Received: 24 January 2025 / Accepted: 19 May 2025 / Published online: 30 June 2025

DOI 10.34689/SH.2025.27.3.024

UDC 616.12-008.46-036.12-02-07

THE SST2 BIOMARKER AS A PREDICTOR OF ADVERSE CLINICAL OUTCOMES IN HEART FAILURE. LITERATURE REVIEW

Anar D. Kozhabayeva[1], https://orcid.org/0000-0003-4132-6755
Jamilya A. Mansurova[1], https://orcid.org/0000-0003-2439-2056
Aisulu S. Zhunuspekova[1], https://orcid.org/0000-0002-2413-317X
Andrey Yu. Orekhov[1], https://orcid.org/0000-0001-7201-1399
Assel A. Kassymova[1], https://orcid.org/0000-0001-9333-4146
Bolat A. Ashirov[2], https://orcid.org/0000-0003-0242-9700
Zhanargul K. Smailova[1], https://orcid.org/0000-0002-4513-4614
Mirgul A. Kapakova[1], https://orcid.org/0000-0003-4186-8933
Nailya M. Urazalina[1], https://orcid.org/0000-0003-0200-1763
Lyudmila K. Karazhanova[1], https://orcid.org/0000-0002-4719-6034

[1] NCJSC «Semey Medical University», Semey, Republic of Kazakhstan;
[2] South Kazakhstan Medical Academy, Shymkent, Republic of Kazakhstan.

Abstract

Introduction. In recent years, there has been a growing number of studies aimed at identifying and evaluating novel biomarkers of cardiovascular diseases, particularly heart failure. This trend is driven by the need to enhance diagnostic accuracy, risk stratification, and personalized treatment approaches. Among these biomarkers, special attention is given to the soluble form of the ST2 receptor (sST2), which has demonstrated significant prognostic value across various forms of heart failure. This review focuses on the analysis of current data regarding the clinical relevance of sST2 and the prospects for its implementation in routine medical practice.

Aim. Analysis of literature data on the biomarker sST2 as a predictor of adverse clinical outcomes in patients with heart failure.

Search Strategy. A literature search was conducted using the scientific databases PubMed, Web of Science, and Google Scholar, as well as electronic scientific libraries eLibrary and CyberLeninka. The search covered a five-year period (2019–2024) and focused on cardiorenal biomarkers as predictors of adverse outcomes in cardiovascular diseases.

Results. This literature review analyzes studies on the prognostic significance of the sST2 biomarker in patients with heart failure. The findings indicate that sST2 reflects key pathophysiological processes, including myocardial fibrosis and systemic inflammation. Evidence from the literature suggests that the integration of sST2 into clinical assessment improves early identification of patients at risk, refines prognostic accuracy, and facilitates ongoing patient monitoring. The integration of this biomarker into clinical practice offers opportunities for more precise risk stratification and a personalized approach to treatment.

Conclusions. A review of contemporary literature on clinical and laboratory predictors of heart failure demonstrates that the biomarker sST2 has high diagnostic and prognostic significance. It reflects myocardial fibrosis and systemic inflammation—processes closely associated with the progression of heart failure. Further research is needed to determine optimal threshold values, validate assessment methodologies, and integrate sST2 into standardized clinical algorithms.

Keywords: *cardiovascular diseases; clinical and laboratory predictors; sST2; prognosis; diagnosis.*

For citation:

Kozhabayeva A.D., Mansurova J.A., Zhunuspekova A.S., Orekhov A.Yu., Kassymova A.A., Ashirov B.A., Smailova Zh.K., Kapakova M.A., Urazalina N.M., Karazhanova L.K. The SST2 biomarker as a predictor of adverse clinical outcomes in heart failure. Literature review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2025. Vol.27 (3), pp. 227-235. *doi 10.34689/SH.2025.27.3.024*

Резюме

БИОМАРКЕР SST2 КАК ПРЕДИКТОР НЕБЛАГОПРИЯТНЫХ КЛИНИЧЕСКИХ ИСХОДОВ ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ. ОБЗОР ЛИТЕРАТУРЫ

Анар Д. Қожабаева[1], https://orcid.org/0000-0003-4132-6755
Джамиля А. Мансурова[1], https://orcid.org/0000-0003-2439-2056
Айсулу С. Жунуспекова[1], https://orcid.org/0000-0002-2413-317X

Андрей Ю. Орехов[1], https://orcid.org/0000-0001-7201-1399
Асель А. Касымова[1], https://orcid.org/0000-0001-9333-4146
Аширов Болат А.[2], https://orcid.org/0000-0003-0242-9700
Жанаргуль К. Смаилова[1], https://orcid.org/0000-0002-4513-4614
Миргуль А. Капакова[1], https://orcid.org/0000-0003-4186-8933
Найля М. Уразалина[1], https://orcid.org/0000-0003-0200-1763
Людмила К. Каражанова[1], https://orcid.org/0000-0002-4719-6034

[1] НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;
[2] Южно-Казахстанская медицинская академия, Шымкент, Республика Казахстан.

Введение. В последние годы наблюдается рост числа исследований, направленных на выявление и оценку новых биомаркеров сердечно-сосудистых заболеваний, в частности сердечной недостаточности. Такая тенденция обусловлена необходимостью повышения точности диагностики, стратификации риска и персонализации терапии. Среди биомаркеров особый интерес вызывает растворимая форма рецептора ST2 (sST2), демонстрирующая высокую прогностическую ценность при различных формах сердечной недостаточности. Настоящий обзор посвящён анализу актуальных данных о клинической роли sST2 и перспективам его применения в рутинной практике.

Цель. Анализ литературных данных о биомаркере sST2 как предикторе неблагоприятных клинических исходов у пациентов с сердечной недостаточностью.

Стратегия поиска. Проведен поиск научных публикаций в поисковых системах PubMed, Web of Science, Google Scholar, в электронных научных библиотеках eLibrary, CyberLeninka. Глубина поиска 5 лет (2019-2024). Поиск информации о кардиоренальных маркерах как предикторах неблагоприятных исходов при сердечно-сосудистых заболеваниях.

Результаты. В настоящем литературном обзоре проанализированы исследования, посвящённые прогностической значимости биомаркера sST2 у пациентов с сердечной недостаточностью. Показано, что sST2 отражает ключевые патофизиологические процессы, включая фиброз миокарда и системное воспаление. Данные литературы подтверждают, что применение sST2 в диагностике и прогнозировании неблагоприятных клинических исходов способствует более раннему выявлению риска, уточнению прогноза и динамическому наблюдению за пациентами. Внедрение этого биомаркера в клиническую практику открывает возможности для более точной стратификации риска и персонализированного подхода к лечению.

Выводы. Обзор современной литературы по клинико-лабораторным предикторам сердечной недостаточности показывает, что биомаркер sST2 обладает высокой диагностической и прогностической значимостью. Он отражает процессы миокардиального фиброза и системного воспаления, ассоциированные с прогрессированием сердечной недостаточности. Дальнейшие исследования необходимы для уточнения пороговых значений, валидации методов оценки и интеграции sST2 в стандартизированные алгоритмы клинической практики.

Ключевые слова: *сердечно-сосудистые заболевания; клинико-лабораторные предикторы; sST2; прогноз; диагностика.*

Для цитирования:

Қожабаева А.Д., Мансурова Ж.А., Жунуспекова А.С., Орехов А.Ю., Касымова А.А., Аширов Б.А., Смаилова Ж.К., Капакова М.А., Уразалина Н.М., Каражанова Л.К. Биомаркер SST2 как предиктор неблагоприятных клинических исходов при сердечной недостаточности. Обзор литературы // Наука и Здравоохранение. 2025. Т.27 (3), С. 227-235. doi: 10.34689/SH.2025.27.3.024

Түйіндеме

SST2 БИОМАРКЕРІ ЖҮРЕК ЖЕТКІЛІКСІЗДІГІ КЕЗІНДЕГІ ЖАҒЫМСЫЗ КЛИНИКАЛЫҚ НӘТИЖЕЛЕРДІ БОЛЖАУШЫ КӨРСЕТКІШ РЕТІНДЕ. ӘДЕБИ ШОЛУ

Анар Д. Қожабаева[1], https://orcid.org/0000-0003-4132-6755
Джамиля А. Мансурова[1], https://orcid.org/0000-0003-2439-2056
Айсулу С. Жунуспекова[1], https://orcid.org/0000-0002-2413-317X
Андрей Ю. Орехов[1], https://orcid.org/0000-0001-7201-1399
Асель А. Касымова[1], https://orcid.org/0000-0001-9333-4146
Аширов Болат А.[2], https://orcid.org/0000-0003-0242-9700
Жанаргуль К. Смаилова[1], https://orcid.org/0000-0002-4513-4614
Миргуль А. Капакова[1], https://orcid.org/0000-0003-4186-8933
Найля М. Уразалина[1], https://orcid.org/0000-0003-0200-1763
Людмила К. Каражанова[1], https://orcid.org/0000-0002-4719-6034

[1] «Семей медицина университеті» КеАҚ, Семей қ., Қазақстан Республикасы;
[2] Оңтүстік Қазақстан медицина академиясы, Шымкент қ., Қазақстан Республикасы.

Кіріспе. Соңғы жылдары жүрек-қан тамыр ауруларының, әсіресе жүрек жеткіліксіздігінің жаңа биомаркерлерін анықтау және бағалауға бағытталған зерттеулердің саны артып келеді. Мұндай үрдіс диагноз қоюдың дәлдігін, қауіп-қатерді стратификациялауды және емдеудің дербестендірілген тәсілдерін жетілдіру қажеттілігімен байланысты. Осы биомаркерлердің ішінде ST2 рецепторының ерігіш формасы (sST2) ерекше қызығушылық тудырып отыр, себебі ол жүрек жеткіліксіздігінің түрлі түрлерінде жоғары прогностикалық құндылық көрсетті. Бұл шолу sST2-нің клиникалық маңыздылығына және оны күнделікті медициналық тәжірибеге енгізу перспективаларына арналған

Мақсат. Жүрек жеткіліксіздігі бар науқастарда жағымсыз клиникалық нәтижелердің предикторы ретінде sST2 биомаркері туралы әдеби деректерді талдау.

Іздеу стратегиясы. Ғылыми мақалалар PubMed, Web of Science, Google Scholar іздеу жүйелерінде, eLibrary және CyberLeninka электрондық ғылыми кітапханаларында ізделді. Іздеу тереңдігі – 5 жыл (2019-2024). Іздеу жүрек-қантамыр аурулары кезіндегі жағымсыз клиникалық нәтижелердің предикторлары ретінде кардиоренальді маркерлерге қатысты ақпаратты қамтыды.

Нәтижелер. Осы әдеби шолуда жүрек жеткіліксіздігі бар науқастарда sST2 биомаркерінің прогностикалық маңыздылығына арналған зерттеулер талданды. Зерттеу нәтижелері бойынша sST2 миокард фиброзы мен жүйелік қабыну сияқты негізгі патофизиологиялық үдерістерді бейнелейді. Әдеби деректер sST2-ні жағымсыз клиникалық нәтижелерді диагностикалау және болжау үшін қолдану тәуекелді ерте анықтауға, болжамды нақтылауға және науқастарды динамикалық бақылауға мүмкіндік беретінін растайды. Бұл биомаркерді клиникалық практикаға енгізу тәуекелді дәлірек стратификациялауға және емдеудің дербестендірілген тәсілдерін жүзеге асыруға жол ашады.

Қорытынды. Жүрек жеткіліксіздігінің клиникалық және зертханалық предикторлары бойынша қазіргі әдебиеттерді шолу sST2 биомаркерінің жоғары диагностикалық және прогностикалық маңызға ие екенін көрсетеді. Бұл биомаркер жүрек жеткіліксіздігінің үдеуіне тікелей байланысты миокард фиброзы мен жүйелік қабыну үдерістерін бейнелейді. sST2 үшін шекті мәндерді нақтылау, бағалау әдістерін валидациялау және оны клиникалық тәжірибеге енгізу мақсатында қосымша зерттеулер қажет.

Түйін сөздер: *жүрек-қантамыр аурулары; клиникалық және зертханалық предикторлар; sST2; болжам; диагностика.*

Дәйексөз үшін:

Қожабаева А.Д., Мансурова Ж.А., Жунуспекова А.С., Орехов А.Ю., Касымова А.А., Аширов Б.А., Смаилова Ж.К., Капакова М.А., Уразалина Н.М., Каражанова Л.К. SST2 биомаркері жүрек жеткіліксіздігі кезіндегі жағымсыз клиникалық нәтижелерді болжаушы көрсеткіш ретінде. Әдебиеттік шолу // Ғылым және Денсаулық. 2025. Т.27 (3), Б.227–235. doi: 10.34689/SH.2025.27.3.024

Introduction

Heart failure is a rapidly escalating public health concern associated with reduced quality of life and increased mortality, affecting approximately 64.3 million individuals worldwide (1). A meta-analysis reported that the 1-year, 2-year, 5-year, and 10-year survival rates for heart failure were 86.5%, 72.6%, 56.7%, and 34.9%, respectively (2). Since 2002, there has been an estimated 25% increase in the prevalence of heart failure, a rise primarily driven by population aging, improved post-coronary event survival, and the escalating prevalence of major risk factors, including hypertension and atrial fibrillation (3). In addition, the rates of both heart failure and obesity are escalating rapidly, representing a growing public health concern. Obesity is present in nearly one out of every three individuals with heart failure and is especially prevalent in cases of heart failure with preserved ejection fraction (HFpEF) (4) (5). In asymptomatic individuals, obesity has been linked to reduced concentrations of brain natriuretic peptide (BNP), while the degradation of natriuretic peptides by adipose tissue has been linked to increased aldosterone activity, plasma volume expansion, and reduced ventricular compliance —key factors in the pathophysiology of HfpEF (6). Currently, the most robust evidence supports the use of natriuretic peptides and cardiac troponins as key biomarkers for prognostic assessment in patients with heart failure (7) (8). Nevertheless, natriuretic peptide has limited informativeness in patients with obesity, as its levels are reduced due to degradation by adipose tissue. This reduction diminishes its diagnostic and prognostic value, particularly in HFpEF, where key pathophysiological factors include increased aldosterone activity, plasma volume expansion, and reduced ventricular compliance (6). The simultaneous evaluation of several biomarkers may offer superior prognostic accuracy for both risk stratification and outcome prediction in individuals with heart failure, compared to the use of a single biomarker (9) (10) (11). sST2 serves as a biomarker of inflammatory and hemodynamic stress and, to some extent, reflects the degree of myocardial strain. Moreover, soluble ST2 (sST2) is critically involved in the process of ventricular remodeling and has been linked to higher mortality rates among patients with established heart failure (15).

Aim. Analysis of literature data on the biomarker sST2 as a predictor of adverse clinical outcomes in patients with heart failure.

Search Strategy. A search for scientific publications was conducted using the databases PubMed, Web of Science, and Google Scholar, as well as the electronic scientific libraries eLibrary and CyberLeninka. The search

covered a five-year period (2019–2024). The focus was placed on biomarkers of adverse outcomes in cardiovascular diseases, with particular emphasis on sST2.

Inclusion criteria: Original studies focusing on the diagnostic and prognostic significance of the specified biomarkers, as well as peer-reviewed full-text publications.

Exclusion criteria: Abstracts, reviews, publication summaries, informational letters, and letters to the editor.

Search queries: English: «cardiovascular diseases», «heart failure», «biomarkers», «sST2», «cardiovascular prognosis», «risk stratification».

Russian language: "cardiovascular diseases", "heart failure", "biomarkers", "sST2", "cardiovascular prognosis," "risk stratification".

In the initial search phase, 3,395 articles were identified. After applying the inclusion criteria, 198 full-text publications were analyzed, of which 59 were included in the review. The distribution of sources was as follows: PubMed (30), Web of Science (15), Google Scholar (7), CyberLeninka (7). Additionally, data from international clinical guidelines and statistical reports were considered.

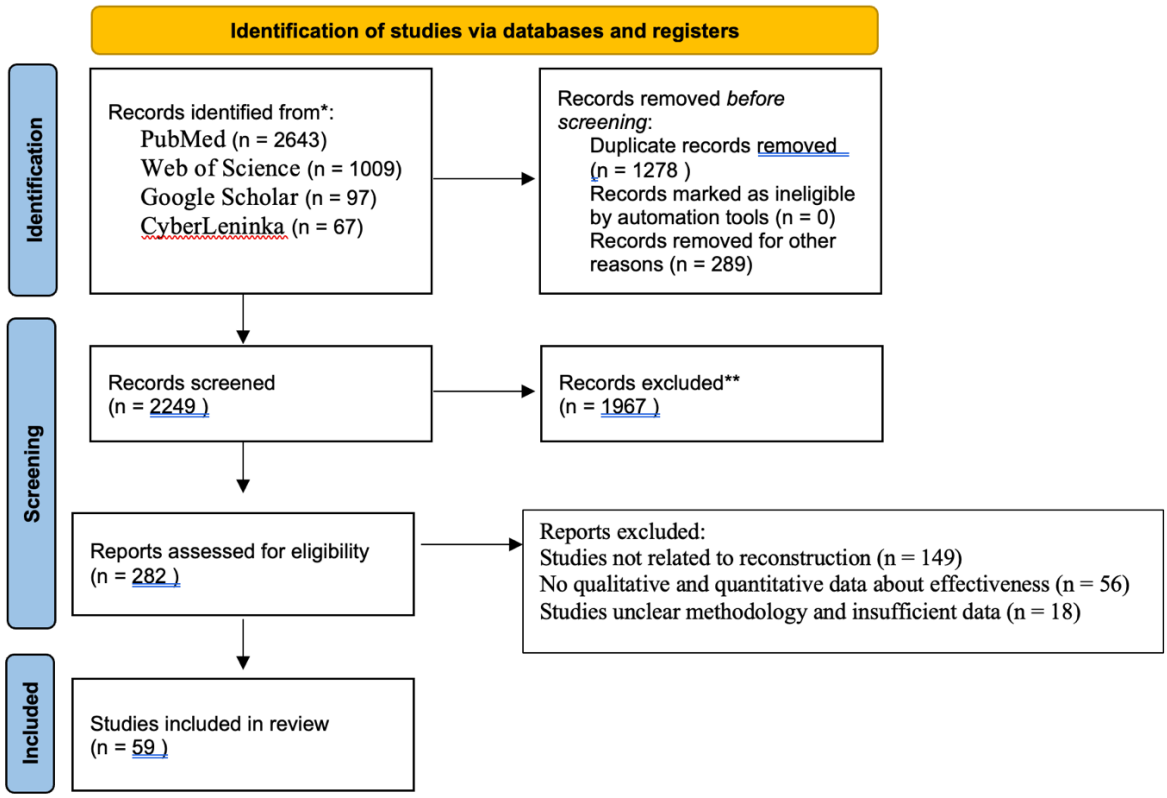

Figure 1. PRISMA flowchart: literature search and study selection.

Results and Discussion

In 1989, the ST2 receptor was first identified by two independent research groups studying fibroblasts activated by growth factors. The name "suppression of tumorigenicity" originated from the hypothesis that ST2 could restrict uncontrolled cell proliferation. Additionally, researcher *Shin-ichi Tominaga* had previously described another protein, later designated as ST1 (19). However, the functional significance of this protein remained undefined for several years. In 2002, *Weinberg et al.* conducted a gene expression analysis involving 7,000 genes in cardiomyocytes subjected to mechanical stress and observed a significant upregulation of ST2 in response to the stimulus (20). ST2 is classified within the interleukin-1 receptor superfamily and is encoded by a gene found at chromosome 2q12, within the interleukin-1 (IL1) gene locus (21). The IL-1 receptor comprises two main isoforms—soluble ST2 (sST2) and transmembrane ST2 (ST2L)—which are largely expressed in cardiomyocytes. In addition to indicating ventricular wall stress, these isoforms contribute to the regulation of immune and inflammatory pathways (22). Cardiac fibroblasts synthesize interleukin-33 (IL-33), an endogenous ligand of the ST2 receptor, while stromal cells release it in both cardiac and extracardiac tissues. The immunological role of IL-33 varies depending on the cellular environment, exhibiting either pro- or anti-inflammatory effects. In the heart, IL-33 interacts with the membrane-bound ST2L isoform, triggering a protective signaling cascade that counteracts cardiomyocyte hypertrophy, limits programmed cell death, and suppresses the development of myocardial fibrosis, thereby contributing to the preservation of cardiac structure and function (23). The binding of IL-33 to the transmembrane ST2L receptor mediates cardioprotective effects by limiting myocardial hypertrophy and preventing fibrotic remodeling. In contrast, the soluble form of ST2 (sST2) acts as a decoy receptor, capturing circulating IL-33 and blocking its beneficial signaling pathways, which contributes to the advancement of cardiac hypertrophy, fibrosis, and impaired ventricular function (24). The cardioprotective effect is mediated exclusively through the ST2L receptor and is not associated with the action of the soluble receptor form (25). Several hypotheses have been proposed to explain the functional role of sST2 in the pathogenesis of various diseases. In line

with the inflammatory hypothesis of atherosclerosis, sST2 binds to IL-33, amplifying inflammatory responses that contribute to plaque instability and elevate the risk of adverse cardiovascular events. Circulating levels of sST2 are regarded as a prognostic indicator of plaque instability, especially in individuals presenting with acute coronary syndrome (26). In oncology, sST2 is considered a key regulator of tumor growth, counteracting the tumorigenic effects of the IL-33/ST2 pathway. It may serve as a diagnostic and prognostic marker, as well as a tool for treatment monitoring. The membrane-bound receptor ST2L is linked to Th2-driven immune responses and serves a pivotal role in modulating immune regulation. The IL-33/ST2L signaling pathway is involved in the development of numerous inflammatory, autoimmune, and fibrotic diseases, including asthma, rheumatoid arthritis, pulmonary fibrosis, and ulcerative colitis (27). n liver diseases, the IL-33/ST2L signaling pathway has been shown to promote fibrotic processes, whereas elevated levels of sST2 have been observed in conditions such as cirrhosis, hepatocellular carcinoma, and hepatitis B infection—potentially reflecting a compensatory response aimed at resolving inflammation or limiting disease progression (28). Thus, sST2 plays a pivotal role in the pathogenesis of various diseases, including cardiovascular and inflammatory conditions, serving as a valuable prognostic and diagnostic marker. In cardiology, BNP and NT-proBNP are the principal biomarkers of heart failure (HF), as they reflect transmural myocardial wall stress and provide critical prognostic information. However, the clinical applicability of these biomarkers is limited by confounding factors, including comorbidities such as atrial fibrillation, renal impairment, and obesity, along with variations related to age and sex. Furthermore, BNP and NT-proBNP capture only specific aspects of the complex pathophysiology of HF (29). This underscores the necessity of expanding the biomarker panel to include sST2 to enhance diagnosis, risk stratification, and treatment monitoring. The prognostic relevance of sST2 was initially established in 2003. A subgroup analysis of the PRAISE-2 trial (Prospective Randomized Amlodipine Survival Evaluation-2), involving 161 patients with advanced heart failure (NYHA class III or IV), demonstrated a positive correlation between baseline sST2 levels and concentrations of natriuretic peptides. Moreover, changes in sST2 levels over two weeks emerged as an independent predictor of all-cause mortality and the need for heart transplantation, irrespective of natriuretic peptide concentrations (30). The strong prognostic significance of sST2, independent of NT-proBNP, was identified in a cohort of 593 patients presenting to the emergency department with acute dyspnea. This association was further validated in a cohort of 209 patients with a confirmed diagnosis of heart failure (31). Similar results were reported by *Müller et al.,* who found that higher sST2 concentrations at the time of admission in patients with acute heart failure were associated with a greater risk of mortality over the follow-up period (32). According to *Pascual-Figal et al.,* an sST2 level of 65 ng/mL serves as a critical cutoff point for identifying patients with acute heart failure who are at increased risk for adverse clinical events (33). Additionally, studies have shown that sST2 levels above 22 ng/mL are associated with a significantly increased risk of reaching the primary endpoint, which may be attributed to the inclusion of a wider array of predictive factors in the analysis (34). The prognostic utility of serial sST2 measurements in the context of acute heart failure has been explored in multiple studies. *Aimo et al.* showed that sST2 levels have significant prognostic value for all-cause mortality, cardiovascular death, and a combined endpoint including both death and heart failure-related hospitalizations in patients with acute decompensated heart failure. Importantly, sST2 concentrations measured at both admission and discharge were found to be predictive of the risk of rehospitalization due to heart failure (35). In a cohort of 150 patients who provided daily blood samples for sST2 measurement, the percentage change in this biomarker was found to be a strong predictor of 90-day mortality. Among patients who exhibited a reduction in sST2 levels of 15.5% or greater during the observation period, the observed mortality rate was 7%. In contrast, for patients with an sST2 reduction of less than 15.5%, the mortality risk reached 33%. The prognostic relevance of dynamic fluctuations in sST2 levels remained independent of concurrent changes in NT-proBNP concentrations (36). A multicenter study from the Netherlands involving 496 patients with acute heart failure reported that elevated baseline sST2 levels were significantly correlated with an increased risk of all-cause mortality and heart failure-related rehospitalization (hazard ratio [HR] per one standard deviation increase in $\log_2$-sST2: 1.30; 95% confidence interval [CI]: 1.08–1.56; p = 0.005). When evaluating repeated sST2 measurements over time, the HR increased to 1.85 (95% CI: 1.02–3.33; p = 0.044). A sub-analysis of the PIONEER-HF trial revealed that baseline sST2 concentrations held prognostic value for predicting both cardiovascular mortality and rehospitalization due to heart failure. Patients receiving sacubitril/valsartan exhibited a more pronounced reduction in sST2 levels as early as one week compared to those receiving enalapril, which correlated with improved clinical outcomes. The reduction in sST2 (6.4%) was less pronounced than that observed for hs-TnT (15.8%) and NT-proBNP (29.4%), likely reflecting the lower dependence of sST2 on decongestion (37). Januzzi et al. proposed an algorithm incorporating sST2 measurements to aid in the differential diagnosis of dyspnea. An sST2 threshold of ≥35 ng/mL was identified as a marker for both the presence of acute heart failure (AHF) and a heightened risk of adverse outcomes. Among patients presenting with dyspnea and elevated natriuretic peptide concentrations, sST2 levels allow for stratification into three distinct prognostic categories:

- sST2 concentrations below 35 ng/mL are observed in less than 10% of patients presenting to the emergency department with suspected AHF, strongly indicating the absence of the condition and aiding in its exclusion as a potential diagnosis.
- sST2 values in the range of 35–70 ng/mL require an assessment of the effectiveness of diuretic therapy in the emergency department; if clinical improvement is observed, the decision regarding the need for hospitalization is made accordingly.
- sST2 values >70 ng/mL are indicative of a high likelihood of AHF and provide strong justification for hospital admission and further clinical management (38).

sST2 levels above approximately 70 ng/mL have been linked to a heightened risk of mortality, both in the early phase (within 30 days) and during extended follow-up periods of up to one year (39). Recent findings indicate that implementing an sST2-guided strategy in patients arriving at the emergency department with dyspnea and elevated natriuretic peptides may improve diagnostic clarity, refine risk assessment, and assist in optimizing treatment decisions (40). Alongside established biomarkers like BNP and NT-proBNP, sST2 offers distinct prognostic value for predicting clinical outcomes. In a study by *Gaggin et al.,* sST2 demonstrated strong predictive power for mortality in both acute and chronic heart failure, underscoring its utility in assessing risk over both short-term and long-term follow-up (41). Research carried out at the Poznan University of Medical Sciences during 2016–2017 identified sST2 as an independent marker associated with all-cause mortality in patients diagnosed with heart failure with reduced ejection fraction (HFrEF). Deceased patients had significantly higher baseline sST2 levels (60.5 ± 53.3 pg/mL vs. 38.8 ± 32.0 pg/mL; p = 0.0029). An sST2 level > 45.8 pg/mL was associated with an increased risk of mortality (50% vs. 21.6%; p = 0.0025) (42). A meta-analysis involving over 4,000 patients confirmed that sST2 levels independently predict both all-cause and cardiovascular mortality, and also serve as a standalone risk factor for heart failure-related hospitalizations. Moreover, elevated sST2 levels were associated with increased concentrations of inflammatory markers, highlighting a potential relationship between inflammation and a heightened risk of adverse clinical outcomes (43). *Dupuy et al.* showed that simultaneous elevations in C-reactive protein (CRP) above 6.4 mg/L and sST2 levels above 47.6 ng/mL were strongly linked to increased mortality risk in patients with chronic heart failure. Importantly, incorporating NT-proBNP into the assessment did not provide additional prognostic benefit in this context (44). A heart failure study carried out in Pennsylvania with 1,141 patients suffering from chronic heart failure with reduced ejection fraction found that sST2 serves as a robust and dependable prognostic indicator. When combined with traditional biomarkers like BNP and pro-atrial natriuretic peptide, sST2 provided a modest improvement in risk stratification. Elevated sST2 concentrations were strongly linked to an increased risk of all-cause mortality or the need for heart transplantation, with this association being particularly pronounced among patients with non-ischemic heart failure (45). Furthermore, *Emdin et al.* showed that sST2 possesses significant prognostic value for the prediction of all-cause mortality, cardiovascular death, and heart failure-related events. Importantly, incorporating sST2 into existing risk prediction models improved risk reclassification beyond that achieved with traditional biomarkers such as NT-proBNP and high-sensitivity troponin T (hs-TnT) (46). The incorporation of sST2 alongside other biomarkers yielded a more precise prognostic evaluation in patients with renal impairment than in the general population (47). *Gruson et al.* established the prognostic significance of sST2 for cardiovascular mortality over a median follow-up period of 4.2 years. Among several prognostic indicators—such as natriuretic peptides, age, left ventricular ejection fraction, and glomerular filtration rate (GFR)—sST2 exhibited the most robust association with cardiovascular mortality (48). sST2 levels have been identified as an independent predictor of atrial fibrillation among patients with heart failure (49), likely reflecting underlying mechanisms related to aging and structural remodeling of the atria that contribute to the development of this arrhythmia (50). Increased sST2 concentrations have been associated with a greater risk of atrial fibrillation recurrence after radiofrequency catheter ablation, suggesting its potential role as a predictive biomarker for evaluating the likelihood of arrhythmia recurrence prior to the procedure (51). In 2011, *Ky et al.* (52) conducted a meta-analysis assessing the prognostic significance of sST2 in chronic heart failure outcomes across three cohorts. These findings were subsequently validated by the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) (53), which contributed to the approval of sST2 for clinical use by regulatory authorities in the United States. In 2016, a comprehensive meta-analysis was conducted, integrating pooled data from seven studies encompassing 6,372 patients. The results indicated that sST2 levels, even without adjustment for other variables, are a significant predictor of both all-cause and cardiovascular mortality in individuals with chronic heart failure (54). An extensive analysis involving 4,268 patients across 11 cohorts demonstrated a clear exponential relationship between elevated sST2 levels and the risks of all-cause mortality, cardiovascular death, and hospitalizations related to heart failure. A threshold of 28 ng/mL was identified as the optimal cutoff for predicting all three outcomes. Patients with median sST2 levels of 27 ng/mL or higher were found to have twice the risk of all-cause mortality, a 50% increase in the risk of cardiovascular death, and a 10% higher likelihood of hospitalization compared to those with lower levels. Furthermore, individuals with median values of all three biomarkers—sST2, NT-proBNP, and hs-TnT—above their respective thresholds experienced dramatic increases in risk: 850% for all-cause mortality, 640% for cardiovascular death, and 590% for hospitalization. Importantly, the prognostic value of sST2 was shown to be independent of NT-proBNP, high-sensitivity troponin T, and other clinical parameters, with no significant association observed between sST2 levels and baseline characteristics such as age, sex, body mass index, or renal function (55). In individuals with chronic heart failure, elevated sST2 concentrations have been recognized as a predictor of sudden cardiac death, offering prognostic information that complements and extends beyond the insights provided by NT-proBNP (56). In the context of acute coronary syndromes, both initial and repeated measurements of sST2 levels have demonstrated high predictive value for future cardiovascular events (57). Elevated serum sST2 concentrations assessed one week after ST-segment elevation myocardial infarction (STEMI) have been independently linked to unfavorable left ventricular remodeling observed at six-month follow-up (58). Moreover, increasing sST2 concentrations have been associated with disease progression and clinical worsening in heart failure patients, underscoring its value as a dynamic biomarker for continuous monitoring and guiding treatment decisions (59). Taken together, current evidence supports the strong potential of sST2 as a tool for risk stratification and for

lowering the likelihood of rehospitalization in patients with heart failure. However, achieving these objectives necessitates further investigation. Future research should aim to refine threshold values, elucidate the mechanistic role of sST2 in clinical outcomes, and assess its integration into established clinical algorithms. These advancements would facilitate the effective implementation of sST2 in optimizing therapeutic strategies and enhancing long-term patient outcomes.

Conclusion.

The biomarker sST2 exhibits high diagnostic and prognostic value in assessing cardiovascular risk. sST2 demonstrates significant promise in stratifying risk and forecasting adverse outcomes in individuals with heart failure. Nevertheless, its routine clinical application requires further investigation to establish optimal threshold values and support its integration into standardized clinical decision-making algorithms. Continued research is essential to validate its utility and enhance its implementation in everyday medical practice.

Conflict of interest: *The authors declare that there is no conflict of interest, and that no part of this article has been published in the open press and is not under consideration by other publishers.*

Contribution of the authors:

Conceptualization – Anar D. Kozhabayeva; methodology – Lyudmila K. Karazhanova, Jamilya A. Mansurova; validation – Aisulu S. Zhunuspekova, Andrey Yu. Orekhov, Mirgul A. Kapakova; data curation – Assel A. Kassymova, Zhanargul K. Smailova; resources – Bolat A. Ashirov, Nailya M. Urazalina; writing – original draft preparation – Anar D. Kozhabayeva, Jamilya A. Mansurova; writing – review and editing – Anar D. Kozhabayeva; project administration – Anar D. Kozhabayeva. All authors have read and agreed to the published version of the manuscript. ***Corresponding author:*** *Jamilya A. Mansurova*

Funding: *This research has been funded under the grant program for scientific start-up projects of academic staff at the NCJSC "Semey Medical University" for 2024–2026, within the framework of the project entitled "Scientific foundations for improving the prognosis in patients with chronic heart failure associated with chronic kidney disease" (Grant Agreement No. 27).*

Literature:

1. Aimo A. [и др.]. Meta-Analysis of Soluble Suppression of Tumorigenicity-2 and Prognosis in Acute Heart Failure // JACC: Heart Failure. 2017. № 4 (5). С. 287–296.

2. Aimo A. [и др.]. Prognostic Value of Soluble Suppression of Tumorigenicity-2 in Chronic Heart Failure: A Meta-Analysis // JACC: Heart Failure. 2017. № 4 (5). С. 280–286.

3. Aleksova A. [и др.]. Cardiac Biomarkers in the Emergency Department: The Role of Soluble ST2 (sST2) in Acute Heart Failure and Acute Coronary Syndrome—There is Meat on the Bone // Journal of Clinical Medicine. 2019. № 2 (8). С. 270.

4. Asferg C.L. [и др.]. Relative atrial natriuretic peptide deficiency and inadequate renin and angiotensin II suppression in obese hypertensive men // Hypertension. 2013. № 1 (62). С. 147–153.

5. Bayes-Genis A. [и др.]. Soluble ST2 Serum Concentration and Renal Function in Heart Failure // Journal of Cardiac Failure. 2013. № 11 (19). С. 768–775.

6. Bayes-Genis A. Ordonez-Llanos J. Multiple biomarker strategies for risk stratification in heart failure. Clinica Chimica Acta. 2015. (443). С. 120–125.

7. Boisot S. [и др.]. Serial Sampling of ST2 Predicts 90-Day Mortality Following Destabilized Heart Failure. Journal of Cardiac Failure. 2008. № 9 (14). С. 732–738.

8. Buyzere M.L. De Multi-biomarker risk stratification in heart failure: a story of diminished marginal returns after Herculean efforts? European Journal of Heart Failure. 2018. № 2 (20). С. 278–280.

9. Chen Y. [и др.]. sST2 and Big ET-1 as Alternatives of Multi-Biomarkers Strategies for Prognosis Evaluation in Patients Hospitalized with Heart Failure. International Journal of General Medicine. 2023. (16). С. 5003.

10. Chen Z.H. [и др.]. Correlation of serum homocysteine and cystatin C levels with prognosis in heart failure with preserved ejection fraction patients // BMC Cardiovascular Disorders. 2024. № 1 (24). С. 510.

11. Chirinos J. A. [и др.]. Multiple Plasma Biomarkers for Risk Stratification in Patients with Heart Failure and Preserved Ejection Fraction. Journal of the American College of Cardiology. 2020. № 11 (75). С. 1281.

12. Cong X., Kong W. Endothelial tight junctions and their regulatory signaling pathways in vascular homeostasis and disease. Cellular Signalling. 2020. (66). С. 109485.

13. Conrad N. [и др.]. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet (London, England). 2018. № 10120 (391). С. 572.

14. Conrad N. [и др.]. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet (London, England). 2018. № 10120 (391). С. 572.

15. Demissei B.G. [и др.]. A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. European Journal of Heart Failure. 2017. № 8 (19). С. 1001–1010.

16. Dudek M. [и др.]. sST2 and Heart Failure—Clinical Utility and Prognosis. Journal of Clinical Medicine. 2023. № 9 (12). С. 3136.

17. Dupuy A.M. [и др.]. Multi-Marker Strategy in Heart Failure: Combination of ST2 and CRP Predicts Poor Outcome. PLoS ONE. 2016. № 6 (11). С. e0157159.

18. Emdin M. [и др.]. sST2 Predicts Outcome in Chronic Heart Failure Beyond NT−proBNP and High-Sensitivity Troponin T. Journal of the American College of Cardiology. 2018. № 19 (72). С. 2309–2320.

19. Emdin M. [и др.]. sST2 Predicts Outcome in Chronic Heart Failure Beyond NT−proBNP and High-Sensitivity Troponin T. Journal of the American College of Cardiology. 2018. № 19 (72). С. 2309–2320.

20. Emdin M. [и др.]. sST2 Predicts Outcome in Chronic Heart Failure Beyond NT−proBNP and High-Sensitivity Troponin T. Journal of the American College of Cardiology. 2018. № 19 (72). С. 2309–2320.

21. Fan J. [и др.]. Higher serum sST2 is associated with increased left atrial low-voltage areas and atrial fibrillation recurrence in patients undergoing radiofrequency ablation. Journal of Interventional Cardiac Electrophysiology. 2022. № 3 (64). С. 733–742.

22. Felker G.M. [и др.]. Soluble ST2 in Ambulatory Patients with Heart Failure Association with Functional

Capacity and Long-Term Outcomes. Circulation: Heart Failure. 2013. № 6 (6). С. 1172–1179.

23. Gaggin H. K. [и др.]. Head-to-Head Comparison of Serial Soluble ST2, Growth Differentiation Factor-15, and Highly-Sensitive Troponin T Measurements in Patients With Chronic Heart Failure. JACC: Heart Failure. 2014. № 1 (2). С. 65–72.

24. Gimbrone M.A., García-Cardeña G. Endothelial Cell Dysfunction and the Pathobiology of Atherosclerosis. Circulation research. 2016. № 4 (118). С. 620.

25. Gruson D. [и др.]. Increased soluble ST2 is a stronger predictor of long-term cardiovascular death than natriuretic peptides in heart failure patients with reduced ejection fraction. International Journal of Cardiology. 2014. № 1 (172). С. e250–e252.

26. Heidenreich P.A. [и др.]. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022. № 18 (145). С. E895–E1032.

27. Homsak E., Gruson D. Soluble ST2: A complex and diverse role in several diseases // Clinica Chimica Acta. 2020. (507). С. 75–87.

28. Januzzi J. L. [и др.]. Measurement of the Interleukin Family Member ST2 in Patients With Acute Dyspnea: Results From the PRIDE (Pro-Brain Natriuretic Peptide Investigation of Dyspnea in the Emergency Department) Study. Journal of the American College of Cardiology. 2007. № 7 (50). С. 607–613.

29. Januzzi J. L., Mebazaa A., Somma S. Di ST2 and prognosis in acutely decompensated heart failure: The international ST2 consensus panel. American Journal of Cardiology. 2015. № 7 (115). С. 26B-31B.

30. Jones N. R. [и др.]. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. European Journal of Heart Failure. 2019. № 11 (21). С. 1306.

31. Jones N.R. [и др.]. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. European Journal of Heart Failure. 2019. № 11 (21). С. 1306.

32. Kakkar R., Lee R.T. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nature reviews. Drug discovery. 2008. № 10 (7). С. 827.

33. Kalstad A.A. [и др.]. Biomarkers of ageing and cardiac remodeling are associated with atrial fibrillation. Scandinavian Cardiovascular Journal. 2021. № 4 (55). С. 213–219.

34. Kercheva M. [и др.]. Serum Soluble ST2 and Adverse Left Ventricular Remodeling in Patients With ST-Segment Elevation Myocardial Infarction. Clinical Medicine Insights. Cardiology. 2019. (13). С. 1179546819842804.

35. Kuro-o M. [и др.]. Mutation of the mouse klotho gene leads to a syndrome resembling ageing. Nature 1997 390:6655. 1997. № 6655 (390). С. 45–51.

36. Kurosu H. [и др.]. Suppression of Aging in Mice by the Hormone Klotho. Science (New York, N.Y.). 2005. № 5742 (309). С. 1829.

37. Ky B. [и др.]. High-Sensitivity ST2 for Prediction of Adverse Outcomes in Chronic Heart Failure. Circulation. Heart failure. 2010. № 2 (4). С. 180.

38. Ky B. [и др.]. High-Sensitivity ST2 for Prediction of Adverse Outcomes in Chronic Heart Failure. Circ Heart Fail. 2011. (4). С. 180–187.

39. Li J. [и др.]. A Review of Novel Cardiac Biomarkers in Acute or Chronic Cardiovascular Diseases: The Role of Soluble ST2 (sST2), Lipoprotein-Associated Phospholipase A2 (Lp-PLA2), Myeloperoxidase (MPO), and Procalcitonin (PCT). Disease Markers. 2021. (2021). С. 6258865.

40. McDonagh T.A. [и др.]. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2021. № 36 (42). С. 3599–3726.

41. Morrow D.A. [и др.]. Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial.

42. Mueller C. [и др.]. Inflammation and long-term mortality in acute congestive heart failure. American Heart Journal. 2006. № 4 (151). С. 845–850.

43. Oztas E. [и др.]. Can Serum ST2 Levels Be Used as a Marker of Fibrosis in Chronic Hepatitis B Infection? Medicine. 2015. № 47 (94). С. e1889.

44. Pandey A. [и др.]. Physical Activity, Fitness, and Obesity in Heart Failure With Preserved Ejection Fraction. JACC: Heart Failure. 2018. № 12 (6). С. 975–982.

45. Pascual-Figal D.A. [и др.]. Soluble ST2 for Predicting Sudden Cardiac Death in Patients With Chronic Heart Failure and Left Ventricular Systolic Dysfunction. Journal of the American College of Cardiology. 2009. № 23 (54). С. 2174–2179.

46. Pascual-Figal D.A. [и др.]. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. European Journal of Heart Failure. 2011. № 7 (13). С. 718–725.

47. Pascual-Figal D.A. [и др.]. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. European Journal of Heart Failure. 2011. № 7 (13). С. 718–725.

48. Ragusa R. [и др.]. Time-course of circulating cardiac and inflammatory biomarkers after Ventricular Assist Device implantation: Comparison between paediatric and adult patients. Clinica Chimica Acta. 2018. (486). С. 88–93.

49. Riccardi M. [и др.]. Soluble ST2 in Heart Failure: A Clinical Role beyond B-Type Natriuretic Peptide. Journal of Cardiovascular Development and Disease. 2023. № 11 (10). С. 468.

50. Sciatti E. [и др.]. Prognostic Value of sST2 in Heart Failure. Journal of Clinical Medicine. 2023. № 12 (12). С. 3970.

51. Tominaga S. ichi Murine mRNA for the β-subunit of integrin is increased in BALB/c-3T3 cells entering the G1 phase from the G0 state. FEBS Letters. 1988. № 2 (238). С. 315–319.

52. Tsigkou V. [и др.]. The Predictive Role for ST2 in Patients with Acute Coronary Syndromes and Heart Failure. Current Medicinal Chemistry. 2019. № 27 (27). С. 4479–4493.

53. Tsutsui H. [и др.]. Natriuretic Peptides: Role in the Diagnosis and Management of Heart Failure: A Scientific Statement From the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. Journal of Cardiac Failure. 2023. № 5 (29). С. 787–804.

54. Villacorta H., Maisel A. S. Soluble ST2 Testing: A Promising Biomarker in the Management of Heart Failure. Arquivos Brasileiros de Cardiologia. 2016. № 2 (106). С. 145.

55. Wang W. [и др.]. Cellular crosstalk in organotypic vasculature: mechanisms of diabetic cardiorenal complications and SGLT2i responses. Cardiovascular Diabetology. 2025. № 1 (24). С. 90.

56. Weinberg E.O. [и др.]. Expression and Regulation of ST2, an Interleukin-1 Receptor Family Member, in Cardiomyocytes and Myocardial Infarction. Circulation. 2002. № 23 (106). С. 2961.

57. Weinberg E.O. [и др.]. Identification of Serum Soluble ST2 Receptor as a Novel Heart Failure Biomarker 2003.

58. Yan X. [и др.]. The sST2 level is an independent influencing factor associated with atrial fibrillation in heart failure patients: a case-control study. Journal of Thoracic Disease. 2022. № 5 (14). С. 1578–1587.

59. Zhang J. [и др.]. Soluble ST2 in coronary artery disease: Clinical biomarkers and treatment guidance. Frontiers in Cardiovascular Medicine. 2022. (9). С. 924461.

Information about the authors:

Anar D. Kozhabayeva- PhD, Doctoral student at the Department of Therapy of the NAO "Semey Medical University", Postal address: 103 Abai Kunanbayev str., Semey, 071400, Republic of Kazakhstan, Abay region, https://orcid.org/0000-0003-4132-6755, e-mail:anik97.kz@bk.ru; Phone number: +7 705 817 9617,

Aisulu S. Zhunuspekova - PhD, Acting Associate Professor of the Department of Therapy of the NAO "Semey Medical University", Postal address: 071400, Republic of Kazakhstan, Abai region, Semey, Abai Kunanbayeva str., 103, https://orcid.org/0000-0002-2413-317X , e-mail: aisulu.zhunuspekova@smu.edu.kz ; Phone number: +7 771 840 5880,

Andrey Yu. Orekhov - PhD, Assistant Professor at the Department of Therapy of the NAO "Semey Medical University", Postal address: 103 Abai Kunanbayeva str., Semey, 071400, Republic of Kazakhstan, Abay region, Semey, https://orcid.org/0000-0001-7201-1399, e-mail: orekhov-andrei@list.ru ; Phone number: +7 777 414 1476,

Assel A. Kassymova – PhD candidate, Department of Therapy of the NAO "Semey Medical University", Postal address: 103 Abai Kunanbayeva str., Semey, 071400, Republic of Kazakhstan, Abay region, Semey, https://orcid.org/0000-0001-9333-4146, e-mail: kassymova2411@gmail.com; Phone number: +7 775 177 4490

Bolat A. Ashirov - Candidate of Medical Sciences, South Kazakhstan Medical Academy, Republic of Kazakhstan, https://orcid.org/0000-0003-0242-9700, e-mail: bolat.baja@mail.

Zhanargyl K. Smailova - Candidate of Medical Sciences, Associate Professor, Vice Rector for Academic and Educational Work, NCJSC «Semey Medical University», phone 8 707 365 82 71, e-mail: zhanargul.smailova@smu.edu.kz; https://orcid.org/0000-0002-4513-4614;

Mirgul A. Kapakova - Candidate of Medical Sciences, Head of the Department of Therapy at the NAO "Semey Medical University", Postal address: 103 Abai Kunanbayev str., Semey, 071400, Republic of Kazakhstan, Abay region, https://orcid.org/0000-0003-4186-8933, e-mail: kma_mira@mail.ru; Phone number: +7 777 278 9724,

Nailya M. Urazalina - Candidate of Medical Sciences, Associate Professor of the Department of physiological disciplines named after honored scientist of the republic of Kazakhstan, professor T.A. Nazarova, NJSC "Semey Medical University", Semey, Kazakhstan; phone: 8 777 907 55 89, e-mail: hakim_15@mail.ru, https://orcid.org/0000-0003-0200-1763,

Lyudmila K. Karazhanova - Doctor of Medical Sciences, Professor of the Department of Therapy of the NAO "Semey Medical University", Postal address: 103 Abai Kunanbayev str., Semey, 071400, Republic of Kazakhstan, Abay region, https://orcid.org/0000-0002-4719-6034, e-mail: kar_ludmila@bk.ru; Phone number: +7 701 355 9976,

***Correspondence author:**

Jamilya A. Mansurova - PhD, Associate Professor, Head of the Department of Therapy at the NAO "Semey Medical University", Semey, Kazakhstan,

Postal code: Republic of Kazakhstan, 071400, Semey city, Abay region, Abay Street 103. 071400.

E-mail: mansurova_dzhami@mail.ru

Phone: +7 777 330 5104,