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Genetic Determinants of the Response to Acute Massive Blood Loss as a Factor in Planning Evacuation Measures in Field Conditions

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Abstract. *Introduction.* Acute massive blood loss and hemorrhagic shock remain major challenges for modern military medicine, accounting for over 90% of preventable battlefield deaths. Traditional methods of monitoring vital signs often prove ineffective in compensated conditions, when blood pressure and heart rate remain stable until sudden decompensation and the loss of more than 40% of circulating blood volume (CBV).
Aim. This study aimed to systematize data on genetic markers that determine individual tolerance to hypovolemia and to justify their integration into digital predictive monitoring systems to optimize evacuation logistics.
Methods. The study methodology included a comprehensive analysis of scientific publications from the PubMed, Scopus, and Google Scholar databases published between 2020 and 2026, as well as a review of current Tactical Combat Casualty Care (TCCC) clinical guidelines.
Results. The analysis revealed that the population of soldiers is heterogeneous in terms of compensatory capacity, with groups demonstrating high tolerance (HT) and low tolerance (LT) identified. The genetic determinants of this distribution include polymorphisms in genes of the renin-angiotensin-aldosterone system (RAAS), specifically variations in angiotensin-converting enzyme (ACE) and angiotensin II receptor type 1 (AGTR1).
Conclusions. The limitations of using genetic data in field conditions are discussed, and it is argued that the integration of molecular markers into tactical medicine is possible only after large-scale clinical validation and currently represents a promising theoretical direction for the development of long-term care protocols.

Keywords: military medicine, hemorrhagic shock, genetic markers, blood coagulation, personalised medicine, triage.

Introduction

Modern armed conflicts have changed the paradigm of trauma care. The concept of the "golden hour" is giving way to strategies of prolonged field care (PFC) due to the impossibility of rapid air evacuation under conditions of drone warfare. Statistics show that 67% of fatalities occur within the first 10 minutes after injury, and 90% of preventable deaths are caused by acute blood loss. Clinical practice shows variability: some wounded soldiers survive with a loss of up to 50% of circulating blood volume (CBV), whereas others decompensate with minimal deficits [1-3].

Aim

To analyse the genetic mechanisms of vascular tone and coagulation regulation as factors of individual resistance to massive blood loss and to substantiate their use for digital prediction of the condition of wounded soldiers when planning evacuation.

Materials and Methods

A literature review was conducted, including a systematic analysis of scientific sources published between 2020 and 2026 in the PubMed, Scopus, and Web of Science databases. Data from multi-omics studies [2], results of testing of the LifeLens and AlphaWear sensor platforms based on the Garmin Fenix 6 [4,5], and Tactical Combat Casualty Care (TCCC) protocols [6] were utilized.

Search queries were formulated using the following keywords: "Compensatory Reserve Measurement" (CRM), "hypovolemia tolerance," "genetic," "multi-omics," "polymorphism," "hemorrhage," "shock," "military medicine," and "triage." The inclusion criteria included original human studies simulating blood loss, field testing of LifeLens and AlphaWear sensors in military conditions, and assessment of the relationships among genetic, transcriptomic, and proteomic profiles, shock compensation, and hemostasis. Only English-language studies were included. The exclusion criteria were animal studies and studies without assessment of CRM or genetic factors.

During the identification phase, 142 records were found in the following databases: PubMed (n=48),

Scopus (n=54), and Web of Science (n=40), and 12 additional sources were identified via clinical trial registries, patents, and official reports, totaling 154 publications. After removal of 38 duplicates, 116 unique records remained. During title and abstract screening, 71 irrelevant publications were excluded, leaving 45 articles for analysis. During the full-text evaluation stage, 26 studies were excluded: 20 due to the absence of specific genetic markers or CRM assessment and 6 due to the use of animal experiments. As a result of the final selection, 19 scientific sources that fully met the established criteria were included in the review (Fig. 1).

Results

Hemorrhagic shock is characterised by acute circulatory failure due to the loss of a significant volume of blood, which leads to systemic hypoxia and irreversible organ damage. In critical situations, the body launches complex compensatory mechanisms aimed at redistributing blood to vital centres – the brain and heart – mainly through intense sympathetic vasoconstriction and activation of neurohumoral axes [2].

The effectiveness of these mechanisms varies considerably. Research confirms the existence of two groups according to the level of tolerance to blood loss: individuals with high tolerance (HT) and individuals with low tolerance (LT). This division has clinical implications for triage of wounded soldiers in the field, as patients in the LT group may enter a state of decompensated shock much earlier than expected [2,7].

Traditional field diagnosis of shock relies on vital signs such as heart rate (HR), blood pressure (BP), and respiratory rate. These parameters may remain within normal limits due to compensation, masking the true severity of life-threatening physiological distress (Table 1).

The presence of the "lethal triad" – the combination of hypothermia, acidosis, and coagulopathy – creates a cycle that leads to death. The combination of trauma, hypothermia, and shock reduces the effectiveness of the natural blood clotting mechanisms, making a genetic predisposition to rapid hemostasis a crucial survival factor [1,3,7,8].

The ability to maintain blood pressure during progressive hypovolemia depends on the activity of the

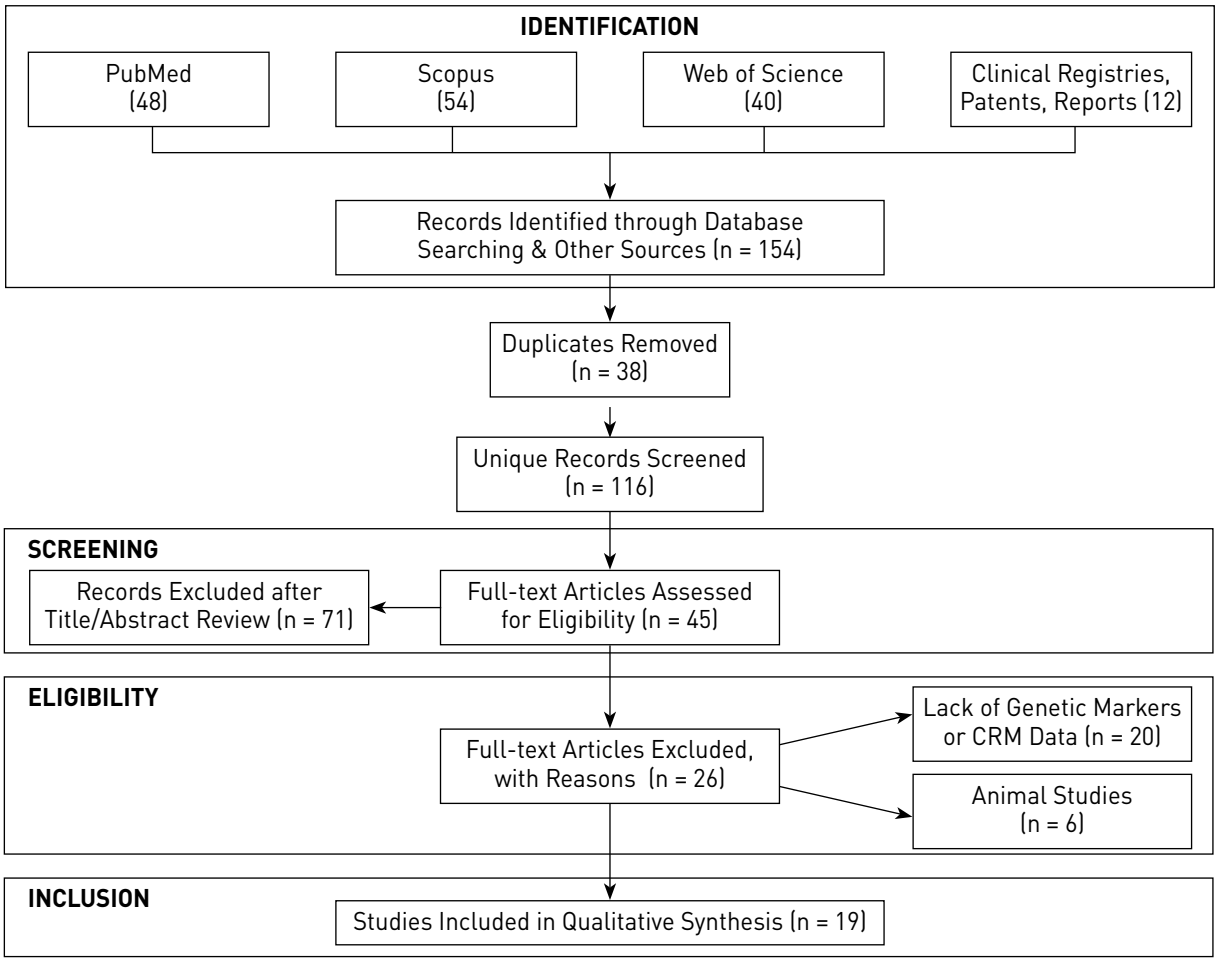

Fig. 1. PRISMA Flowchart for Selecting Scientific Sources for Analysis

Source: created using ConceptViz

Table 1. Prognostic Vital Signs and Their Consequences

Prognostic Factor	Clinical and Threshold Value	Forecast and Associations	Source
Shock Index (SI)	> 0.9	Correlates with the need for massive transfusion and high mortality.	[1]
Mean Arterial Pressure (MAP)	< 65-85 mm Hg	A sign of late decompensation and critical decrease in perfusion.	[9]
Hemoglobin (Hb) level	< 5 g/dL or 20% decrease	Associated with mortality in polytrauma.	[1, 8]
Serum lactate	Increase > 2 mmol/L	Indicator of tissue hypoxia and acidosis.	[9]

renin-angiotensin-aldosterone system (RAAS) and the adrenergic response. Genetic variations in these systems determine the intensity of vasoconstriction and baroreflex sensitivity [10].

The key enzyme of the RAAS is angiotensin-converting enzyme (ACE), which converts angiotensin I to the active vasopressor angiotensin II while inactivating the vasodilator bradykinin. ACE gene polymorphism is one of the most studied markers of cardiovascular resistance [11].

The presence of the deletion allele (D allele) is associated with higher plasma ACE levels. Individuals with the DD genotype have a stronger response to hypotension, which may provide better short-term compensation for blood loss but increases the risk of hypertension and prolonged tissue ischemia in the long term [11,12].

The A1166C (rs5182) variant in the Angiotensin II receptor type 1 (AGTR1) gene affects the affinity of the receptors for angiotensin II. The combined presence of the D allele of the ACE gene and the C allele of the AGTR1 gene increases the risk of cardiovascular complications and dysregulation of vascular tone [11,12].

Alpha-2 adrenoceptors play an important role in shock compensation. Neural and vascular mechanisms are responsible for sympathetic baroreflex regulation of blood pressure in humans. Genetic variations in adrenoceptor genes determine the strength of the sympathetic "surge" in response to blood loss, correlating with the time to circulatory collapse [13].

Control of bleeding is the first step to survival. Genetic factors influence the blood clotting rate, the stability of the formed thrombus under conditions of intense stress, and the development of traumatic coagulopathy.

The leucine-rich repeat flightless-interacting protein 1 (LRRFIP1) gene encodes a protein that is a structural component of the platelet skeleton. It plays a role in maintaining the cellular structure of platelets and their ability to aggregate. Genetic variants may lead to the formation of functionally weaker platelets, slowing the control of massive bleeding [14].

The COMM domain-containing 7 (COMMD7) gene is associated with the intensity of thrombus formation. Experimental data suggest that suppression of its expression reduces the ability of blood to clot, making this gene a potential marker of high risk of uncontrolled bleeding [15].

The genetic profile of polymorphisms in vitamin K epoxide reductase complex subunit 1 (VKORC1) and gamma-glutamyl carboxylase (GGCX) determines sensitivity to vitamin K, which is essential for the synthesis of clotting factors. In the context of massive blood loss, individuals with certain variants may deplete their stores of coagulation factors more quickly, requiring earlier administration of plasma or cryoprecipitate (Table 2) [16].

The transition from theory to practical application is achieved through the development and implementation of high-tech monitoring devices.

LifeLens Technologies has developed a non-invasive abnormal physiological event detection system to monitor casualties during delayed evacuation. The device reads 25 different data channels and generates over 400 physiological and contextual metrics, including ECG, heart rate (HR), heart rate variability (HRV), blood oxygen saturation (SpO_2), skin temperature, respiration, and precise body posture. The system hub can store up to 72 hours of data, allowing clinicians to see a complete picture of the dynamics of the patient's condition over the previous three days [4].

The AlphaWear platform uses high-resolution data from commercial devices, such as the Garmin Fenix 6, to create decision-making aids. The algorithm analyses raw interbeat interval (IBI) data, ensuring safety and speed [5].

The main component of modern hemorrhagic shock monitoring systems is Compensatory Reserve Measurement (CRM). It is an artificial intelligence algorithm based on pulse wave analysis that estimates the residual physiological potential of the body [3,4,15]. It uses convolutional neural networks (CNNs) to analyse non-invasive photoplethysmography (PPG) signals. Unlike blood pressure, which does not

Table 2. Effect of Major Genetic Polymorphisms on Survival from Blood Loss

Regulation System	Gen / Locus	Biological Effect of the Variant	Impact on Survival in Shock	Source. type of evidence
RAAS (vascular tone)	ACE (I/D)	The D allele increases angiotensin II levels	Hyperreactive vasoconstriction, masking shock	[11, 12] Indirect cardiovascular data, hypothesis
RAAS (reception)	AGTR1 (rs5182)	Increased sensitivity to pressors	High risk of ischemic organ disease after resuscitation	[11, 12] Indirect cardiovascular data, hypothesis
Coagulation	LRRFIP1	Platelet skeleton protein	Low expression variants = weak thrombus	[14] Experimental data, hypothesis
Thrombus formation	COMMD7	Blood clotting ability	High risk of uncontrolled bleeding.	[15] Experimental data, hypothesis
Vitamin K sensitivity	VKORC1, GGCX	Synthesis of blood clotting factors	Rapid depletion of coagulation factor stores	[16] Pharmacogenetic data, a biologically plausible hypothesis

change until 30%-40% of CBV is lost, CRM decreases linearly and proportionally to the volume of blood loss (Table 3) [3,17].

Table 3. Interpretation of Compensatory Reserve Measurement (CRM) Indicators

CRM Level	Risk Zone	Forecast	Source
100-70 %	Green	Stable.	[17]
69-40 %	Yellow	Depletion of reserves.	[17]
< 40%	Red	Inevitable collapse.	[17]

The use of explainable machine learning models (Explainable ML) will allow us to identify the specific elements of the arterial wave that correlate with CRM. It will help us divide patients into subgroups according to the quality of their compensatory mechanisms, which is a "digital phenotype" of genetic tolerance to shock [7].

Evacuation planning should be based on current clinical guidelines that take into account technical means of bleeding control and the latest monitoring methods. The Tactical Combat Casualty Care (TCCC) standards are the main document in this area. According to their guidelines, the primary task is to stop life-threatening external bleeding using tourniquets, hemostatics, and transfusion of whole blood or its components (plasma, red blood cells, platelets) [6].

Understanding the conception of the survival threshold based on genetic data and CRM will allow us to change the sorting logic:

- Urgent category. Injured with CRM <40%, high SI (>0.9), and a genetic profile of low tolerance (ACE DD genotype, low LRRFIP1 expression) [1,11,12,14,17].
- Priority category. Injured patients in whom predictive systems (AlphaWear) show a steady deterioration in HRV over the last few hours, indicating depletion of reserves, even with normal blood pressure at the moment [5,18,19].
- Routine category. Individuals in the high tolerance (HT) group whose CRM remains stable (>80%) after initial bleeding control [17].

The rate of CRM decline from 40% to 20% in individuals with low genetic tolerance (LT) is twice as high as in HT, making CRM a key indicator for triage in delayed evacuation.

Discussion

Integrating genetic data into military medicine may allow a shift from reactive to proactive casualty management. Individuals with the DD genotype of the ACE gene may appear clinically stable even with critical blood loss, leading to erroneous triage into the "Priority" category instead of "Urgent." Using the AlphaWear platform could help circumvent this trap by analysing individual "digital phenotypes."

Although the concept of using rapid genotyping for triage of wounded soldiers is promising, at the current stage of technological development, it remains largely theoretical and faces a number of obstacles.

Current portable platforms require 45-60 minutes to detect single-nucleotide polymorphisms (SNPs). Such a wait is unacceptable during the "golden hour" in cases of massive bleeding. The devices produce raw allelic data that require interpretation by specialists rather than ready-to-use clinical recommendations.

The implementation of molecular diagnostics during the casualty collection phase is limited by the lack of a cold chain for storing chemical reagents. This creates an excessive cognitive burden on combat medics, whose training focuses on life-saving skills rather than the analysis of genomic information.

Genetic data are immutable, so compromising a soldier's DNA reveals information about their relatives. This raises the threats of mass biometric surveillance, unauthorized tracking of personnel, and genetic discrimination during military service.

Currently, there are no clinically validated algorithms that integrate genetic profiles with real-time biometric trends. The use of untested mathematical models in conditions of mass casualties risks misclassifying patients due to sensor drift, motion artifacts, or false test results, which could lead to delays in providing emergency care to critically injured patients.

Conclusions

Genetic determinants, in particular polymorphisms of RAAS (ACE, AGTR1) and coagulation factors (LRRFIP1), are crucial in determining the individual survival threshold for acute blood loss. The difference in oxygen delivery between the HT and LT groups requires a personalised approach to triage.

The LifeLens and AlphaWear systems provide a prediction of decompensation, which is important for evacuation planning. The CRM algorithm is a more sensitive marker of shock than traditional vital signs and should be incorporated into the practice of combat medics following clinical validation.

Article Declarations

Prospects for Further Scientific Research. Further work will focus on validating microRNAs (miRNAs) as rapid circulating biomarkers of shock that can be determined using portable analysers.

Raw Data and Materials. The raw data and materials supporting the findings of this study are available from the corresponding author upon reasonable request.

Study Limitations. This study has several limitations, including the limited sample size and the single-center nature of the study, which may restrict the generalizability of the findings. Further studies with larger cohorts are needed to confirm the obtained results.

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Ethics Approval Statement. Ethical approval was not required.

Conflict of Interest. The authors declare no conflict of interest. All interested parties have given consent for publication.

AI Statement. When preparing the study, AI tools were used, in particular Gemini, for searching and structuring information, followed by thorough proofreading and editing.

Author Contributions (CRediT)

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References:

1. Belkhou Y, Benzakour M, et al. Predictors of Mortality in Hemorrhagic Shock among Polytraumatized Patients. IJHMR. 2026;5(1):1-4. doi: 10.58806/ijhmr.2026.v5i1n01.
2. Misganaw B, Muhie S, et al. Multiomics alterations associated with tolerance and response to simulated progressive hemorrhage in healthy adult humans. Physiological Genomics. 2026;58(2):102-114. doi: 10.1152/physiolgenomics.00253.2025.
3. Convertino VA, Schauer SG, et al. Wearable Sensors Incorporating Compensatory Reserve Measurement for Advancing Physiological Monitoring in Critically Injured Trauma Patients. Sensors. 2020;20(22):6413. doi: 10.3390/s20226413.
4. Reddy MK, Fleischman BA, et al. Expected and Perceived Usability of a Wearable Device That Monitors Physiological Metrics. Military Medicine. 2025;190(2):109-116. doi: 10.1093/milmed/usaf102.
5. Hegarty CM, Davis WH, et al. AlphaWear Platform: Translating Wearable Sensors Data Into Decision Aids Using Open-Source Techniques. Military Medicine. 2025;190(2):26-32. doi: 10.1093/milmed/usaf059.
6. Tactical Combat Casualty Care (TCCC) Guidelines. 2024. https://learning-media.allogy.com/api/v1/pdf/f4cf1d4e-3191-443a-befc-415838fb04f2/contents.
7. Bedolla CN, Gonzalez JM, Vega SJ, Convertino VA, Snider EJ. An Explainable Machine-Learning Model for Compensatory Reserve Measurement: Methods for Feature Selection and the Effects of Subject Variability. Bioengineering. 2023;10(5):612. doi: 10.3390/bioengineering10050612.
8. Zhao Y, Jia L, et al. A New Time-Window Prediction Model For Traumatic Hemorrhagic Shock Based on Interpretable Machine Learning. SHOCK. 2022;57(1):48-56. doi: 10.1097/shk.0000000000001842.
9. Taghavi S, Nassar AK, Askari R. Hypovolemia and Hypovolemic Shock. StatPearls. 2025. https://www.ncbi.nlm.nih.gov/books/NBK513297/.

10. Manosroi W, Williams GH. Genetics of Human Primary Hypertension: Focus on Hormonal Mechanisms. Endocrine Reviews. 2019;40(3):825-856. doi: 10.1210/er.2018-00071.
11. Bhushan S, Xiao Z, et al. Role and Interaction Between ACE1, ACE2 and Their Related Genes in Cardiovascular Disorders. Current Problelms in Cardiology. 2023;48(8):101162. doi: 10.1016/j.cpcardiol.2022.101162.
12. Potaskalova VS, Khaitovych NV, et al. The effect of nos3 and agtr1 genotypes on the course of the arterial hypertension for the overweight or obese patients. Wiadomości Lekarskie. 2022;75(2):533-540. doi: 10.36740/WLek202202137.
13. Spafford JE, Limberg JK, et al. The role of α2-adrenergic mechanisms in sympathetic baroreflex control of human blood pressure. American Journal of Physiology-Heart and Circulatory Physiology. 2025;329(5):H1229-H1243. doi: 10.1152/ajpheart.00403.2025.
14. Luquero A, Pimentel N, et al. LRP5, a WNT signalling pathway receptor, and platelet activation. European Heart Journal. 2025;47(16): 1964-1978. doi: 10.1093/eurheartj/ehaf772.
15. Ambrosio AL, Febvre HP, et al. Syntaxin 12 and COMMD3 are new factors that function with VPS33B in the biogenesis of platelet α-granules. Blood. 2022;139(6):922-935. doi: 10.1182/blood.2021012056.
16. Crosier MD, Peter I, et al. Association of Sequence Variations in Vitamin K Epoxide Reductase and γ-Glutamyl Carboxylase Genes with Biochemical Measures of Vitamin K Status. Journal of Nutritional Science and Vitaminology. 2009;55(2):112-119. doi: 10.3177/jnsv.55.112.
17. Ortiz R, Gonzalez JM, et al. Experimental evaluation of a real-time implementation of compensatory reserve measurement in a human model of hemorrhagic shock. Front. Bioeng. Biotechnol. 2026;14. doi: 10.3389/fbioe.2026.1756626.
18. Gaur P, Temple DS, et al. Continuous Monitoring of Heart Rate Variability in Free-Living Conditions Using Wearable Sensors: An Exploratory Observational Study. JMIR Form Res. 2024;8:e53977. doi: 10.2196/53977.
19. Stallings JD, Laxminarayan S, et sl. APPRAISE-HRI: An Artificial Intelligence Algorithm for Triage of Hemorrhage Casualties. Shock. 2023;60(2):199-205. doi: 10.1097/SHK.0000000000002166.

Генетичні детермінанти відповіді на гостру масивну крововтрату як чинник планування евакуаційних заходів у польових умовах

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Анотація. *Вступ.* Гостра масивна крововтрата та геморагічний шок залишаються одними з основних викликів для сучасної військової медицини, зумовлюючи понад 90% смертей на полі бою, яким можна запобігти. Традиційні методи моніторингу життєвих показників часто виявляються неефективними в умовах компенсації, коли артеріальний тиск і частота серцевих скорочень залишаються стабільними до моменту раптової декомпенсації та втрати понад 40% об'єму циркулюючої крові.
Мета. Метою дослідження була систематизація даних щодо генетичних маркерів, які визначають індивідуальну толерантність до гіповолемії, а також обґрунтування їх інтеграції в цифрові системи предиктивного моніторингу для оптимізації евакуаційної логістики.
Матеріали та методи. Методологія дослідження включала комплексний аналіз наукових публікацій у базах даних PubMed, Scopus та Google Scholar за 2020-2026 роки, а також вивчення актуальних клінічних настанов Tactical Combat Casualty Care (TCCC).
Результати. У результаті аналізу встановлено, що популяція військовослужбовців є неоднорідною за рівнем компенсаторних можливостей: виділено групи з високою (HT) та низькою (LT) толерантністю. Генетичними детермінантами цього розподілу є поліморфізми генів ренін-ангіотензин-альдостеронової системи (РААС), зокрема варіанти генів angiotensin-converting enzyme (ACE) та angiotensin II receptor type 1 (AGTR1).
Висновки. Розглянуто обмеження використання генетичних даних у польових умовах та обґрунтовано, що інтеграція молекулярних маркерів у тактичну медицину можлива лише після масштабної клінічної валідації і наразі є перспективним теоретичним напрямом розвитку протоколів тривалого догляду.

Ключові слова: військова медицина, геморагічний шок, генетичні маркери, зсідання крові, персоніфікована медицина, сортування.

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