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SCIENTIFIC REVIEWS

I.Sh. Kurbanaliev, M.V. Jalilov, A.A. Genzheeva, A.M. Magaramov

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PROGNOSTIC BIOMARKERS OF RECOVERY FROM TRAUMATIC BRAIN INJURY: ASSESSMENT OF EFFECTIVENESS AND PROSPECTS OF APPLICATION

Relevance. Traumatic brain injury is one of the leading causes of disability and mortality worldwide. Despite significant progress in treatment strategies, diagnosis and prediction of outcomes remain challenging. Biomarkers such as proteins, metabolites, and other biological molecules found in biological fluids are a valuable tool that can improve understanding of the pathophysiological processes in TBI and contribute to the development of promising therapeutic approaches. Materials and methods. A systematic literature search was conducted in the Web of Science, Scopus, PubMed (MEDLINE), and eLibrary databases.RU and Cochrane Database of Systematic Reviews, focusing on studies containing data on biomarkers associated with recovery from TBI. The entire cycle of search, selection and analysis of publications followed the principles of the PRISMA methodology. As a result, 57 studies meeting the established criteria were included in the analysis out of 4002 initial publications, after duplicates were removed and irrelevant articles were excluded. Results. Studies demonstrate that biomarkers such as GFAP, S-100b, UCH-L1, and others can significantly improve the diagnosis and prediction of outcomes in patients with TBI. They not only reflect the degree of damage to neurons, but also help to distinguish the stages of injury, as well as predict long-term neurological consequences. Conclusions. The results of the systematic review show that biomarkers have significant potential for clinical application, but further standardization of technologies for their detection and analysis is required. The development of new platforms, such as POC systems using electrochemical biosensors, can provide fast and reliable diagnosis at all stages of TBI treatment. For further in-depth study, it is necessary to combine the efforts of the interdisciplinary research community, which will create personalized treatment strategies and improve long-term outcomes for patients.

Keywords: traumatic brain injury, biomarkers of recovery, prognostic biomarkers, diagnosis

KURBANALIEV Ismail Shamilevich – student, Dagestan State Medical University, bob_bn@bk.ru, ORCID: 0009-0002-8666-2525; **JALILOV Magamedali Valentinovich** – student, Dagestan State Medical University, magomedbroo@mail.ru, ORCID: 0009-0001-4704-0777 - **GENZHEEVA Amina Alievna** – student, Dagestan State Medical University, Amina.genjeeva@mail.ru, ORCID: 0009-0003-9909-2987; **MAGARAMOV Abdulla Magaramovich** – assistant of the Department of Traumatology, Orthopedics and Agricultural Sciences, head of the educational part, Dagestan State Medical University, abdulla-magaramov@yandex.ru, ORCID: 0009-0005-3150-9664

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Introduction. Traumatic brain injury (TBI) is a serious public health problem affecting about 69 million people annually worldwide [52]. The success of TBI treatment depends on the effectiveness of trauma care systems and emergency medicine services, which includes rapid diagnosis and surgical interventions [28]. International research supported by the World Health Organization points to TBI as the main cause of neurosurgery, especially in low- and middle-income countries.

Computed tomography (CT) is important for the early diagnosis of primary brain damage, but its limitations in detecting secondary damage and assessing cellular responses create the need for additional examination methods [2]. Advanced neuromonitoring systems are often used to assess secondary changes such as intracranial pressure and cerebral perfusion. Brain tissue damage may also be associated with deficiencies in the organization of medical care, which exacerbates secondary injury [4].

In recent years, biomarkers have been actively researched that can track the progression of damage and predict the degree of brain damage even before they are visualized using traditional methods [5]. Biomarkers are able to detect early cellular, biochemical, and molecular changes, which allows for improved diagnosis and monitoring of TBI treatment. These molecules can detect changes in the microvascular system that are not available for standard imaging techniques [1].

The integration of biomarkers with clinical examinations and imaging techniques helps doctors accurately assess the severity of injury and predict outcomes. The development of reliable biomarkers is important for early diagnosis of TBI, which allows for timely treatment, especially in low-income countries, where up to 25% of patients do not receive adequate medical care in the early stages [6].

The aim of the research is to systematically evaluate current data on prognostic biomarkers associated with TBI recovery in order to improve diagnosis, prognosis, and develop new treatment approaches.

Materials and methods. For a systematic review of prognostic biomarkers of recovery in TBI, a literature search was conducted in the database: Web of Science, Scopus, PubMed (MEDLINE), eLibrary.RU and Cochrane Database of Systematic Reviews. Keywords relevant to the subject of the study were used, including: "biomarkers of recovery", "traumatic brain injury", "prognosis of the disease" and "recovery after TBI".

As a result of the search, 4002 publications were found. After removing 1,702 duplicates, 2,300 potentially relevant research papers remained. The study of headlines and annotations led to the exclusion of 2,000 articles that did not meet the inclusion criteria. The full texts of the 300 remaining articles were studied in more detail, and the final analysis included 57 studies that meet the criteria of quality and relevance to the research topic. The PRISMA block diagram is shown in the figure (Fig.1).

Inclusion and exclusion criteria: To be included in the analysis, the study had to provide data on biomarkers associated with recovery from TBI, be published in English or Russian, and demonstrate the results of human research. Articles that were reviews without original data, as well as studies that did not fully describe aspects related to TBI, were excluded.

This approach provided a comprehensive overview of current scientific evidence regarding predictive biomarkers that contribute to understanding recovery mechanisms and potential treatment strategies for TBI.

In the table (table.1) All demographic and technical data are listed. Among the 57 selected studies, both randomized controlled trials, meta-analyses, and systematic reviews were reviewed. Special attention was paid to the quality of the methodology and the approaches used in the research.

The obtained results allowed us to draw reasonable conclusions about the influence of the studied factors, as well as to identify areas requiring further research.

Results. The analysis of the conducted studies highlights the importance of biomarkers in clinical practice for the diagnosis and prediction of TBI. Modern biomarkers such as GFAP, S-100b and UCH-L1 demonstrate high efficiency in determining the extent of brain damage and predicting treatment outcomes, which strengthens their role in medical practice since their identification in the 1950s. Since then, biomarkers have attracted the attention of researchers, and published reviews agree on the need to further explore their capabilities [11, 38].

For the clinical significance of biomarkers, it is important to understand their interpretation.

Each biomarker, whether physical or biological, serves as a surrogate indicator reflecting the patient's well-being, functionality, or survival [12]. An ideal TBI biomarker should accurately reflect the degree of neuronal damage, have a linear relationship with brain function, and predict the outcome of the disease. Prostate-specific antigen (PSA) is an example of successful biomarker use, and similar approaches can improve TBI diagnosis and treatment monitoring [22].

In 1983, Bakay and Ward developed ideal characteristics for TBI biomarkers, but at the moment no biomarker has been found that meets all the criteria. Research shows that it may be more important to use a combination of different biomarkers to improve diagnostic accuracy. For example, lactate dehydrogenase (LDH), first described in 1965, demonstrates changes in TBI levels, but previously expressed doubts about its specificity and sensitivity make interpretation difficult [52, 37, 43].

An analysis of the "methodological shortcomings" of research in the 1970s showed that the use of biomarkers for the diagnosis of TBI requires more rigorous methods and validated scales, such as the Glasgow Coma Scale (GCS). This highlights the need for extensive and high-quality research to improve the clinical diagnosis and management of brain injuries.

Biomarkers of traumatic brain injury: features of manifestations. TBI varies in severity, including mild, moderate, and severe forms [20]. Mild TBI can occur due to bumps or sudden head movements, such as in an accident. While such injuries often do not cause visible brain damage, 15% of those affected may develop long-term cognitive impairments, despite the rapidly passing symptoms in most people [49].

The pathogenesis of TBI includes primary and secondary phases. Prima-

ry trauma is associated with mechanical damage to tissues, causing necrosis and deformation of brain cells [35]. The secondary phase is characterized by processes that exacerbate the effect of primary damage: disruption of the integrity of the blood-brain barrier, triggering inflammatory processes and protein degradation [42]. These changes lead to an imbalance in the blood supply to the brain, hypoxia, decreased mitochondrial functionality and metabolic disorders, and further deterioration of the brain [47].

For effective use of biomarkers in the diagnosis of TBI, they must appear after injury and be easily detectable in biological fluids [40]. The concentration of biomarkers should differ among the victims and correlate with the severity of the injury, consistent with data from methods such as the Glasgow Coma Scale, computed tomography and MRI. Thus, biomarkers can help improve the diagnosis and treatment of TBI.

Glial fibrillar acidic protein. Glial fibrillar acid protein (GFAP) is an important marker of astrocyte damage, the level of which increases dramatically after TBI. GFAP is involved in the support and functioning of astroglia and, along with the fatty acid binding protein, has a significant impact on the diagnosis of TBI, showing sensitivity up to 100% [7, 15]. Interleukin-1 (IL-1), which acts as a mediator of inflammation, is also an important biomarker, especially its IL-1b form, the level of which increases critically during injury, deepening damage due to the inflammatory cascade [24, 29].

TAU protein (MAPT) and neuron-specific enolase (NSE) also play an important role in the prediction and diagnosis of TBI. MAPT is involved in the maintenance of axonal structures, and its changes in the blood after TBI can serve as a predictor of injury [19]. NSE, released primarily due to cell death, directly indicates neuronal damage, but its level may also increase during hemolysis, which requires careful interpretation [43].

Phosphodiesterases and other markers, such as pro-inflammatory cytokines (for example, IL-1b and TNF-α), play a key role in the development of damage after TBI [15]. Indicators of axonal damage are also important, such as the calpain-cleaved III-spectrin N-terminal fragment, which signals violations in axonal integrity [29]. The development and use of these biomarkers continues to improve the diagnosis and treatment of TBI.

Creatine Kinase. There are three known creatine kinase isotypes, with brain creatine kinase (CK-BB) localized in astrocytes of the central nervous system (CNS). Although lower concentrations of CK-BB may be present in the abdominal organs, they are absent in red blood cells, which causes their physiologically low serum levels [11]. Studies have shown that the concentration of CK-BB in serum and cerebrospinal fluid increases after TBI, reaching a maximum in the acute phase of injury, and then returning to normal values. There was also a significant increase in the level of CK-BB in the cerebrospinal fluid after hypoxic brain damage, for example, during cardiac arrest. One study revealed the possibility of CK-BB release due to brain hypoperfusion due to systemic trauma. Nevertheless, Ingebrigtsen and Romney concluded that CK-BB has low specificity and sensitivity for the diagnosis of TBI [7].

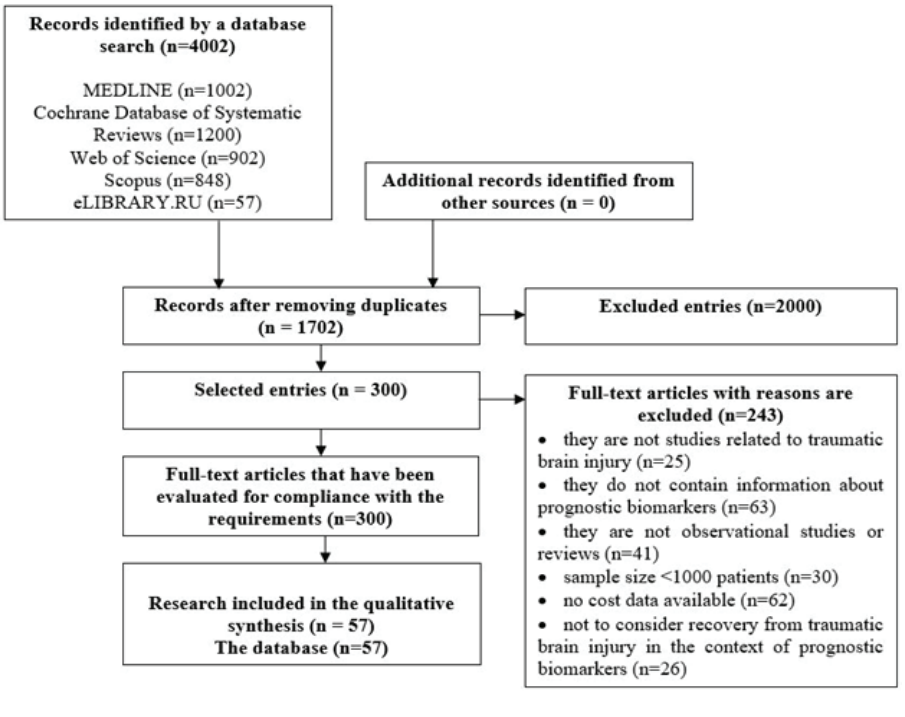
Biomarkers of inflammation in traumatic brain injury. TBI initiates a complex inflammatory process in the nervous tissue, accompanied by the release of cytokines that enhance the inflammatory response through cascading interactions with target cells [17, 27]. Inflammation plays a dual role: it is necessary for the regeneration and removal of damaged cells, but it can cause chronic damage with excessive activity. Understanding the balance between beneficial and harmful effects of inflammation is key to developing therapies that minimize adverse outcomes in patients with TBI [43].

Biomarkers such as cytokines provide insight into the processes activated after TBI. They regulate the immune response and promote recovery, classified into pro-inflammatory and anti-inflammatory. For example, IL-1, IL-12, and TNF-α stimulate inflammation, while IL-4 and IL-10 reduce it. Despite progress, gaps remain in understanding the relationship between cytokines and the long-term effects of TBI [15, 26].

The constant release of pro-inflammatory cytokines can lead to neurodegeneration, which makes microglia a source of neurotoxic substances such as TNF-α and nitric oxide [16]. Studies show differences in IL-1b levels in patients with acute TBI, emphasizing its role in the early inflammatory response, but the need for further investigation of chronic inflammation remains [26].

Extracellular vesicles and non-coding RNAs in traumatic brain injury. After TBI, secondary processes develop quickly and for a long time, such as excitotoxicity, free radical formation, and neuroinflammation, which cause significant damage to neurons and blood vessels [11]. Primary injury stimulates the release of DAMPs molecules, leading to an active immune response enhanced by microglial activation and the penetration of immune cells [48, 25, 21]. Extracellular vesicles (VNV) produced by CNS cells play a key role in neuroimmune interactions, participating in the regulation of neuroinflammation and intercellular communication [15].

TBI changes the amount and composition of VNV, which may contain specific neurotoxic proteins and microRNAs from



Preferred reporting elements for systematic reviews and meta-analyses (PRISMA)

Table 1

Demographic and technical information on studies on prognostic biomarkers of recovery from traumatic brain injury (compiled by the authors)

Reference	Country	Types of injuries	Note
Olczak M, Niderla-Bielinska J, Kwiatkowska M, et al. [48]	Poland	Traumatic brain injury	Postmortem evaluation; investigation of the possibilities of using tau protein as a biomarker
Manivannan S, Makwana M, Ahmed AI, et al. [36]	Great Britain	Traumatic brain injury	Profiling of biomarkers of axonal injury; a mouse-to-human study
Lewis LM, Schloemann DT, Papa L, et al. [56]	USA	Mild TBI	Analysis of serum biomarkers for diagnosis and stratification
Welch REM, Lewis L, Ayaz S, et al. [31]	USA	Traumatic brain injury	Concentrations of various biomarkers in serum are kinetically modeled
Hill-Pryor CWK, Papa L, Lopez M, et al. [50]	USA	Mild TBI	Assessment of the temporal course and diagnostic accuracy of glial and neuronal biomarkers
Mrozek S, Geeraerts T, Dumurgier J, et al. [13]	France	Acute TBI	Investigation of the interest and limitations of biomarkers in the context of acute brain injury
Bazarian J, Zemlan F, Mookerjee S, et al. [44]	USA	Mild TBI	Poor predictors of long-term outcomes for serum biomarkers S-100B and cleaved tau
Lööv C, Nadadhur A, Hillered L, et al. [25]	Sweden	Traumatic brain injury	Extracellular ezrin as a new biomarker for traumatic brain injury
Friedman A, Bar-Klein G, Serlin Y, et al. [46]	Israel	Traumatic brain injury	Investigation of the role of losartan after brain injury
Li J, Yu C, Sun Y, Li Y [45]	China	Traumatic brain injury	Systematic review and meta-analysis of biomarkers
Arun P, Abu-Taleb R, Oguntayo S, et al. [9]	USA	Explosion injury	The potential role of mitochondrial dysfunction after explosive effects
Alluri H, Wiggins-Dohlvik K, Davis ML, et al. [17]	USA	Traumatic brain injury	Dysfunction of the blood-brain barrier after TBI
Ramezani F, Bahrami-Amiri A, Babahajian A, et al. [53]	Iran	Traumatic brain injury	UCHL1 for predicting CT results in brain injury
Dewan MC, Rattani A, Gupta S, et al. [24]	Global assessment	Traumatic brain injury	Assessment of the global incidence of traumatic brain injury
Stenberg M, Koskinen LD, Jonasson P, et al. [21]	Finland	Severe TBI	CT and clinical outcomes in patients with severe traumatic brain injury

astrocytes, which highlights their potential as biomarkers [15]. The involvement of VNV in neuroinflammation is reinforced by their release by brain endothelial cells and microglia, as well as an increase in their concentration in serum and cerebrovascular blood after injury [7, 27, 33, 40, 49, 55]. VNV can carry injury-related molecules such as tau protein and β-amyloid, which is associated with unfavorable neurological outcomes in patients with mild TBI [25, 30].

Changes in the content of VNV in cerebrospinal fluid and peripheral blood open up possibilities for their use in the diagnosis and assessment of the severity of TBI. Protein changes and the expression of specific microRNAs in the VNV can serve as diagnostic tools for assessing the condition after injury [16].

Clinical significance of biomarkers. Neuroimaging is considered the preferred method for diagnosing intracranial injury after traumatic brain injury due to the lack of resources in medical institutions. This stimulated research aimed at reducing the use of imaging in the diagnosis of brain injuries [23].

Several studies have been initiated in the field of neuroproteomics to establish a link between the levels of certain biomarkers in the blood and imaging data. If the indicators are below a certain threshold, this may reduce the use of medical resources. A recent multicenter study (ALERT-TBI) evaluated the usefulness of the GFAP and UCH-L1 proteins for predicting CT TBI in patients with such injuries. The results showed that the use of these proteins with existing criteria achieved 97% sensitivity and 99% specificity in detecting intracranial injuries [15].

Predicting outcomes using biomarkers. Biomarkers are usually used at an early stage of injury and during 6-12 months of disease development. Most studies have identified relationships that help predict patient outcomes. When the S-100b protein level in the blood is more than 0.7 ng/ml, an association with mortality and functional outcomes is observed six months after injury according to the Glasgow outcome scale [15]. GFAP is also considered as a potential predictor of outcomes and mortality after six months. Evaluation of the UCH-L1 protein together with GFAP helps predict the condition of patients on the second day after injury.

The relationship between biomarkers and the need for surgery. Changes in the levels of various biomarkers in patients with TBI were studied to determine how much the severity of the injury is related to the need for surgery [54]. The study of the levels of GFAP and UCH-L1 biomarkers in combination with computed tomography data made it possible to identify patients who potentially require surgical treatment with 100% accuracy. In addition, the use of the S100b protein to predict the need for surgical intervention in patients turned out to be insufficiently sensitive (Table 2).

Table 2 contains information on the

Table 2

Sensitivity and specificity of key biomarkers in traumatic brain injury, as well as their threshold values in blood tests (compiled by the authors)

Biomarker	Sensitivity (%)	Specificity (%)	Concentration (ng/ml)
S-100b	100	46	0. 1376
UCH-L1	100	38	0.05
GFAP	100	55	0. 066

Note* GFAP = glial fibrillar acidic protein, S-100b = S-100 beta, TBI = traumatic brain injury, UCH-L1= ubiquitin C-terminal hydrolase-L1.

sensitivity and specificity of biomarkers S100b, UCH-L1 and GFAP in TBI, depending on their concentration in blood samples, as shown in numerous studies. In a study concerning the erS-100b biomarker, 46% specificity and 100% sensitivity were found at a threshold level of 0.1376 ng/ml in patients with mild TBI.

Regarding the prognostic value of UCH-L1, this biomarker showed a significant association with TBI during the first six hours after injury. However, despite this, a number of studies and meta-analysis of biomarker data still show some ambiguity in assessing the severity of damage, and its control values vary according to the results of different studies [39]. The GFAP biomarker, measured in blood at a threshold value of 0.066 ng/ml, demonstrates a specificity of 55% and sensitivity of 100% for detecting pathologies during computed tomography in patients with cranial fractures [10].

Future directions and recommendations. To increase the clinical effectiveness of inflammatory markers in the diagnosis of mild TBI, it is necessary to take into account the variability of research and analysis methods. Multicenter studies such as CENTER-TBI and TRACKING-TBI can improve statistical analysis by taking into account factors such as age and concomitant injuries. It remains important to distinguish neuroinflammation and systemic inflammation from extracranial injuries. [10, 11, 12, 21, 43].

Various strategies can be proposed to solve this problem, including the use of statistical correction, the analysis of inflammatory markers in extractable vesicles, the study of microRNAs, and the use of proteomics to identify unique biomarkers of neuroinflammation [26]. It is also promising to switch to rapid analysis (POC) platforms, which make it possible to quickly determine the concentration of markers at the scene using electrochemical biosensors, which may be useful for early assessment of TBI [18].

Mild TBI can increase the risk of neurodegenerative diseases if recovery is insufficient, which is especially important for athletes and military personnel. Exosomal biomarkers can function as a "liquid biopsy," providing information about specific changes in the brain after injury and helping to study the long-term effects of TBI, including the risks of diseases such as Alzheimer's disease. [50, 44, 17, 19]. Expanding research in this area and creating an interdisciplinary community is the key to improving diagnosis, prevention, and long term treatment outcomes for patients with mild TBI.

Conclusion. A systematic review of prognostic biomarkers associated with recovery from TBI has shown their significant potential in improving diagnosis and predicting outcomes. Leading biomarkers such as glial fibrillar acid protein (GFAP), S-100b protein, and ubiquitin C-terminal hydrolase-L1 (UCH-L1) have demonstrated high sensitivity and specificity for assessing damage and clinical outcomes. Their use allows not only to diagnose the severity of TBI, but also to predict long-term outcomes and risks of complications. However, for a more accurate application of these biomarkers in clinical practice, standardization of methods for evaluating and interpreting data is necessary, which underscores the need for further research in this area.

The authors declare no conflict of interest.

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E.N. Suprun, S.V. Suprun, G.P. Evseeva, O.A. Lebedko

EXOGENOUS FACTORS INFLUENCING THE COURSE OF BRONCHIAL ASTHMA

This systematic literature review analyzes the environmental factors that affect the course of bronchial asthma. Based on 46 studies, a number of factors have been identified whose impact has been reliably confirmed, including sudden changes in daytime temperatures, vitamin D levels, micronutrient status, persistence of herpes-like viruses, and the specific sensitization spectrum of a particular region.

A comprehensive approach to the diagnosis, prevention, and treatment of bronchial asthma, taking these factors into account, will allow for personalized treatment of individual patients and improve its effectiveness.

Keywords: bronchial asthma, climate, vitamin D, viral infections, sensitization spectrum.

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Khabarovsk branch of the Federal State Budgetary Scientific Institution "Far Eastern Scientific Center for Physiology and Pathology of Respiration" - Research Institute for Maternal and Child Health: **SUPRUN Evgeny Nikolaevich** – Candidate of Medical Sciences, senior researcher, associate professor of the Far Eastern State University, evg-suprun@yandex.ru, orcid.org/0000-0002-1089-8884; **SUPRUN Stefania Viktorovna** – Doctor of Medical Sciences, Chief Science Officer, orcid.org/0000-0001-6724-3654; **EVSEEVA Galina Petrovna** – Doctor of Medical Sciences, Chief Science Officer, orcid.org/0000-0002-752-75; **LEBEDKO Olga** – 23 Doctor of Medical Sciences, Director, Head. lab., orcid.org/0000-0002-8855-7422

Introduction. Bronchial asthma (BA) is one of the most common chronic diseases of the respiratory system in both adults and children. In recent decades, there has been an increase in asthma, and by now its incidence has reached 15-18% among the world's child population [21]. Russia as a whole [4] and Khabarovsk Krai [7], in particular, are no exception to this trend. Atopic inflammation, which, as a rule, underlies the pathogenesis of asthma in children, is primarily due to innate factors, however, the probability and duration of their implementation, as well as the course of the disease itself, can be significantly modified by a variety of exogenous influences [10, 17, 29].

The purpose of this review is to analyze environmental factors in asthma, their clinical implementation, and the possibility of selecting a therapy algorithm based on them. Based on a review of the literature data from PubMed, ScienceDirect, Google Scholar, Research Gate, and eLibrary databases.RU for the period 1997-2025. 192 publications were analyzed as a result of a search for the following keywords: "climatic effects in bronchial asthma", "vitamin D in bronchial asthma", "trace elements in bronchial asthma", "viruses in bronchial asthma",