Ref: Ro J Pharm Pract. 2022;15(3)
DOI: 10.37897/RJPhP.2022.3.3

The search for novel biomarkers in sepsis-induced cardiomyopathy – A new challenge to overcome

Cristian Sorin PREPELIUC[1,2], Ionela Larisa MIFTODE[1,2], Maria Antoanela PASARE[1,2], Radu Stefan MIFTODE [1,3], Lidia Oana STAMATEANU[1,2], Irina Iuliana COSTACHE[1,3], Alexandru Dan COSTACHE[1,4], Egidia MIFTODE[1,2]

[1]Faculty of Medicine, "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania
[2]"Sf. Parascheva" Clinical Hospital of Infectious Diseases, Iasi, Romania
[3]"Sf. Spiridon" Clinical Emergency Hospital, Iasi, Romania
[4]Clinical Hospital of Recovery, Iasi, Romania

Abstract

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and it remains the most frequent cause of death amongst critically ill patients worldwide, despite recent medical advancements. The cardiac involvement in sepsis, better known as sepsis-induced cardiomyopathy, represents a form of cardiac dysfunction identified in septic patients, characterized by ventricular dilation, myocardial involvement, decreased ejection fraction and reversibility. Although the implications of cardiac involvement in sepsis can be extremely severe, this affliction has not been intensely debated in literature. Therefore, in order to better understand this affliction, we need to identify new markers. Two biomarkers, endothelin-1 (ET-1) and the soluble form of suppression of tumorigenicity 2 protein (sST2) have previously been linked to both sepsis and acute/chronic heart failure.

Endothelin-1 is part of a family of amino acid peptides, that is mainly produced by endothelial cells and exerts a vasoconstrive effect, but also causes fibrosis of the vascular cells, stimulates production of reactive oxygen species and induces proinflammatory mechanisms. During sepsis, it induces coronary vasoconstriction, decreased cardiac output, increased vascular resistance and permeability and increased fluid flux into the extravascular space on cardiac level, as well as affecting the contractility of myocardial myocytes. High values of serum ET-1 have also been identified in septic shock and in endotoxin-induced febrile responses in rats.

The Suppression of tumorigenicity 2 protein (ST2) is a member of the interleukin-1 receptor family and is involved in T helper 2 cells-associated immune response. Recent studies identified a close link between ST2 and both inflammatory and heart diseases. Furthermore, it was recently approved by the Food and Drug Administration as a prognostic biomarker in heart failure and is recommended for the evaluation of additional cardiovascular risk.

Keywords: sepsis, cardiomyopathy, biomarker, endothelin-1, ST2

INTRODUCTION

According to its present definition, established in 2016 by a task force with expertise in sepsis pathobiology, clinical trials, and epidemiology, convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, sepsis represents a

Corresponding authors:
Egidia Miftode, Cristian Sorin Prepeliuc
E-mails: emiftode@yahoo.co.uk, cristiprep94@gmail.com

Article History:
Received: 27 September 2022
Accepted: 30 September 2022

life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Therefore, sepsis requires two criteria: a primary infection and an organ dysfunction, away from the main infection site.

The organ dysfunction can be evaluated by the use of The SOFA score (Sequential Organ Failure Assessment). This score includes data related to clinical findings, laboratory data or therapy, in regards to respiration (PaO2/FIO2), coagulation (platelet count), liver function (bilirubin levels), cardiovascular function (arterial pressure values and/or the use of dopamine, dobutamine, epinephrine or norepinephrine), renal function (creatinine levels) and central nervous system (Glasgow Coma Scale). A higher SOFA score is associated with an increased probability of mortality, a score of 2 points or more being associated with an in-hospital mortality greater than 10% [1,2].

Despite recent medical advancements in sepsis therapy, this pathology remains the most frequent cause of death amongst critically ill patients worldwide [3]. The World Health Organization (WHO) identified the fact that five of the top ten mortality causes meet the criteria for sepsis. Furthermore, septic shock was found to determine more deaths than acute myocardial infarction [4].

The cardiac involvement in sepsis, better known as sepsis-induced cardiomyopathy, represents a form of transient cardiac dysfunction identified in septic patients. Although, at the moment, this pathology has not been clearly defined, multiple studies have identified a few of its characteristics: ventricular dilation, myocardial involvement, decreased ejection fraction (with more than 10% of the initial value, up to 50%) and reversibility [3,5]. This pathological entity has been identified primarily in younger male patients, in patients with high severity scores, patients previously diagnosed with heart failure, as well as in diabetic patients. Among septic patients, its prevalence ranges between 10 and 70% [3].

In order to diagnose and evaluate the severity of sepsis-induced cardiomyopathy, echocardiography represents the golden standard, by determining the ejection fraction. Complementary to echocardiography, there is a series of biomarkers that can be used to determine the severity and prognosis. In practice, the most commonly used biomarkers are troponin (especially the T, I and C isoforms) and N-terminal pro b-type natriuretic peptide (NT-proBNP) [4].

Although the implications of cardiac involvement in sepsis can be extremely severe, this affliction has not been intensely debated in literature [4]. Moreover, despite modern diagnosis techniques and treatment options, the mortality rate of patients with sepsis who develop cardiac dysfunction is extremely high, some studies suggesting that it can reach up to 90% [5]. Furthermore, although echocardiography is an excellent, simple method to evaluate these patients and determine the prognosis, recent studies have shown that the mere identification of the ejection fraction is a poor evaluation technique, because it does not ascertain other traits of sepsis-induced cardiomyopathy, like the myocardial involvement [3].

Therefore, we need to identify other markers that could help us better understand this affliction. To that purpose, two biomarkers that have previously been identified in both sepsis and acute and chronic heart failure have shown potential for further study: endothelin-1 (ET-1) and the soluble form of suppression of tumorigenecity 2 protein (sST2).

ENDOTHELIN-1

The endothelins are a family of 21 amino acid peptides, that consist of three isoforms: endothelin-1 (ET-1), endothelin-2 (ET-2) and endothelin-3 (ET-3) and are the product of different genes, located on chromosomes 6, 1 and 20, respectively. Of these, endothelin-1 is the isoform found in the human body in the highest concentrations. It is also the one best described in medical literature. ET-2 and ET-3 were identified later and are not as well studied [6,7].

ET-1 is produced by many types of cells (mainly by endothelial cells – hence its name, but by cardiomyocytes, neurons, renal medulla, macrophages, leukocytes and fibroblasts as well) and there are many factors involved in its secretion. ET-1 mainly exerts a vasoconstrictive effect, however, it also causes fibrosis of the vascular cells and stimulates production of reactive oxygen species. It is claimed that ET-1 induces proinflammatory mechanisms, by activation of transcription factors such as NF-κB, increasing superoxide anion production and cytokine secretion (including including TNF-α, IL-1, and IL-6). In turn, these transcription factors and proinflammatory cytokines can stimulate ET-1 production. Also, the ET-1 gene expression in endothelial cells is activated by physical and chemical stimulants, through the binding of transcription factors such as activator protein-1,

GATA-2, smad, hypoxia inducible factor-1 and NF-κB [6,7]

Other studies have revealed that endothelin-1 might also have an oedema-promoting effect, especially in septic patients, being related to the augmented levels of heparin-binding protein (HBP) accompanying sepsis. HBP is a protein released from neutrophils, which induces vascular hyperpermeability and contributes to oedema formation during endotoxaemia [6]. Furthermore, endothelin-1 was found to increase Ca2+ transient and mitochondrial ROS production and to enhance the consumption of ATP [8].

Endothelin-1 acts through two types of receptors that have been identified in all mammals – ETA and ETB. They are part of the G protein coupled receptors (GPCRs) family. ETA receptors are located mainly in the vascular smooth muscle tissue from blood vessels and take part in vascular wall contraction, cellular proliferation, while also manifesting a proinflammatory effect. In addition, ETA receptors in the brain play a role in reducing the mortality of animals with sepsis [6-8]. ETB receptors include two subtypes: ETB1, which is expressed on endothelial cells and evokes nitric oxide-mediated vasodilation, and ETB2, also present in vascular smooth muscle cells, which causes contraction [6,8]. ETB receptors in the central nervous system also induce fever, when stimulated [7]. However, ETB1 stimulation also provides tissue protection in pro-inflammatory and ischemia-reperfusion conditions in the peripheral and central nervous system, and may have significant peripheral microcirculatory effects through its influence on the reuptake of ET-1 [8]. Furthermore, some studies suggest the fact that ETB receptors are also involved in the clearance of endothelin-1 and both ETA and ETB receptors are involved in the generation of reactive oxygen species [6]. Therefore, the hypoxia-sensitive endothelin system plays an important role in circulatory regulation, sepsis being associated with microcirculatory and mitochondrial disturbances along with tissue hypoxia [8].

The involvement of endothelin-1 in the pathophysiology of sepsis has been observed in numerous reviews. High values of serum ET-1 have been identified in septic shock, leading to development of inflammation inside vascular walls [increasing the expression of adhesion molecules on vascular endothelial cells and stimulating the aggregation of polymorphonuclear neutrophils) [6], by increasing vascular permeability, cytokine release and leukocyte migration [9]. Therefore, during sepsis, the vascular tone is impaired in part due to the disrupted production of cytokines such as nitric oxide (NO), prostacyclin, and endothelin [10].

Experiments performed on lab rats proved the involvement of this cytokine in febrile responses induced by injecting toxins released by pathogens, such as lipopolysaccharide . These experiments showed that 3 hours after LPS injection, there was an increase in the concentration of ET-1 in the cerebrospinal fluid and a decrease in its precursor big-endothelin [7]. Moreover, some toxins released by Gram-negative microorganisms, such as endotoxin, can stimulate the production and secretion of endothelin in the bloodstream. Likewise, the expression levels of ETA and ETB receptors is also increased in some tissues [6]. Additionally, the experiments on rats proved that the LPS-induced febrile response could be blocked by ETB receptor antagonists, but not by ETA receptor antagonists, which suggests that ET-1 would participate in the endotoxin-induced febrile response only by activating ETB receptors. On the other hand, the administration of an ETA receptor antagonist 2 hours after the administration of LPS, significantly and clearly reduced the febrile response induced by this stimulus. This result would suggest that ET-1 participates in the febrile response induced by high doses of LPS through the activation of ETA receptors as well, but at a later stage of the response. Therefore, we can deduce the implications of endothelin-1 in febrile response induced by bacteria and fungi [7]. In addition, other studies have shown that septic animals were hypotensive with elevated plasma levels of ET-1 [8].

A number of human studies have found that the direct administering of endothelin-1 in humans, can lead to cardiovascular changes similar to those found in sepsis, like decreased cardiac output, pulmonary artery vasoconstriction or impairment of renal and splanchnic circulation, as well as liver and lung dysfunction [6].

On cardiac level, during sepsis and septic shock, ET-1 induces vasoconstriction, decreased cardiac output, increased vascular resistance and permeability and increased fluid flux into the extravascular space, leading to the hypodynamic state of septic shock. Moreover, during this state, endothelin-1 may increase the activity of the sinoatrial node and determine tachycardia [11]. With other cytokines, such as nitric oxide, prostaglandins (PGI2, PGF2, PGE2) and angiotensin II, ET-1 acts inside the endocardial endothelium and

affects the contractility of myocardial myocytes [12], including during sepsis. In the past, studies performed on rats revealed that ET-1 upregulation appears within 6 hours of inducing sepsis and during the hyperdynamic period of septic shock, ET-1 production increases for 12 hours and returns to baseline levels 24 hours post shock. This phenomenon is followed by an increase in ET receptors expression, as well as the enhanced expression of endothelin converting enzyme in heart tissue. In a very recent study, it was revealed that acute heart failure induced by sepsis is attributed to the downregulation of FKBP12.6 and SERCA2a, which is related to an activated ET system. Therefore, we have proof of the role played by endothelin-1 and ET receptors in the pathogenesis of sepsis-induced cardiomyopathy [13].

High serum levels of endothelin-1 have also been correlated with increased severity and mortality in septic patients [6,8,14]. A cohort study has revealed that serum levels in patients with mild and severe sepsis were significantly higher than those in the control group, and the levels in the severe sepsis group were significantly higher than those in the mild sepsis group. Moreover, deceased patients had significantly higher levels of ET-1 in their serum than surviving patients [14].

In the past, techniques to measure the levels of endothelin-1 in patient's plasma have not been reliable due to its rapid clearance from the circulation, limiting its use in practice. This lead to the development of new sandwich assays that measure its more stable precursor fragments, like CT-proET-1, given the fact that CT-proET-1 levels exhibited an increase from patients with SIRS to those with septic shock. Furthermore, studies have revealed that baseline CT-proET-1 values of all patients correlated with other markers of infection, like procalcitonin and CRP, as well as with mean blood pressure [15]. However, the tight correlations between increased serum levels of ET-1 in septic patients and the degree of cardiovascular impairment, disease severity, as well as increased mortality rates [6, 8] impose further study of this biomarker.

SUPPRESSION OF TUMORIGENECITY 2

The Suppression of tumorigenecity 2 protein (ST2), also known as T1, Fit-1, and DER4 is a member of the interleukin-1 receptor family (formally known as interleukin-1 receptor like 1 IL1RL-1). The human ST2 gene is located on chromosome 2 and encodes at least three isoforms: a transmembrane receptor (ST2L), a secreted soluble form (sST2) and a variant form (ST2 V). Recent reviews identified a close link between ST2 and both inflammatory and heart diseases, being considered as a prognostic marker for both [16,17,18].

Discovered in 1989 by two separate research groups who studied fibroblasts stimulation, ST2 is involved in activating t-helper 2 cells (Th2), in the production of Th2-associated cytokines (IL-4, IL-5, and IL-13) and in cell proliferation. ST2 is also expressed on membranes of mast cells, therefore serum protein levels are increased in patients with asthma and allergic airways inflammation [17,18].

High concentrations of ST2 (especially sST2 isoform) in blood can be identified in patients suffering from diseases associated with an abnormal immune response mediated by Th2 cells (for example, systemic lupus erythematosus and asthma), as well as in inflammatory conditions that are mainly independent of a Th2 response, such as septic shock or trauma [16]. Therefore, ST2 has emerged as a useful prognostic biomarker in patients with cardiovascular disease and dyspnea [17]. Furthermore, the interleukin-33/ST2L signaling plays a major part in the cardioprotective mechanism in case of mechanical overload [16] and by releasing sST2 from cardiomyocytes, this process leads to fibrosis and cardiac remodeling and therefore ST2 levels can reflect myocardial stress and degree of fibrosis and left ventricular stiffness, more in HF with preserved ejection fraction (HFpEF) than in HF with reduced ejection fraction (HFrEF). sST2 can bind to IL-33 and limit the interaction between IL-33 and ST2L, thus hindering its beneficial effects. This makes it a useful biomarker in predicting future heart failure (HF) in patients with myocardial ischemia (STEMI or NSTEMI), as well as in those with coronary bypass and heart surgery, stable coronary artery disease, valvular disease and cardiomyopathy, acute HF, chronic HF, acute cardiac allograft rejection or acute Kawasaki disease [17,19,20-22]. Another study found an association between ST2 levels, right ventricular pressure overload and dysfunction, as well as systemic congestion [22]. In addition, studies have shown that high sST2 values (above 35 ng/mL) are correlated with a less favorable prognosis in patients suffering from heart failure or myocardial infarction, even more than traditional biomarkers [16,20,22].

In rat LPS-induced shock models, ST2 was found to enhance survival rate and suppress IL-6, IL-12, and TNF-a production by acting directly on macrophages via

the ST2-TLR-4 route. Also, ST2 expression was shown to be induced by IL-1b, IL-1a, and TNF-a in fibroblasts, macrophages, muscle, and in spleen after LPS infusion, thus macrophages produce Th2-associated cytokines, that in turn increase the expression of sST2 [18].

Regarding the differences between genders, some studies demonstrated the fact that there is a significant difference between sST2 baseline values in men and women, the mean concentration of sST2 plasma levels being almost two times higher in men, in comparison to women [16].

In pathological conditions, slightly higher levels of sST2 have been identified in patients with various degrees of heart failure, moderate levels have been identified in patients with pneumonia or chronic obstructive pulmonary disease (COPD), moderately high levels in patients with both pneumonia and heart failure, while high levels have been identified in sepsis. In addition, serum levels of sST2 were significantly increased in sepsis compared with trauma. Recently, high levels of serum sST2 have been identified in idiopathic pulmonary fibrosis and various autoimmune diseases as well [16,18]. In normal conditions, higher levels of sST2 have been reported in studies after exercise [20].

A recent review revealed that high levels of serum sST2 can also be identified in COVID-19 patients without underlying cardiovascular pathology. Furthermore, sST2 levels were significantly correlated with the severity of the inflammation and implicitly of the disease. Therefore, these results further tie the connection between this marker and inflammatory diseases (given the proinflammatory status associated with COVID-19) [23].

Furthermore, high serum levels of sST2 associated with increased levels of other biomarkers involved in cardiac dysfunction (such as NT-proBNP), have been correlated with a worse severity poorer prognosis in patients with acute myocardial infarction and/or acute or chronic heart failure, as well as a lower survival rate post-open heart surgery [19,22]. Also, a recent meta-analysis proved that discharge ST2 levels are predictive of adverse effects in acute heart failure [22]. In addition, sST2 was identified as a useful biomarker for the evaluation of prognosis in patients with acute dyspnea, independent of its cause [17].

ST2 was recently approved by the Food and Drug Administration as a prognostic biomarker in heart failure [24] and was proposed as the new gold standard biomarker for the evaluation of heart failure prognosis. Based on current data, the 2013 American Heart Association and American Association of Clinical Chemistry guidelines recommend ST2 measurement in order to evaluate additional cardiovascular risk in patients with acute or chronic heart failure (some studies revealed that serum ST2 levels over 54 ng/mL correlate with adverse effects occurring within 6 months in patients with heart failure and diabetes mellitus type 2 and a poor prognosis) [22,25]. However, ST2 measurement has low specificity and therefore is not a useful option for the differential diagnosis of certain pathologies [25].

Although multiple reviews have shown the correlation between sepsis and the increase of ST2 plasma levels, as well as the link between heart failure and ST2 [16-25], there are not sufficient data in literature to describe an association between this biomarker and the cardiac involvement in sepsis.

CONCLUSIONS

Given the fact that despite recent medical advancements in sepsis therapy, this pathology remains the most frequent cause of death amongst critically ill patients worldwide, we need to identify some markers that could help us better understand this affliction. Endothelin-1 and ST2 are two biomarkers that could prove to have significant prognostic power in patients with sepsis-induced cardiomyopathy, given the fact that they are both correlated with sepsis severity and cardiac dysfunction. However, we have not found any studies that can correlate these markers and the cardiovascular dysfunction determined by sepsis. Therefore, more studies in this field are required in order to find out the prognostic value of endothelin-1 and ST2 in patients with sepsis-induced cardiomyopathy.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016 Feb 23;315(8):801-10. doi: 10.1001/jama.2016.0287. PMID: 26903338; PMCID: PMC4968574.
2. Sandulescu O, Streinu-Cercel A, Streinu-Cercel Ad. Sepsisul. In: Ceausu E, ed. Tratat de Boli infecțioase vol. 2. Bucharest: Editura Medicala, 2018. p. 773 – 789.
3. L'Heureux M, Sternberg M, Brath L, Turlington J, Kashiouris MG. Sepsis-Induced Cardiomyopathy: A Comprehesive Review. *Current Cardiology Reports*. 2020;22(5):35.
4. Walley KR. Sepsis-induced myocardial dysfunction. *Current Opinion in Critical Care.* 2018 Aug;24(4):292-9.
5. Arfaras-Melainis A, Polyzogopoulou E, Triposkiadis F, Xanthopoulos A, Ikonomidis I, Mebazaa A, Parissis J. Heart failure and sepsis: practical recommendations for the optimal management. *Heart Failure Reviews.* 2020;25:183-194.
6. Kowalczyk A, Kleniewska P, Kolodziejczyk M, Skibska B, Goraca A. The role of endothelin-1 and endothelin receptor antagonists in inflammatory response and sepsis. *Archivum Immunologiae et Therapiae Experimentalis.* 2015 Feb;63(1): 41-52.
7. Lomba LA, Leite-Avalca MCG, Zampronio AR. ET A receptors are involved in the febrile response induced by high dose of bacterial endotoxin. *J Thermal Biol.*
8. Rutai A, Fejes R, Juhasz L, Tallosy SP, Poles MZ, Foldesi I, et al. Endothelin A and B Receptors: Potential Targets for Microcirculatory-Mitochondrial Therapy in Experimental Sepsis. *Shock*. 2020 Jul;54(1):87-95.
9. Inostroza-Nieves Y, Valentin-Berrios S, Vega C, Prado GN, Luciano-Montalvo C, Romero JR, Rivera A. Inhibitory effects of Syzygium jambos extract on biomarkers of endothelial cell activation. *BMC Comp Med Therap*. 2022;22(1):101.
10. Joffre J, Hellman J, Ince C, Ait-Oufella H. Endothelial Responses in Sepsis. *Am J Respir Critic Care Med.* 2020 Aug 1;202(3):361-70. doi: 10.1164/rccm.201910-1911TR. PMID: 32101446.
11. Ozer EK, Iskit AB. Effects of endothelin and nitric oxide on cardiac muscle functions in experimental septic shock model. *Hum ExpToxicol.* 2016;35(3):267-75.
12. Smiljic S. The clinical significance of endocardial endothelial dysfunction. *Medicina*. 2017;53(5):295-302.
13. Seki Y, Jesmin S, Shimojo N, Islam MM, Rahman MA, Khatun T, et al. Significant reversal of cardiac upregulated endothelin-1 system in a rat model of sepsis by landiolol hydrochloride. *Life Sci.* 2014;118(2):357-63.
14. Li XG, Yan BQ. Research on the effect of cytokine concentration on the immune level and survival conditions of elderly patients with sepsis. Experimental and Therapeutic *Medicine*. 2018;16(2):842-6.
15. Schuetz P, Christ-Crain M, Morgenthaler NG, Struck J, Bergmann A, Müller B. Circulating precursor levels of endothelin-1 and adrenomedullin, two endothelium-derived, counteracting substances, in sepsis. *Endothelium*. 2007 Nov-Dec;14(6):345-51. doi: 10.1080/10623320701678326. PMID: 18080871; PMCID: PMC2430170.
16. Dieplinger B, Januzzi JL, Steinmair M, Gabriel C, Poelz W, Haltmayer M, Mueller T. Analytical and clinical evaluation of a novel high-sensitivity assay for measurement of soluble ST2 in human plasma – The Presage ™ ST2 Assay. *Clin Chim Acta.* 2009;409(1-2):33-40.
17. Salvagno GL, Pavan C. Prognostic biomarkers in acute coronary syndrome. *Ann of Translat Med.* 2016;4(13).
18. Brunner M, Krenn C, Roth G, Moser B, Dworschak M, Jensen-Jarolim ES, et al. Increased levels of soluble ST2 protein and IgG1 production in patients with sepsis and trauma. *Intensive Care Medicine.* 2004;30:1468-73.
19. Ramkumar N, Jacobs JP, Berman RB, Parker DM, MacKenzie TA, Likosky DS, et al. Cardiac Biomarkers Predict Long-term Survival After Cardiac Surgery. *Ann Thorac Sur.* 2019;108(6):1776-1782.
20. Costa AM, Teixeira R, Vilela EM, Tavares A, Torres S, Sampaio F, et al. Suppression of tumorigenicity 2 after exercise: a systematic review. *Monaldi Arch Chest Dis.* 2022;92:1839.
21. Sugano A, Seo Y, Ishizu T, Yamamoto M, Hamada Y, Machino-Ohtsuka T, et al. The Value of Galectin-3 and ST-2 for Prediction of Prognosis in Patients with Acute Decompensated Heart Failure. *J Card Fail.* 2016 Sep;22(9):S181-S182.
22. Ruocco G, Evangelista I, Franci B, Lucani B, Martini S, Nuti R, Palazzuoli A. Combination of ST2 and B-type natriuretic peptide in diabetic patients with acute heart failure: Relation with ventricular stiffness and outcome. *J Cardiovas Medicine.* 2019;20(2):81–90.
23. Miftode RS, Serban IL, Timpau AS, Miftode IL, Ion A, Buburuz AM, et al. Syndecan-1: A review on its role in heart failure and chronic liver disease patients' assessment. *Cardiol Res Pract.* 2019;2019:4750580
24. Dutka M, Bobinski R, Ulman-Wlodarz I, Hajduga M, Bujok J, Pajak C, Cwiertnia M. Various aspects of inflammation in heart failure. *Heart failure reviews.* 2020;25(3):537-548.
25. Le Goff C, Kaux JF, Segura JF, Stojkovic V, Ancion A, Seidel L, et al. Evolution of the slopes of ST2 and galectin-3 during marathon and ultratrail running compared to a control group. *Clinic chem laborator med.* 2020;58(2):314-321.