioned against the buccal mucosa. The active compound is absorbed directly through the oral mucosal vasculature into the systemic circulation, providing rapid analgesic onset without the need for intravenous access. The illustration is author-generated and intended for explanatory purposes only.

1.2. Sufentanil Sublingual Tablet (SST)

SST 30 µg demonstrated rapid absorption (Figure 3), favorable pharmacokinetics, and a comparatively advantageous therapeutic index [42,43]. Studies reported a median three-hour duration of effect and reduced dosing errors due to the single-dose applicator design [44,45]. Reviews consistently confirmed analgesic efficacy in acute pain settings [46].

Operational analyses suggested potential advantages over OTFC, including greater dosing accuracy and lower incidence of euphoria-related side effects [47]. However, regulatory guidance (DSUVIA™, DZUVEO™) mandates administration under trained supervision, which limits applicability for lower-level providers during MASCAL events [48,49]. Intranasal sufentanil showed promise but requires further validation for emergency use [50].

1.3. Other opioids

Evidence for intravenous fentanyl or morphine in austere prehospital settings was limited [51]. Logistical and safety barriers – including the need for intravenous (IV) access, risk of hypotension, and continuous monitoring – restricted their relevance to MASCAL care [52,53]. No included study supported widespread IV opioid administration by non-physician personnel during mass-casualty events [54]. Analyses of care during the Afghanistan conflict highlighted complexities surrounding prehospital opioid use [55], and systematic reviews reinforced the need for caution when employing opioids for acute prehospital pain [56].

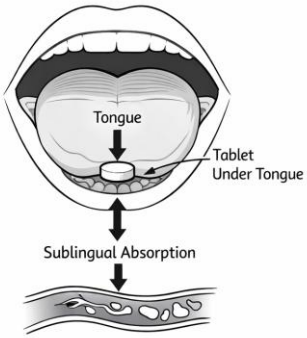
2. Dissociative Analgesia: Ketamine

Ketamine was the most consistently supported agent across the reviewed literature [57,58]. Multiple military and civilian trauma studies confirmed reliable analgesia with preserved airway reflexes and cardiovascular stability [59,60]. Rapid onset (minutes) and multiple administration routes (IV; intramuscular; IN, intranasal) enabled effective use across variable provider skill levels [61,62]. Studies specific to combat casualty care demonstrated strong safety and efficacy profiles [63-65].

Evidence from high-throughput or resource-limited settings reported minimal need for airway intervention [66,67]. Adverse effects – including dysphoria and emergence reactions – were infrequent at analgesic doses and typically manageable with reassurance or adjunct benzodiazepines [68,69]. No significant incidence of respiratory depression was reported at standard analgesic dosing [70]. Systematic reviews supported ketamine's favorable benefit-to-risk ratio for prehospital acute pain [71,72].

Overall, ketamine emerged as the most operationally robust analgesic for MASCAL environments, requiring minimal monitoring while maintaining safety [73,74]. Intranasal ketamine has been highlighted as a simple, logistically advantageous option for battlefield analgesia [75].

Figure 3: Conceptual representation of sublingual tablet administration.



Diagrammatic depiction of sublingual placement of a tablet beneath the tongue. The medication dissolves and is absorbed through the highly vascularized sublingual mucosa, facilitating rapid systemic uptake and analgesic effect. The figure is an original author-created schematic for educational clarification.

3. Opioid-sparing and adjunctive agents

3.1. Cannabinoid-based agents

Cannabinoid preparations (THC, CBD, mixed formulations, oromucosal sprays) demonstrated mixed and generally low-quality evidence for acute pain [76,77]. Systematic reviews noted analgesic effects comparable to placebo in trauma and postoperative contexts [78,79], with some studies reporting increased postoperative pain or hypotension when used as adjuncts [80,81].

Critically, no included study supported cannabinoid use in prehospital trauma or MASCAL environments [82]. Unpredictable onset, variable pharmacokinetics, and psychoactive effects were consistently identified as limiting factors [83,84]. No article recommended cannabinoid use for operational analgesia outside controlled trials [85]. Emerging research on cannabis-derived terpenes remains experimental and lacks relevance to acute trauma care [86,87].

2.2. α2-Adrenergic agonists: Clonidine and Dexmedetomidine

Clonidine and dexmedetomidine were primarily evaluated in perioperative or intensive care contexts [88,89]. Clonidine demonstrated modest opioid-sparing effects [90,91], while dexmedetomidine produced sedation and sympatholysis but carried risks of bradycardia and hypotension requiring continuous monitoring [92,93].

No included study supported dexmedetomidine for prehospital trauma or MASCAL settings [94], and monitoring demands preclude use by non-physician providers [95]. Clonidine showed theoretical adjunctive value but lacked operational data supporting field application [96].

4. Operational and provider-level considerations

Across studies, provider training, monitoring capability, and environmental constraints were consistently identified as the decisive factors shaping analgesic suitability [97,98]. Recurring themes included:

- Essential airway-rescue capability when using opioids, particularly OTFC or SST [99,100].
- Increased risks associated with sedative or respiratory-depressant agents in low-monitoring MASCAL settings [101,102].
- Wide variation in provider qualifications (CLS, medic, physician) influencing safe medication use [103,104].
- Impact of analgesic choice on evacuation timelines and triage throughput [27,105].

Additional studies described organizational challenges during mass-casualty incidents, including hospital flow during terrorist attacks [106], triage simplification [107], and the need for multinational coordination [108]. Military triage research provided insights relevant to MASCAL planning [109-111].

Evidence-based prehospital pain management guidelines [115] and long-term battlefield experiences [116–120] further informed operational considerations.

Only ketamine and single-dose transmucosal opioids (OTFC, SST) demonstrated consistent evidence supporting use in austere environments [94,117]. No other analgesic showed sufficient safety or operational feasibility for widespread prehospital use without substantial governance measures [118]. The operational characteristics of all evaluated agents appear in Table 1.

Table 1: Operational Characteristics of Analgesic Options for Military Prehospital and MASCAL Environments.

Agent	Onset	Duration	Route(s)	Dose Guardrails	Monitoring Requirements	Reversal / Mitigation	Key Operational Advantages	Contraindications / Limitations
OTFC, 800 µg	5-10 min	30-60 min	Transmucosal	One lozenge only; remove if AMS develops	Requires the ability to monitor respirations; airway-rescue capability	Naloxone	No IV needed; rapid relief; simple administration	Narrow therapeutic index; risk of respiratory depression in low-monitoring settings
SST, 30 µg	~15 min	≈3 h	Sublingual	Single-dose applicator; no immediate redosing	Opioid monitoring; avoid in AMS / hypoxia	Naloxone	Accurate dosing; higher therapeutic index than OTFC	Requires trained supervision; regulatory restrictions for unsupervised use
Ketamine (analgesic dose 0.1-0.3 mg/kg IV or 0.3-0.5 mg/kg IM/IN)	Minutes	20-40 min	IV, IM, IN	Avoid repeated full-dose boluses	Minimal airway monitoring; no airway-rescue required routinely	Benzodiazepines for dysphoria	Preserves airway reflexes; stable hemodynamics; safe for low-monitoring MASCAL	Emergence reactions in a small %; avoid in severe HTN

NSAIDs (e.g., Meloxicam, Ibuprofen)	20-40 min	4-8 h	PO	Standard dosing	No special monitoring	None	Safe profile; suitable for mild–moderate pain	Slow onset; contraindications in bleeding, renal injury, or dehydration
α_2-Agonists (Clonidine)	30-60 min	Several hours	PO, transdermal, adjunct	Not the primary agent	BP/HR monitoring required	None specific	Adjunct opioid-sparing effect	Hypotension, bradycardia; limited field evidence
Dexmede-tomidine	Slow (IV infusion)	Variable	IV	Requires titrated infusion; not suitable for bolus	Continuous HR/BP/O_2 monitoring	None	Sedation + analgesia synergy	Not suitable for prehospital or MASCAL settings; hemodynamic instability
Cannabinoids (various)	Variable (slow)	Variable	PO, oromucosal spray	Not standardized dosing for acute trauma	Cognitive monitoring	None	Limited/no acute analgesia evidence	Not recommended; unpredictable effects

* Abbreviations: IV, intravenous; IM, intramuscular; IN, intranasal; PO, per os (orally); BP, blood pressure; HR, heart rate; O2, oxygen saturation; AMS, altered mental status; HTN, hypertension.

DISCUSSION

Effective analgesia in military mass-casualty (MASCAL) incidents requires agents that balance potency, safety, rapid onset, and logistical feasibility under limited monitoring and variable provider proficiency. The findings of this scoping review demonstrate that, despite significant advances in combat casualty care, only a narrow subset of pharmacologic options meets the operational requirements of prehospital battlefield and MASCAL environments [3,37]. These results closely align with prior analyses of TCCC-based pain management and highlight the persistent trade-off between clinical effectiveness and field applicability [5]. Table 2 provides a triage-linked framework mapping analgesic selection to provider qualifications and minimum monitoring thresholds during MASCAL operations.

Table 2: MASCAL Workflow Linking Triage Category to Permissible Analgesic Agents, Provider Level, and Minimum Monitoring.

Triage Category	Permissible Analgesic Agents	Provider Level	Minimum Monitoring Requirements	Evacuation Implications
Immediate (Red)	Ketamine (IV/IM/IN); OTFC; SST (only if airway stable); limited IV opioids (physician only)	Medic / Physician	Respiratory rate; mental status; SpO_2 if available	Rapid evacuation; avoid agents requiring prolonged observation
Delayed (Yellow)	Ketamine; OTFC; SST; NSAIDs	CLS / Medic / Physician	Periodic airway check; RR; mental status	Analgesia should not delay triage assignment or evacuation timing
Minimal (Green)	NSAIDs; PO analgesics only	CLS	No continuous monitoring required	Evacuate after higher-priority categories
Expectant (Black)	Symptom-relief analgesia (ketamine IM/IN as available)	Medic / Physician	Comfort-focused monitoring	Analgesia should not divert resources from salvageable casualties

* Abbreviations: CLS, Combat Lifesaver (basic medical training); Medic (advanced tactical medic); Physician (medical officer). IV, intravenous; IM, intramuscular; IN, intranasal; OTFC, oral transmucosal fentanyl citrate; SST, sufentanil sublingual tablet; NSAIDs, non-steroidal anti-inflammatory drugs; PO, per os; RR, respiratory rate; SpO2, peripheral oxygen saturation.

1. Opioids: Benefits and persistent operational limitations

Opioids remain central to battlefield analgesia due to their established efficacy and familiarity among military personnel [4]. OTFC provides rapid, non-invasive analgesia compatible with TCCC priorities [5,36], but its narrow therapeutic index and risk of respiratory depression require airway-rescue capability and frequent observation – conditions difficult to maintain during high-throughput MASCAL operations [6,36,40]. These limitations increase vulnerability to dosing variability and monitoring gaps when administered by lower-level providers or during large casualty influxes [7].

SST offers advantages over OTFC, including a higher therapeutic index and reduced dosing variability [43]. However, regulatory mandates for trained supervision (EMA/FDA) restrict its use among providers such as combat lifesavers and medics during MASCAL events [44,45,48,49]. No included study supported unsupervised SST use in mass-casualty settings.

2. Ketamine as the most operationally feasible agent

Ketamine demonstrated the strongest evidence base across prehospital, trauma, and operational contexts [59]. Its preservation of airway reflexes, cardiovascular stability, and flexible administration routes make it uniquely suited for MASCAL conditions with limited monitoring capacity and variable provider skill [62]. No study reported significant respiratory compromise at analgesic doses, and psychoperceptual effects were infrequent and manageable [68]. These findings reinforce existing TCCC guidance and consensus statements positioning ketamine as the cornerstone of battlefield analgesia [57,121,122].

3. Cannabinoids and α2-adrenergic agonists: Insufficient evidence for field use

Although cannabinoids have been proposed as opioid-sparing agents, high-quality systematic reviews consistently demonstrate no clinically meaningful benefit for acute trauma pain, with effects comparable to placebo [78]. Their variable onset, psychoactive properties, and risk of hypotension render them inappropriate for prehospital or MASCAL use [80]. None of the included studies recommended cannabinoid use for operational trauma analgesia [79].

Similarly, α2-agonists demonstrated sedative and analgesic-sparing effects in controlled clinical settings [89], but all studies required continuous monitoring for bradycardia and hypotension [90,92,93]. Dexmedetomidine is clearly unsuitable for MASCAL conditions, while clonidine lacks operational evidence for prehospital trauma care [96]. The review found no support for deploying α2-agonists as primary or adjunct analgesics in MASCAL environments.

4. Operational implications: training, monitoring, and governance

Operational constraints consistently shaped analgesic appropriateness across included studies [99]. Limited monitoring, variable provider competency, and accelerated triage cycles restrict the safe use of many agents during MASCAL incidents [101]. These findings echo longstanding recommendations emphasizing strict governance, standardized dosing protocols, and provider-level limitations to minimize risk during battlefield analgesia [37,123].

A triage-linked algorithm integrating casualty category, provider qualification (CLS, medic, physician), and minimum monitoring requirements is therefore essential [40,125,126]. Opioids – whether OTFC or SST – should be limited to providers trained in airway management and supported by naloxone availability [99,100]. In contrast, ketamine's superior safety profile permits broader application across provider levels under austere conditions [57,62]. These findings directly inform the MASCAL workflows and decision tables (Tables 1 and 2). Additional work on prolonged field care indicates the need for specialized protocols when monitoring is extended or evacuation is delayed [127], while ongoing research continues to refine intranasal ketamine use for battlefield analgesia [128].

5. Synthesis and future directions

This review identifies a persistent gap between available analgesics and the operational demands of MASCAL military care [118]. Among evaluated agents, only ketamine and single-dose transmucosal opioids demonstrated sufficient feasibility for large-scale prehospital application [58,74,129]. Future research should prioritize:

- controlled field comparisons of OTFC and SST under MASCAL conditions [43];
- evaluation of opioid-sparing strategies that do not require continuous monitoring [77,81];
- development of simplified provider-level dosing schemas to reduce error risk [103];
- integration of portable physiological monitoring technologies for austere environments [102].

Given current evidence, operational doctrine must rely on agents with both pharmacologic validity and demonstrated field feasibility [11,37]. This review provides an evidence-based foundation for updated, triage-linked analgesia protocols specifically designed for military mass-casualty environments.

CONCLUSION

Effective analgesia in military mass-casualty (MASCAL) incidents requires agents that combine rapid onset, operational feasibility, and safety under conditions of limited monitoring and variable provider capability. This scoping review identified ketamine and single-dose transmucosal opioids (OTFC, SST) as the only pharmacologic options with consistent support for prehospital battlefield use, with ketamine demonstrating the most robust safety profile and flexibility. Evidence for cannabinoids and α2-adrenergic agonists remains insufficient for field implementation, particularly in environments requiring hemodynamic stability and predictable dosing.

A persistent gap remains in structured, triage-linked analgesia algorithms tailored to MASCAL operations. Standardized protocols aligned with provider qualifications, operational constraints, and evacuation priorities are essential for reducing adverse events and improving casualty flow. Future operational research should refine governance measures, evaluate emerging agents, and strengthen evidence-based battlefield pain management.

Actionable Recommendations for Military MASCAL Analgesia

1. Implement a triage-linked analgesia algorithm

Align analgesic choice with triage category and provider level, integrating protocols into SOPs and TCCC training.

2. Prioritize ketamine as first-line MASCAL analgesia

Utilize IV/IM/IN ketamine across provider levels; standardize dose cards to reduce variability.

3. Restrict opioid use to trained personnel with airway-rescue capability

Use OTFC and SST only when monitoring is feasible; ensure naloxone availability at all echelons of care.

4. Avoid cannabinoids and α2-agonists in prehospital or MASCAL care

Current evidence does not support their operational adoption outside controlled clinical environments.

5. Strengthen documentation and provider training

Use simplified field documentation and focused training on opioid safety, ketamine effects, and MASCAL-specific decision-making.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

This research received no external funding.

Authors' contribution

Conceptualization, G.S., and A.N.; methodology, G.S., and A.N.; investigation, G.S., and A.N.; resources, G.S., and A.N; data curation, A.N.; writing – original draft preparation, G.S.; writing – review and editing, A.N., and D.D.; visualization, A.N.; supervision, D.D.; project administration, A.N., and D.D. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable

References

1. Morone NE, Weiner DK. Pain as the fifth vital sign: exposing the vital need for pain education. Clin Ther, 2013, 35, 11, 1728-1732, doi 10.1016/j.clinthera.2013.10.001.

2. Butler FK, Haymann J, Butler EG. Tactical Combat Casualty Care in special operations. Mil Med, 1996,161, Suppl, 3-16, doi 10.1007/978-3-319-56780-8_1.

3. Butler FK. Two decades of saving lives on the battlefield: Tactical Combat Casualty Care turns 20. Mil Med, 2017, 182, 3, e1563-e1568, doi 10.7205/MILMED-D-16-00214.

4. Fisher AD, DesRosiers TT, Drew BG. Prehospital analgesia and sedation: A perspective from the battlefield. Curr Trauma Rep, 2020, 6, 207-217, doi 10.1007/s40719-020-00199-2.

5. Wedmore IS, Kotwal RS, McManus JG, Pennardt A, Talbot TS, et al. Safety and efficacy of oral transmucosal fentanyl citrate for prehospital pain control on the battlefield. J Trauma Acute Care Surg, 2012, 73, 6 Suppl 5, S490- S495, doi: 10.1097/TA.0b013e3182754674.

6. Naylor JF, April MD, Thronson EE, Hill GJ, Schauer SG. U.S. Military medical evacuation and prehospital care of pediatric trauma casualties in Iraq and Afghanistan. Prehosp Emerg Care, 2020, 24, 2, 265-272, doi: 10.1080/10903127.2019.

7. Kotwal RS, Howard JT, Orman JA, Tarpey BW, Bailey JA, et al. The effect of a golden hour policy on the morbidity and mortality of combat casualties. JAMA Surg, 2016, 151, 1, 15-24, doi: 10.1001/jamasurg.2015.3104.

8. Bennett AS, Guarino H, Britton PC, O'Brien-Mazza D, Cook SH, et al. U.S. Military veterans and the opioid overdose crisis: A review of risk factors and prevention efforts. Ann Med, 2022, 54, 1, 1826-1838, doi: 10.1080/07853890.2022.2092896.

9. Wilson N, Kariisa M, Seth P, Smith H, Savis NL. Drug and opioid involved overdose deaths - United States, 2017-2018. MMWR Morb Mortal Wkly Rep, 2020, 69, 11, 290-297, doi 10.15585/mmwr.mm6911a4.

10. Peltzman T, Ravindran C, Schoen PM, Morley SW, Draxler K, et al. Brief report: Opioid-involved overdose mortality in United States veterans. Am J Addict, 2020, 29, 4, 340-344, doi 10.1111/ajad.13027.

11. Fisher AD, DesRosiers TT, Papalski W, Remley MA, Schauer SG, et al. Analgesia and sedation for Tactical Combat Casualty Care: TCCC proposed change 21-02. J Spec Oper Med, 2022, 22, 2, 154-165, doi 10.55460/8CBI-GAOD.

12. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med, 2018, 169, 7, 467-473, doi: 10.7326/M18-0850.

13. Hirshon JM, Risko N, Calvello EJ, Stewart de Ramirez S, Narayan M, et al. Acute care research collaborative at the University of Maryland Global Health Initiative. Health systems and services: The role of acute care. Bull World Health Organ, 2013, 91, 5, 386-388, doi: 10.2471/BLT.12.112664.

14. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, et al. Death on the battlefield (2001-2011): Implications for the future of combat casualty care. J Trauma Acute Care Surg, 2012, 73, 6 Suppl 5, S431- S437, doi: 10.1097/TA.0b013e3182755dcc. Erratum in: J Trauma Acute Care Surg, 2013, 74, 2, 706.

15. Brennan F, Carr DB, Cousins M. Pain management: A fundamental human right. Anesth Analg, 2007, 105, 1, 205-221, doi: 10.1213/01.ane.0000268145.52345.55.

16. Risavi BL, Terrell MA, Lee W, Holsten DL Jr. Prehospital mass-casualty triage training-written versus moulage scenarios: How much do EMS providers retain? Prehosp Disaster Med, 2013, 28, 3, 251-256, doi: 10.1017/S1049023X13000241.

17. Suda AJ, Franke A, Hertwig M, Gooßen K. Management of mass casualty incidents: A systematic review and clinical practice guideline update. Eur J Trauma Emerg Surg, 2025, 51, 1, 5, doi: 10.1007/s00068-024-02727-0.

18. National Library of Medicine. PubMed User Guide. Available online: https://pubmed.ncbi.nlm.nih.gov/help/ (accessed on 25 June 2025).

19. National Library of Medicine. Search Strategy Used to Create the PubMed Systematic Reviews Filter. Available online: https://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html (accessed on 20 February 2019).

20. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. MMWR Recomm Rep, 2022, 71, 3, 1-95, doi: 10.15585/mmwr.rr7103a1.

21. Schauer SG, Naylor JF, Fisher AD, April MD, Hill R, et al. An analysis of 13 years of prehospital combat casualty care: Implications for maintaining a ready medical force. Prehosp Emerg Care, 2022, 26, 3, 370-379, doi: 10.1080/10903127.2021.1907491.

22. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: Audit of primary sources. BMJ, 2005, 331, 7524, 1064-1065, doi: 10.1136/bmj.38636.593461.68.

23. Bramer WM, de Jonge GB, Rethlefsen ML, Mast F, Kleijnen J. A systematic approach to searching: An efficient and complete method to develop literature searches. J Med Libr Assoc, 2018, 106, 4, 531-541, doi: 10.5195/jmla.2018.283.

24. Methley AM, Campbell S, Chew-Graham C, McNally R, Cheraghi-Sohi S. PICO, PICOS and SPIDER: A comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. BMC Health Serv Res, 2014, 14, 579, doi: 10.1186/s12913-014-0579-0.

25. Bossers SM, Schwarte LA, Loer SA, Twisk JW, Boer C, et al. Experience in prehospital endotracheal intubation significantly influences mortality of patients with severe traumatic brain injury: A systematic review and meta-analysis. PLoS One, 2015, 10, 10, e0141034, doi: 10.1371/journal.pone.0141034.

26. Elster EA, Butler FK, Rasmussen TE. Implications of combat casualty care for mass casualty events. JAMA, 2013, 310, 5, 475-476, doi: 10.1001/jama.2013.167481.

27. Jenkins DH, Winchell RJ, Coimbra R, Rotondo MF, Weireter LJ, et al. Position statement of the American College of Surgeons Committee on Trauma on the National Academies of Sciences, Engineering and Medicine Report, A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury. J Trauma Acute Care Surg, 2016, 81, 5, 819-823, doi: 10.1097/TA.0000000000001217.

28. Aromataris E, Munn Z, editors. JBI Manual for Evidence Synthesis. JBI; 2020.

29. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ, 2021, 372, n71, doi: 10.1136/bmj.n71.

30. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med, 2009, 6, 7, e1000097, doi: 10.1371/journal.pmed.1000097.

31. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker Det al. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc, 2015, 13, 3, 141-146, doi: 10.1097/XEB.0000000000000050.

32. Whiting P, Savović J, Higgins JP, Caldwell DM, Reeves BC, et al. ROBIS group. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol, 2016, 69, 225-234, doi: 10.1016/j.jclinepi.2015.06.005.

33. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, et al. Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme. Lancaster University, 2006, doi: 10.13140/2.1.1018.4643.

34. Hsu EB, Jenckes MW, Catlett CL, Robinson KA, Feuerstein C, et al. Effectiveness of hospital staff mass-casualty incident training methods: A systematic literature review. Prehosp Disaster Med, 2004, 19, 3, 191-199, doi: 10.1017/s1049023x00001771.

35. Rogers E, Wright C, King P. Fentanyl lozenge story part 2: From military procurement to package. J R Army Med Corps, 2018, 0, 1-5, doi: 10.1136/jramc-2017-000901.

36. Pietsch U, Fischer H, Rüst CA, Hossfeld B, Grünenfelder A, et al. Oral transmucosal fentanyl citrate analgesia in prehospital trauma care: An observational cohort study. Scand J Trauma Resusc Emerg Med, 2023, 31, 1, 2, doi: 10.1186/s13049-023-01066-0.

37. Montgomery HR, Butler FK Jr. Tactical Combat Casualty Care updates. J Spec Oper Med, 2017, 17, 3, 154, doi: 10.55460/LNUM-OWI0.

38. Hill R, Santhakumar R, Dewey W, Kelly E, Henderson G. Fentanyl depression of respiration: Comparison with heroin and morphine. Br J Pharmacol, 2020, 177, 2, 254-266, doi: 10.1111/bph.14860.

39. Carenzo L, McDonald A, Grier G. Pre-hospital oral transmucosal fentanyl citrate for trauma analgesia: Preliminary experience and implications for civilian mass casualty response. Br J Anaesth, 2022, 128, 2, e206-e208, doi: 10.1016/j.bja.2021.08.017.

40. Bazyar J, Farrokhi M, Khankeh H. Triage systems in mass casualty incidents and disasters: A review study with a worldwide approach. Open Access Maced J Med Sci, 2019, 7, 3, 482-494, doi: 10.3889/oamjms.2019.119.

41. Lewis P, Wright C, Hooper C. Opioid analgesia on the battlefield: A retrospective review of data from Operation HERRICK. J R Army Med Corps, 2018, 164, 5, 328-331, doi: 10.1136/jramc-2017-000897.

42. Minkowitz HS, Leiman D, Melson T, Singla N, DiDonato KP, et al. Sufentanil sublingual tablet 30 mcg for the management of pain following abdominal surgery: A randomized, placebo-controlled, phase-3 study. Pain Pract, 2017, 17, 7, 848-858, doi: 10.1111/papr.12531.

43. Kim SY, Buckenmaier CC, Howe EG, Choi KH. The newest battlefield opioid, sublingual sufentanil: A proposal to refine opioid usage in the U.S. military. Mil Med, 2022, 187, 3-4, 77-83, doi: 10.1093/milmed/usab395.

44. Hutchins JL, Leiman D, Rafique Z, DiDonato KP, Palmer PP. Pooled dosing and efficacy analysis of the sufentanil sublingual tablet 30 mcg across demographic subgroups for the management of moderate-to-severe acute pain. J Perianesth Nurs, 2020, 35, 1, 22-28, doi: 10.1016/j.jopan.2019.08.009.

45. Babazade R, Turan A. Sufentanil sublingual tablet system for the management of postoperative pain. Expert Opin Pharmacother, 2016, 17, 17, 2351-2357, doi: 10.1080/14656566.2016.1254190.

46. Reardon CE, Kane-Gill SL, Smithburger PL, Dasta JF. Sufentanil sublingual tablet: A new option for acute pain management. Ann Pharmacother, 2019, 53, 12, 1220-1226, doi: 10.1177/1060028019863144.

47. Viscusi ER, Skobieranda F, Soergel DG, Cook E, Burt DA, et al. APOLLO-1: A randomized placebo and active-controlled phase III study investigating oliceridine (TRV130), a G protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy. J Pain Res, 2019, 12, 927-943, doi: 10.2147/JPR.S171013.

48. Aschenbrenner DS. Approval of new opioid raises concerns. Am J Nurs, 2019, 119, 2, 20-21, doi 10.1097/01.NAJ.0000553201.28965.89.

49. Dsuvia: Dsuvia sufentanil sublingual tablet. Available online: https://www.dsuvia.com (accessed 31 January 2025).

50. Corcostegui SP, Commeau D, Galant J, Ramon F, Boutillier du Retail C. Intranasal sufentanil given in the emergency department triage zone for severe acute traumatic pain-a randomized double-blind controlled trail: Comment. Intern Emerg Med, 2019, 14, 4, 635-636, doi: 10.1007/s11739-019-02069-5. Erratum in: Intern Emerg Med, 2019, 14, 7, 1189, doi: 10.1007/s11739-019-02080-w.

51. Beaudoin FL, Lin C, Guan W, Merchant RC. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: Results of a randomized, double-blind, clinical trial. Acad Emerg Med, 2014, 21, 11, 1193-1202, doi: 10.1111/acem.12510.

52. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: A systematic review. Acta Anaesthesiol Scand, 2011, 55, 6, 638-643, doi: 10.1111/j.1399-6576.2011.02446.x.

53. Porter K. Ketamine in prehospital care. Emerg Med J, 2004, 21, 3, 351-354, doi: 10.1136/emj.2003.010843.

54. de Rocquigny G, Dubecq C, Martinez T, Peffer J, Cauet A, et al. Use of ketamine for prehospital pain control on the battlefield: A systematic review. J Trauma Acute Care Surg, 2020, 88, 1, 180-185, doi: 10.1097/TA.0000000000002522.

55. Hudson IL, Staudt AM, Burgess M, Hinojosa-Laborde C, Schauer SG, et al. Patterns of palliation: A review of casualties that received pain management before reaching role 2 in Afghanistan. Mil Med, 2023, 188, 1-2, 108-116, doi: 10.1093/milmed/usac211.

56. Friesgaard KD, Vist GE, Hyldmo PK, Raatiniemi L, Kurola J, et al. Opioids for treatment of pre-hospital acute pain: A systematic review. Pain Ther, 2022, 11, 1, 17-36, doi: 10.1007/s40122-021-00346-w.

57. Yousefifard M, Askarian-Amiri S, Rafiei Alavi SN, Sadeghi M, Saberian P, et al. The efficacy of ketamine administration in prehospital pain management of trauma patients; A systematic review and meta-analysis. Arch Acad Emerg Med, 2019, 8, 1, e1.

58. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: A randomized controlled trial. Ann Emerg Med, 2012, 59, 6, 497-503, doi: 10.1016/j.annemergmed.2011.11.012.

59. Cohen SP, Bhatia A, Buvanendran A, Schwenk ES, Wasan AD, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med, 2018, 43, 5, 521-546, doi: 10.1097/AAP.0000000000000808.

60. Shimonovich S, Gigi R, Shapira A, Sarig-Meth T, Nadav D, et al. Intranasal ketamine for acute traumatic pain in the Emergency Department: A prospective, randomized clinical trial of efficacy and safety. BMC Emerg Med, 2016, 16, 1, 43, doi: 10.1186/s12873-016-0107-0.

61. Andolfatto G, Willman E, Joo D, Miller P, Wong WB, et al. Intranasal ketamine for analgesia in the emergency department: A prospective observational series. Acad Emerg Med, 2013, 20, 10, 1050-1054, doi: 10.1111/acem.12229.

62. Karlow N, Schlaepfer CH, Stoll CRT, Doering M, Carpenter CR, et al. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the Emergency Department. Acad Emerg Med, 2018, 25, 10, 1086-1097, doi: 10.1111/acem.13502.

63. Moy R, Wright C. Ketamine for military prehospital analgesia and sedation in combat casualties. J R Army Med Corps, 2018, 164, 6, 436-437, doi: 10.1136/jramc-2018-000910.

64. Cohen B, Talmy T, Gelikas S, Radomislensky I, Kontorovich-Chen D, Cohen B, Benov A, Avital Get al. Opioid sparing effect of ketamine in military prehospital pain management – A retrospective study. J Trauma Acute Care Surg, 2022, 93, 2S Suppl 1, S71-S77, doi: 10.1097/TA.0000000000003695.

65. Dubecq C, Montagnon R, Morand G, De Rocquigny G, Petit L, et al. Combat casualties treated with intranasal ketamine for prehospital analgesia: A case series. J Spec Oper Med, 2023, 23, 1, 84-87, doi: 10.55460/OE4C-60HM.

66. Motov S, Mai M, Pushkar I, Likourezos A, Drapkin J, et al. A prospective randomized, double-dummy trial comparing IV push low dose ketamine to short infusion of low dose ketamine for treatment of pain in the ED. Am J Emerg Med, 2017, 35, 8, 1095-1100, doi: 10.1016/j.ajem.2017.03.004.

67. Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: A randomized controlled trial. Am J Emerg Med, 2015, 33, 3, 402-408, doi: 10.1016/j.ajem.2014.12.058.

68. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med, 2008, 26, 9, 985-1028, doi: 10.1016/j.ajem.2007.12.005. Erratum in: Am J Emerg Med, 2009, 27, 4, 512.

69. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, et al. Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. Pharmacol Rev, 2018, 70, 3, 621-660, doi: 10.1124/pr.117.015198. Erratum in: Pharmacol Rev, 2018, 70, 4, 879, doi: 10.1124/pr.116.015198err.

70. Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, et al. Esketamine counters opioid-induced respiratory depression. Br J Anaesth, 2018, 120, 5, 1117-1127, doi: 10.1016/j.bja.2018.02.021.

71. Sandberg M, Hyldmo PK, Kongstad P, Dahl Friesgaard K, Raatiniemi L, et al. Ketamine for the treatment of prehospital acute pain: A systematic review of benefit and harm. BMJ Open, 2020, 10, 11, e038134, doi: 10.1136/bmjopen-2020-038134.

72. Bansal A, Miller M, Ferguson I, Burns B. Ketamine as a prehospital analgesic: A systematic review. Prehosp Disaster Med, 2020, 35, 3, 314-321, doi: 10.1017/S1049023X20000448.

73. Sobieraj DM, Martinez BK, Miao B, Cicero MX, Kamin RA, et al. Comparative effectiveness of analgesics to reduce acute pain in the prehospital setting. Prehosp Emerg Care, 2020, 24, 2, 163-174, doi: 10.1080/10903127.2019.1657213.

74. Song C, Wang D, Chen B. A systematic review and meta-analysis comparing the efficacy and safety of ketamine versus morphine for the treatment of acute pain. Minerva Anestesiol, 2024, 90, 1-2, 77-86, doi: 10.23736/S0375-9393.23.17561-4.

75. Montagnon R, Py N, Dubecq C. The intranasal route for ketamine administration may be a simple way to improve battlefield analgesia. J Trauma Acute Care Surg, 2023, 94, 6, e47-e48, doi: 10.1097/TA.0000000000003878.

76. Wang L, Hong PJ, May C, Rehman Y, Oparin Y, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: A systematic review and meta-analysis of randomised clinical trials. BMJ, 2021, 374, n1034, doi: 10.1136/bmj.n1034.

77. Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev, 2018, 3, 3, CD012182, doi: 10.1002/14651858.CD012182.pub2.

78. Stevens AJ, Higgins MD. A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. Acta Anaesthesiologica Scand, 2017, 61, 3, 268-280, doi 10.1111/aas.12851.

79. Abdallah FW, Hussain N, Weaver T, Brull R. Analgesic efficacy of cannabinoids for acute pain management after surgery: A systematic review and meta-analysis. Reg Anesth Pain Med, 2020, 45, 7, 509-519, doi 10.1136/rapm-2020-101340.

80. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: A systematic review. Can Med Assoc J, 2008, 178, 13, 1669-1678, doi 10.1503/cmaj.071178.

81. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, et al. Cannabinoids for medical use: A systematic review and meta-analysis. JAMA, 2015, 313, 24, 2456-2473, doi: 10.1001/jama.2015.6358. Erratum in: JAMA, 2015, 314, 5, 520, doi: 10.1001/jama.2015.8253. Erratum in: JAMA, 2015, 314, 8, 837, doi: 10.1001/jama.2015.9010. Erratum in: JAMA, 2015, 314, 21, 2308, doi: 10.1001/jama.2015.15929. Erratum in: JAMA, 2016, 315, 14, 1522, doi: 10.1001/jama.2016.3470.

82. Häuser W, Finn DP, Kalso E, Krcevski-Skvarc N, Kress HG, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain, 2018, 22, 9, 1547-1564, doi: 10.1002/ejp.1297.

83. Klumpers LE, Beumer TL, van Hasselt JG, Lipplaa A, Karger LB, et al. Novel Δ(9)-tetrahydrocannabinol formulation Namisol® has beneficial pharmacokinetics and promising pharmacodynamic effects. Br J Clin Pharmacol, 2012, 74, 1, 42-53, doi 10.1111/j.1365-2125.2012.04164.x.

84. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol, 2008, 153, 2, 199-215, doi: 10.1038/sj.bjp.0707442.

85. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research; The National Academies Press: Washington, DC, 2017.

86. Liktor-Busa E, Keresztes A, LaVigne J, Streicher JM, Largent-Milnes TM. Analgesic potential of terpenes derived from Cannabis sativa. Pharmacol Rev, 2021, 73, 4, 98-126, doi: 10.1124/pharmrev.120.000046.

87. Lee MT, Mackie K, Chiou LC. Alternative pain management via endocannabinoids in the time of the opioid epidemic: Peripheral neuromodulation and pharmacological interventions. Br J Pharmacol, 2023, 180, 7, 894-909, doi: 10.1111/bph.15771.

88. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet, 2017, 56, 8, 893-913, doi: 10.1007/s40262-017-0507-7.

89. Barends CR, Absalom A, van Minnen B, Vissink A, Visser A. Dexmedetomidine versus midazolam in procedural sedation. A systematic review of efficacy and safety. PLoS One, 2017, 12, 1, e0169525, doi: 10.1371/journal.pone.0169525.

90. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: Systematic review and meta-analysis of randomized controlled trials. Anesthesiology, 2012, 116, 6, 1312-1322, doi: 10.1097/ALN.0b013e31825681cb.

91. Birkebæk S, Juul N, Rasmussen MM, Uhrbrand PG, Nikolajsen L. Intraoperative clonidine in spine surgery: A randomised controlled trial. Acta Anaesthesiol Scand, 2025, 69, 6, e70048, doi: 10.1111/aas.70048.

92. Gerlach AT, Murphy CV, Dasta JF. An updated focused review of dexmedetomidine in adults. Ann Pharmacother, 2009, 43, 12, 2064-2074, doi: 10.1345/aph.1M310.

93. Pan W, Wang Y, Lin L, Zhou G, Hua X, et al. Outcomes of dexmedetomidine treatment in pediatric patients undergoing congenital heart disease

surgery: A meta-analysis. Paediatr Anaesth, 2016, 26, 3, 239-248, doi: 10.1111/pan.12820.

94. Keene DD, Penn-Barwell JG, Wood PR, Hunt N, Delaney R, et al. Died of wounds: A mortality review. J R Army Med Corps, 2016, 162, 5, 355-360, doi: 10.1136/jramc-2015-000490.

95. Alaifan T, Sakhakhni A, Khojah A, Alraddadi EA, Alkhaibary A, et al. Impact of dexmedetomidine on hospital and intensive care unit stay duration in adult traumatic brain injury patients: A systematic review. Drug Healthc Patient Saf, 2025, 17, 157-171, doi: 10.2147/DHPS.S517119.

96. Capino AC, Miller JL, Johnson PN. Clonidine for sedation and analgesia and withdrawal in critically Ill infants and children. Pharmacotherapy, 2016, 36, 12, 1290-1299, doi 10.1002/phar.1850.

97. Lairet JR, Bebarta VS, Burns CJ, Lairet KF, Rasmussen TE, et al. Prehospital interventions performed in a combat zone: A prospective multicenter study of 1,003 combat wounded. J Trauma Acute Care Surg, 2012, 73, 2 Suppl 1, S38- S42, doi: 10.1097/TA.0b013e3182606022.

98. Mabry RL, Apodaca A, Penrod J, Orman JA, Gerhardt RT, et al. Impact of critical care-trained flight paramedics on casualty survival during helicopter evacuation in the current war in Afghanistan. J Trauma Acute Care Surg, 2012, 73, 2 Suppl 1, S32- S37, doi: 10.1097/TA.0b013e3182606001.

99. Butler FK Jr, Holcomb JB, Giebner SD, McSwain NE, Bagian J. Tactical Combat Casualty Care 2007: Evolving concepts and battlefield experience. Mil Med, 2007, 172, 11 Suppl, 1-19, doi: 10.7205/milmed.172.supplement_1.1.

100.Littlejohn L, Bennett BL, Drew B. Application of current hemorrhage control techniques for backcountry care: Part two, hemostatic dressings and other adjuncts. Wilderness Environ Med, 2015, 26, 2, 246-254, doi: 10.1016/j.wem.2014.08.018.

101.Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL. Serum lactate and base deficit as predictors of mortality in normotensive elderly blunt trauma patients. J Trauma, 2009, 66, 4, 1040-1044, doi: 10.1097/TA.0b013e3181895e9e.

102.Eastridge BJ, Jenkins D, Flaherty S, Schiller H, Holcomb JB. Trauma system development in a theater of war: Experiences from Operation Iraqi Freedom and Operation Enduring Freedom. J Trauma, 2006, 61, 6, 1366-1373, doi: 10.1097/01.ta.0000245894.78941.90.

103.Gerhardt RT, De Lorenzo RA, Oliver J, Holcomb JB, Pfaff JA. Out-of-hospital combat casualty care in the current war in Iraq. Ann Emerg Med, 2009, 53, 2, 169-174, doi: 10.1016/j.annemergmed.2008.04.013.

104.Kotwal RS, Montgomery HR, Kotwal BM, Champion HR, Butler FK Jr, et al. Eliminating preventable death on the battlefield. Arch Surg, 2011, 146, 12, 1350-1358, doi: 10.1001/archsurg.2011.213.

105.Holcomb JB, Stansbury LG, Champion HR, Wade C, Bellamy RF. Understanding combat casualty care statistics. J Trauma, 2006, 60, 2, 397-401, doi: 10.1097/01.ta.0000203581.75241.f1.

106.Friemert B, Achatz G, Hoth P, Paffrath T, Franke A, et al. Specificities of terrorist attacks: Organisation of the in-hospital patient-flow and treatment strategies. Eur J Trauma Emerg Surg, 2020, 46, 4, 673-682, doi: 10.1007/s00068-020-01390-5.

107.James A, Yordanov Y, Ausset S, Langlois M, Tourtier JP, et al. Assessment of the mass casualty triage during the November 2015 Paris area terrorist attacks: Towards a simple triage rule. Eur J Emerg Med, 2021, 28, 2, 136-143, doi: 10.1097/MEJ.0000000000000771.

108.Ratnayake A, Abayajeewa K, Samarakoon S, Worlton T, ESARC group. A call for a global terrorism-related mass casualty incident response research consortium. Eur J Trauma Emerg Surg, 2021, 47, 1, 275-276, doi: 10.1007/s00068-020-01572-1.

109.Falzone E, Pasquier P, Hoffmann C, Barbier O, Boutonnet M, et al. Triage in military settings. Anaesth Crit Care Pain Med, 2017, 36, 1, 43-51, doi: 10.1016/j.accpm.2016.05.004.

110.Khorram-Manesh A, Nordling J, Carlström E, Goniewicz K, Faccincani R, et al. A translational triage research development tool: Standardizing prehospital triage decision-making systems in mass casualty incidents. Scand J Trauma Resusc Emerg Med, 2021, 29, 1, 119, doi: 10.1186/s13049-021-00932-z.

111.Kamler JJ, Taube S, Koch EJ, Lauria MJ, Kue RC, et al. Effectiveness of and adherence to triage algorithms during prehospital response to mass casualty incidents. J Spec Oper Med, 2023, 23, 1, 59-66, doi: 10.55460/73Y0-FSLB.

112.Lockey D. Pre-hospital critical care at major incidents. Br J Anaesth, 2022, 128, 2, e82-e85, doi: 10.1016/j.bja.2021.10.002.

113.Marcussen CE, Bräuner KB, Alstrøm H, Møller AM. Accuracy of prehospital triage systems for mass casualty incidents in trauma register studies - A systematic review and meta-analysis of diagnostic test accuracy studies. Injury, 2022, 53, 8, 2725-2733, doi: 10.1016/j.injury.2022.05.006.

114.Bazyar J, Farrokhi M, Salari A, Safarpour H, Khankeh HR. Accuracy of triage systems in disasters and mass casualty incidents; A systematic review. Arch Acad Emerg Med, 2022, 10, 1, e32, doi: 10.22037/aaem.v10i1.1526.

115.Lindbeck G, Shah MI, Braithwaite S, Powell JR, Panchal AR, et al. Evidence-based guidelines for prehospital pain management: Recommendations. Prehosp Emerg Care, 2023, 27, 2, 144-153, doi: 10.1080/10903127.2021.2018073.

116.Nakar H, Sorkin A, Nadler R, Tsur AM, Gelikas S, et al. Trends in prehospital pain management: Two decades of point-of-injury care. Isr Med Assoc J, 2022, 24, 9, 584-590.

117.Schauer SG, Arana AA, Naylor JF, Hill GJ, April MD. Prehospital analgesia for pediatric trauma patients in Iraq and Afghanistan. Prehosp Emerg Care, 2018, 22, 5, 608-613, doi: 10.1080/10903127.2018.1428839.

118.Blackbourne LH, Baer DG, Eastridge BJ, Kheirabadi B, Bagley S, et al. Military medical revolution: Prehospital combat casualty care. J Trauma Acute Care Surg, 2012, 73, 6 Suppl 5, S372-S377, doi: 10.1097/TA.0b013e3182755662. Erratum in: J Trauma Acute Care Surg, 2013, 74, 2, 705. Erratum in: J Trauma Acute Care Surg, 2013, 74, 1, 347.

119.Benov A, Salas MM, Nakar H, Antebi B, Tarif B, et al. Battlefield pain management: A view of 17 years in Israel Defense Forces. J Trauma Acute Care Surg, 2017, 83, 1 Suppl 1, S150-S155, doi: 10.1097/TA.0000000000001481.

120.Schauer SG, Naylor JF, Maddry JK, Hinojosa-Laborde C, April MD. Trends in prehospital analgesia administration by US Forces from 2007 through 2016. Prehosp Emerg Care, 2019, 23, 2, 271-276, doi: 10.1080/10903127.2018.

121.Bebarta VS, Mora AG, Bebarta EK, Reeves LK, Maddry JK, et al. Prehospital use of ketamine in the combat setting: A sub-analysis of patients with head injuries evaluated in the prospective life saving intervention study. Mil Med, 2020, 185, Suppl 1, 136-142, doi: 10.1093/milmed/usz302.

122.Stark TR, Davidson NL, Cannon JW, Polk TM, Shackelford SA, et al. Battlefield pain summit 2022: Expert consensus statements. J Trauma Acute Care Surg, 2022, 93, 2S Suppl 1, S12-S15, doi: 10.1097/TA.0000000000003711.

123.Savage E, Forestier C, Withers N, Tien H, Pannell D. Tactical Combat Casualty Care in the Canadian Forces: Lessons learned from the Afghan war. Can J Surg, 2011, 54, 6, S118-S123, doi: 10.1503/cjs.025011.

124.Yousefifard M, Askarian-Amiri S, Madani Neishaboori A, Sadeghi M, Saberian P, et al. Pre-hospital pain management; A systematic review of proposed guidelines. Arch Acad Emerg Med, 2019, 7, 1, e55.

125.Valence T, Suppan L. Time to reconsider analgesia in mass casualty incidents. Wilderness Environ Med, 2023, 34, 4, 524-527, doi: 10.1016/j.wem.2023.09.003.

126.Wang J, Lu W, Hu J, Xi W, Xu J, et al. The usage of triage systems in mass casualty incident of developed countries. OJEM, 10, 2, 124-137, doi: 10.4236/ojem.2022.102011.

127.Pamplin JC, Fisher AD, Penny A, Olufs R, Rapp J, et al. Analgesia and sedation management during prolonged field care. J Spec Oper Med, 2017, 17, 1, 106-120, doi: 10.55460/KNC7-FF9M.

128.Shaw BH, Ross M. Is intranasal ketamine safe and effective as a prehospital analgesic? CJEM, 2020, 22, 1, 31-32, doi: 10.1017/cem.2019.433.

129.Altirkistani BA, Ashqar AA, Bahathiq DM, Bougis SM, Aljabri AM, et al. The effectiveness of ketamine versus opioids in patients with acute pain in the Emergency Department: A systematic review and meta-analysis. Cureus, 2023, 15, 3, e36250, doi: 10.7759/cureus.36250.

APPENDIX 1. PRISMA-SCR SEARCH STRATEGY

Database Searched

PubMed/MEDLINE
Date of last search: **1 June 2023**
Time window: **1 January 2017 – 1 June 2023**

1. MeSH Terms and Keywords Used

Analgesia / Pain

PubMed/MEDLINE

- “analgesia”[MeSH]
- “acute pain”
- “pain management”
- “trauma pain”

Military / Battlefield / Prehospital

- “battlefield”
- “combat”
- “military”
- “prehospital”
- “tactical combat casualty care”
- “TCCC”

Mass-Casualty Context

- “mass casualty”
- “MASCAL”
- “triage”

Analgesic Agents

- “opioids”
- “fentanyl”
- “oral transmucosal fentanyl citrate”

- “OTFC”
- “sufentanil”
- “sublingual sufentanil”
- “ketamine”
- “cannabinoids”
- “CBD”
- “THC”
- “alpha-2 agonists”
- “clonidine”
- “dexmedetomidine”

2. Full Search String Used in PubMed

Primary combined search:

("analgesia"[MeSH] OR "acute pain" OR "pain management")
AND ("combat" OR "battlefield" OR "military" OR "prehospital")
AND ("mass casualty" OR "MASCAL" OR "triage")
AND ("opioids" OR "fentanyl" OR "OTFC" OR "sufentanil" OR "ketamine"
OR "cannabinoids" OR "CBD" OR "THC"
OR "alpha-2 agonists" OR "clonidine" OR "dexmedetomidine")

3. Filters Applied

- Publication date: 2017-2023
- Language: English
- Species: Humans (when applicable)

4. Search Validation

The search strategy was tested iteratively to confirm:

- Retrieval of sentinel articles known to be relevant to battlefield analgesia
- Inclusion of key TCCC analgesia guideline papers
- Capture of opioid-sparing adjunct literature

Reference lists of eligible articles were screened to ensure completeness.

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 covers the basic sciences and experimental work, particularly those 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 uses 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.

All figures, images, and tables should be original and acknowledged as such by the authors. However, if figures, images, or tables from other sources are included, the copyright must be obtained from the authors of the original article, and proof of the copyright waiver must be provided to the Editors of RJMM. In case of any uncertainty regarding the copyright, the Editors may request the authors to remove from the article certain figures/tables/images.

Generative AI use

The journal requires a statement from the authors confirming that no generative AI tools were used to produce the articles. Still, if AI tools have been used to generate the main text, then this aspect should be clearly disclosed in the acknowledgments, specifying the purpose, specific areas of use, and acknowledging that the final responsibility for the text remains with the authors.

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 when 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.

Always insert the DOI of the article, if available.

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.

Figure legends

Type figure legends on a separate page. Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement. Indicate the stains used in histopathology. Identify statistical measures of variation, such as standard deviation and standard error of the mean.

Figures

All illustrations (line drawings and photographs) are classified as figures. Figures should be numbered using Arabic numerals and cited in consecutive order in the text. Each figure should be supplied as a separate file, with the figure number incorporated in the file name.

Preparation of Electronic Figures for Publication:

Although low-quality images are adequate for review purposes, publication requires high-quality images to prevent the final product from being blurred or fuzzy.

SUBMISSION REQUIREMENTS

Manuscripts should be submitted online at 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 (https://revistamedicinamilitara.ro/author-submission/).

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.

PUBLICATION PROCESS AFTER ACCEPTANCE

Accepted Articles

Accepted Articles are published online after final acceptance, and appear in PDF format only.

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.

COPYRIGHT, LICENSING, AND ONLINE OPEN

Details are on the Copyright Agreement Form that must be completed and signed when the Article is submitted.

Romanian Journal of
Military Medicine

New Series, Vol. 129, No 3/2026, May
ISSN-L 1222-5126; eISSN 2501-2312; pISSN 1222-5126