

Soluble Suppression of Tumorigenicity 2: A Role in Biomarker-Guided Therapy of Heart Failure

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: May 31, 2019

Revised: May 31, 2019

Accepted: May 31 2019

Published online: July 3, 2019

ABSTRACT

Current clinical guidelines of European Society of Cardiology and American Heart Association regarding the diagnosis and treatment of acute and chronic HF recommend to use natriuretic peptides (NPs) as powerful diagnostic and predictive biomarker, while other biomarkers, such as galectin-3, cardiac troponins, and soluble suppressor of tumorigenicity (ST2) are embedded onto American Heart Association statement to improve a risk stratification, as well as NPs are considered for performing biomarker-guided therapy. The aim of the Editorial is to summarize knowledge among clinical efficacy of heart failure (HF) guidance care based on serial measure

of sST2. Elevated levels of sST2 are established biomarker of high risk of all-cause and cardiovascular mortality, new diagnosed HF and re-admission due to HF decompensation. Therefore, a trend to declined serum levels of sST2 was associated with improved survival and decreased re-hospitalization in patients with different phenotypes of HF. It has shown that serial measure of sST2 concentrations in HF patients can predict poor clinical outcomes and personally optimize treatment care, especially in combination with repetitive measure of NT-proBNP levels. However, the role of combined biomarker approach (sST2 + NT-proBNP) in the clinical care of the HF patient is not yet partially defined and more large clinical trials are needed.

Key words: Heart failure; Biomarkers; Soluble ST2; Guided therapy; Prediction; Outcomes

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Berezin AE, Berezin AA. Soluble Suppression of Tumorigenicity 2: A Role in Biomarker-Guided Therapy of Heart Failure. *Journal of Cardiology and Therapy* 2019; **6(1)**: 789-792 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/2605>

INTRODUCTION

The prevalence of heart failure (HF), which is associated with cardiovascular (CV) morbidity and mortality, is increasing worldwide^[1]. Although during last decade there was rather an increase in prevalence of HF with preserved ejection fraction (HFpEF) than HF with reduced ejection fraction (HFrEF), which remained stable for this period or even occurred to have declined in developed countries, the prognosis of HF regardless of phenotypes continued poor^[2,3]. Patients with acute or actually decompensated heart failure (HF) are at high risk of cardiovascular (CV) death and even over next 30 days after discharged from the hospital expecting rate for HF-related outcomes remained to be extremely high^[4,5]. Moreover, incidences for CV events and mortality in hemodynamically stable out-patients with overall types of HF have been widely recognized to be unchanged across last two decades^[5]. It has been noted that majority of death causes in HFpEF out-patients are CV, whereas the proportion of non-CV deaths is higher in HFpEF than HFrEF. Perhaps, our understanding regarding optimal medication and risk factors control

should be reappraised. In this context, circulating biomarkers, which reflect several pathogenetic stages of HF development, may be useful tool to revolutionize the diagnosis, prognosis and guidance in therapy of HF^[6,7]. However, current clinical guidelines of European Society of Cardiology and American Heart Association regarding the diagnosis and treatment of acute and chronic HF recommend to use natriuretic peptides (NPs) as powerful diagnostic and predictive biomarker, while other biomarkers, such as galectin-3, cardiac troponins, and soluble suppressor of tumorigenicity (ST2) are embedded onto American Heart Association statement to improve a risk stratification, as well as NPs are considered for performing biomarker-guided therapy^[8,9]. Table 1 is reported clinical relevance of circulating biomarkers for HF diagnosis, prediction, stratification and guided therapy. Previously, biomarker-guided therapy of HF has been found to be similarly efficient to clinical-guided care in routine practice, but nowadays there is a large number of evidence regarding new perspectives for biological markers in this field^[10,11]. Indeed, changes in NPs (brain NP [BNP] and NT-proBNP) were significantly associated with risk of hospital stay for HF worsening^[12], whereas increased biological variability, relation to body mass / obesity, decreased kidney clearance, other CV and non-CV disease, such as atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, pulmonary hypertension, and infections, shape serious problems in interpretations of data received^[13]. It has been suggested that multiple biomarker models could be the best decision to improve an ability of longitudinal changes of circulating biomarkers to predict poor outcomes and modify personal care^[14]. The aim of the Editorial is to summarize knowledge among clinical efficacy of HF guidance care based on serial measure of soluble ST2.

SOLUBLE ST2 IN HF DIAGNOSIS, PREDICTION AND STRATIFICATION

ST2 is the receptor for interleukin-33 (IL-33), which is presented in two isoforms including soluble (sST2) isoform and the transmembrane receptor ST2L isoform^[15]. ST2 belongs to the IL-1 receptor family and is released by several cells (fibroblasts, cardiac myocytes, macrophages, mononuclears, progenitor precursors, endothelial cells) due to inflammatory activation, necrosis / apoptosis and ischemia^[16]. Recent studies have shown that IL-33/ST2L signaling mechanism had cardioprotective capabilities that are mediated through binding sST2 with IL-33. The result of this interaction is an improvement of cell viability after ischemia / injury due to suppression of nuclear factor kappa-B in fibroblasts and immune cells, preventing mitochondrial dysfunction and oxidative stress, unleash to up-expression of the anti-apoptotic factors (XIAP, cIAP1) and hypoxia induce factor-1, and preventing fibrosis and inflammation^[17,18].

There is a large body of evidence regarding predictive capability of elevating levels of sST2 in general population for CV mortality and disease, as well as a high risk of poor prognosis in patients with established HF^[19,20]. There is data clarifying that acute HF in-patients with low sST2 (<35 ng/mL) also presented better probability to short-term survival and less hospital stay than individuals with high sST2 concentration (≥35 ng/mL) regardless of NP levels^[21]. Moreover, measure of sST2 levels can help to stratify acute and acutely decompensated HF patients as higher risk of death and re-admission at discharge^[22,23]. sST2 can be valuable for improvement of the diagnostic and predictive of acute myocardial infarction and adverse cardiac remodeling leading to HF I patients underwent percutaneous coronary intervention (PCI) regardless of numerous co-morbidities

including diabetes mellitus, abdominal obesity, atrial fibrillation, kidney dysfunction^[24]. Yet, elevated levels of sST2 were found to be superior NPs for assay of an increased risk of readmission or 30-days mortality after cardiac surgery and PCI^[25]. Overall, face-to-face comparison of sST2 and NT-proBNP in HF individuals for prediction of long-term HF-related outcomes has revealed superiority of sST2, whereas NPs were most optimal for prediction of in-hospital stay long and re-admission^[6]. Another advantage of sST2 in comparison with traditional biomarkers (NPs, cardiac troponins and galectin-3) is an ability to predict clinical outcomes in patients with different phenotype of HF^[26]. Once the diagnosis of HF has been established, a potential approach should implement to a panel of biomarkers to identify the HF phenotypes (HF_{rEF}, HF_{pEF}, HF_{mrEF}), guiding towards more appropriate therapeutic strategies. Interestingly, serum levels of sST2 can be modified during treatment that opens perspectives for optimized therapy in HF patients under control of biomarker levels. Indeed, the TRIUMPH (TRANslational Initiative on Unique and novel strategies for Management of Patients with Heart failure) study has revealed that serial sST2 measurements appeared to be a strong predictor of poor clinical outcome in acute HF patients independent of serial measured NT-pro brain NP^[27]. Overall, measure of serum sST2 levels appears to be promising tool to HF prognosis and perhaps treatment monitoring, while evidence regarding serial sST2 measures for guidance therapy of HF gave controversial results.

SOLUBLE ST2 AS POTENTIAL TARGET OF INTERVENTION IN HF PATIENTS

Early clinical trials have shown that continuous monitoring of sST2 concentrations in acute and chronic HF patients were associated with impending cardiac failure to reduce filling pressures and 90-day impending events that was accompanied to benefit from specific

Table 1 Clinical relevance of circulating biomarkers for HF diagnosis, prediction, stratification and guided therapy.

Biomarkers	Heart failure			
	diagnosis	outcomes	guided therapy	risk stratification
hs-troponin T/1#	-	++	--	+
NPs##	++	+++	+	++
MR-proADM	+	+++	-	++
Galectin-3#	-	+	-	+
sST2#	--	++	+	-
Copeptin	+	++	-	+
GDF15	--	++	-	+
hs-CRP	--	+	-	-
IL-1β	--	+	-	+
IL-6	--	+	-	+
MMP-2	--	+	--	--
MMP-9	--	+	--	--
CTPpC-I	--	+	--	+
APpC-III	--	+	--	+
miRNAs	--	+	+	+

Notes: "--" mild disagree; "--" moderate disagree; "+" mild agree; "++" moderate agree; "+++ strong agree; #, approved by European Society of Cardiology (2016); * approved by American College of Cardiology/ American Heart Association (2017).

Abbreviations; hs, high sensitive; HF, heart failure; NPs, natriuretic peptides; sST2, soluble suppression of tumorigenicity-2; MR-proADM, mid-regional pro-adrenomedullin; GDF, growth / differential factor; CRP, C-reactive protein; miRNAs, micro-ribonucleic acids; MMP, matrix metalloproteinase; CTPpC-I, carboxytelopeptides of procollagen type I; APpC-III, aminopeptide of procollagen type III.

HF therapy changes^[28-30]. For instance, the results of the MUSIC study have been yielded that declined serum sST2 (<0.23 ng/mL) was able to predict lowered risk of sudden death^[30]. Additionally, the MOCA (Multinational Observational Cohort) study has revealed an ability to the trend of sST2 concentration to suggest all-cause mortality^[31]. These findings were extremely important, because they have shown a benefit of serial measure of the biomarker despite the biological variability^[32,33]. Finally, serum levels of sST2 defined as 35ng/mL were suggested as a target for the personalized therapy of patients with acute and acutely decompensated HF^[34]. Moreover, sST2 values, which were complementary to serum levels of NPs, may shape a new approach for serial testing in the acutely admitted HF patient to predict poor outcomes^[35]. Indeed, HF patients who were attained lowered levels of sST2 (<35ng/mL) and NT-proBNP (<1000 pg/mL) in contrast to those have higher levels of both biomarkers ($\geq 35\text{ng/mL}$ and $\geq 1000\text{ pg/mL}$, respectively) during treatment had been found improved survival and decreased need for re-admission^[36,37]. In fact, multiple biomarker model based on both sST2 and NT-pro-BNP was able not just predict clinical outcomes during HF therapy, but yet to improve accuracy of prognostication for both HFpEF and HFrEF^[38]. Although circulating levels of sST2 were predominantly associated with all-cause mortality and non-CV death in HF out-patients showing strong association with systemic inflammation and malnutrition, while NT-proBNP levels were associated with CV death and re-admission^[39], the combined use of both biomarkers for personalizing optimization of HF care appears to be promising. Large clinical trials with adequate sample size are required to shape the most optimal strategy of biomarker-guided therapy in patients with several phenotypes of HF.

CONCLUSION

Serial measure of sST2 concentrations in HF patients can help to predict clinical outcomes and personally optimize treatment strategy, especially in combination with repetitive measure of NT-proBNP levels, but their role in the clinical care of the HF patient is not yet partially defined and more large clinical trials are needed.

ACKNOWLEDGEMENTS

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

- van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail.* 2016; **18(3)**: 242-52. [DOI: 10.1002/ejhf.483]
- Bouthoorn S, Valstar GB, Gohar A, den Ruijter HM, Reitsma HB, Hoes AW, Rutten FH. The prevalence of left ventricular diastolic dysfunction and heart failure with preserved ejection fraction in men and women with type 2 diabetes: A systematic review and meta-analysis. *Diab Vasc Dis Res.* 2018; **15(6)**: 477-493. [DOI: 10.1177/1479164118787415]
- Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, Killian JM, Roger VL. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* 2015; **175**: 996-1004. [DOI: 10.1001/jamainternmed.2015.0924]
- Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2017; **14(10)**: 591-602. [DOI: 10.1038/nrcardio.2017.65]
- Tsao CW, Lyass A, Enserro D, Larson MG, Ho JE, Kizer JR, Gottdiener JS, Psaty BM, Vasan RS. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. *JACC Heart Fail.* 2018; **6(8)**: 678-685. [DOI: 10.1016/j.jchf.2018.03.006]
- Chang KW, Fox S, Mojaver S, Maisel AS. Using biomarkers to guide heart failure management. *Expert Rev Cardiovasc Ther.* 2017; **15(10)**: 729-741. [DOI: 10.1080/14779072.2017.1366312.
- Berezin AE, Kremzer AA, Martovitskaya YV, Samura TA, Berezina TA. The novel biomarker risk prediction score in patients with chronic heart failure. *Clinical Hypertension.* 2016; **22(3)**: 1 [DOI: 10.1186/s40885-016-0041-1]
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129-2200. [DOI: 10.1093/eurheartj/ehw128]
- Chow SL, Maisel AS, Anand I, Bozkurt B, de Boer RA, Felker GM, Fonarow GC, Greenberg B, Januzzi JL Jr, Kiernan MS, Liu PP, Wang TJ, Yancy CW, Zile MR; American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology; Council on Basic Cardiovascular Sciences; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation; Council on Epidemiology and Prevention; Council on Functional Genomics and Translational Biology; and Council on Quality of Care and Outcomes Research. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement From the American Heart Association. *Circulation.* 2017; **135(22)**: e1054-e1091. [DOI: 10.1161/CIR.0000000000000490]
- Gaggin HK, Januzzi JL Jr. Biomarkers and diagnostics in heart failure. *Biochim Biophys Acta.* 2013; **1832(12)**: 2442-50. [DOI: 10.1016/j.bbdis.2012.12.014]
- Savarese G, Musella F, D'Amore C, Vassallo E, Losco T, Gambardella F, Cecere M, Petraglia L, Pagano G, Fimiani L, Rengo G, Leosco D, Trimarco B, Perrone-Filardi P. Changes of natriuretic peptides predict hospital admissions in patients with chronic heart failure: a meta-analysis. *JACC Heart Fail.* 2014; **2(2)**: 148-58. [DOI: 10.1016/j.jchf.2013.11.007]
- Morrow DA, Velazquez EJ, DeVore AD, Prescott MF, Duffy CI, Gurmu Y, McCague K, Rocha R, Braunwald E. Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial. *Eur Heart J.* 2019. pii: ehz240. [DOI: 10.1093/eurheartj/ehz240. [Epub ahead of print]
- Berezin AE. Circulating Biomarkers in Heart Failure. *Adv Exp Med Biol.* 2018; **1067**: 89-108. [DOI: 10.1007/5584_2017_140]
- Berezin AE. Biomarkers in heart failure. *Journal of Blood & Lymph.* 2017; **7 (3)**: 172-179. [DOI: 10.4172/2165-7831.1000172]
- Bayés-Genis A, González A, Lupón J. ST2 in Heart Failure. *Circ Heart Fail.* 2018; **11(12)**: e005582. [DOI: 10.1161/CIRCHEARTFAILURE.118.005582]
- Pascual-Figal DA, Januzzi JL. The biology of ST2: The international ST2 consensus panel. *Am J Cardiol.* 2015; **115(Suppl)**: 3B-7B. [DOI: 10.1016/j.amjcard.2015.01.034]
- Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity.* 2005; **23(5)**: 479-490 [DOI: 10.1016/j.immuni.2005.09.015]

18. Asensio-Lopez MC, Lax A, Fernandez Del Palacio MJ, Sassi Y, Hajjar RJ, Januzzi JL, Bayes-Genis A, Pascual-Figal DA. Yin-Yang 1 transcription factor modulates ST2 expression during adverse cardiac remodeling post-myocardial infarction. *J Mol Cell Cardiol.* 2019; 130: 216-233. [DOI: 10.1016/j.yjmcc.2019.04.009.]
19. Berezin AE. Current understanding of the role of new cardiac biomarkers in prediction of heart failure. *Biological Markers and Guided Therapy* 2017; **4(1)**: 49-55 [DOI: 10.12988/bmgt.2017.736]
20. Shah R, Chen-Tournoux A, Picard M, van Kimmenade R, Januzzi JL. Serum levels of the interleukin-1 receptor family member ST2, cardiac structure and function, and long-term mortality in patients with acute dyspnea. *Circ Heart Fail.* 2009; **2(4)**: 311-319 [DOI: 10.1161/CIRCHEARTFAILURE.108.833707]
21. Pascual-Figal DA, Bayes-Genis A, Asensio-Lopez MC, Hernández-Vicente A, Garrido-Bravo I, Pastor-Perez F, Diez J, Ibáñez B, Lax A. The Interleukin-1 Axis and Risk of Death in Patients With Acutely Decompensated Heart Failure. *J Am Coll Cardiol.* 2019; **73(9)**: 1016-1025. [DOI: 10.1016/j.jacc.2018.11.054]
22. Manzano-Fernandez S, Mueller T, Pascual-Figal D, Truong QA, Januzzi JL. Usefulness of soluble concentrations of interleukin family member ST2 as a predictor of mortality in patients with acutely decompensated heart failure relative to left ventricular ejection fraction. *Am J Cardiol.* 2011; **107(2)**: 259-267 [DOI: 10.1016/j.amjcard.2010.09.011]
23. Aleksova A, Paldino A, Beltrami AP, Padoan L, Iacoviello M, Sinagra G, Emdin M, Maisel AS. 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. *J Clin Med.* 2019; **8(2)**. pii: E270. [DOI: 10.3390/jcm8020270]
24. Somuncu MU, Akgun T, Cakır MO, Akgul F, Serbest NG, Karakurt H, Can M, Demir AR. The Elevated Soluble ST2 Predicts No-Reflow Phenomenon in ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *J Atheroscler Thromb.* 2019. [DOI: 10.5551/jat.48413]
25. Parker DM, Everett AD, Stabler ME, Vricella L, Jacobs ML, Jacobs JP, Thiessen-Philbrook H, Parikh CR, Brown JR. Biomarkers associated with 30-day readmission and mortality after pediatric congenital heart surgery. *J Card Surg.* 2019; **34(5)**: 329-336. [DOI: 10.1111/jocs.14038]
26. D'Elia E, Vaduganathan M, Gori M, Gavazzi A, Butler J, Senni M. Role of biomarkers in cardiac structure phenotyping in heart failure with preserved ejection fraction: critical appraisal and practical use. *Eur J Heart Fail.* 2015; **17(12)**: 1231-9. [DOI: 10.1002/ejhf.430]
27. van Vark LC, Lesman-Leegte I, Baart SJ, Postmus D, Pinto YM, Orsel JG, Westenbrink BD, Brunner-la Rocca HP, van Miltenburg AJM, Boersma E, Hillege HL, Akkerhuis KM; TRIUMPH Investigators. Prognostic Value of Serial ST2 Measurements in Patients With Acute Heart Failure. *J Am Coll Cardiol.* 2017; **70(19)**: 2378-2388. [DOI: 10.1016/j.jacc.2017.09.026]
28. Zilinski JL, Shah RV, Gaggin HK, Gantzer ML, Wang TJ, Januzzi JL Jr. Measurement of multiple biomarkers in advanced stage heart failure patients treated with pulmonary artery catheter guided therapy. *Crit Care.* 2012; **16(4)**: R135 [DOI: 10.1186/cc11440]
29. Boisoit S, Beed J, Isakson S, Chiu A, Clopton P, Januzzi J, et al. Serial sampling of ST2 predicts 90-day mortality following destabilized Heart failure. *J Card Fail.* 2008; **14(9)**: 732-738. [DOI: 10.1016/j.cardfail.2008.06.415]
30. Pascual-Figal DA1, Ordoñez-Llanos J, Tornel PL, Vázquez R, Puig T, Valdés M, Cinca J, de Luna AB, Bayes-Genis A; MUSIC Investigators. Soluble ST2 for predicting sudden cardiac death in patients with chronic heart failure and left ventricular systolic dysfunction. *J Am Coll Cardiol.* 2009; **54(23)**: 2174-9. [DOI: 10.1016/j.jacc.2009.07.041]
31. Lassus J, Gayat E, Mueller C, Peacock WF, Spinar J, Harjola VP, et al. Incremental value of biomarkers to clinical variables for mortality prediction in acutely decompensated heart failure: the Multinational Observational Cohort on acute heart failure (MOCA) Study. *Int J Cardiol.* 2013; **168(3)**: 2186-2194 [DOI: 10.1016/j.ijcard.2013.01.228]
32. Wu AH, Wians F, Jaffe A. Biological variation of galectin-3 and soluble ST2 for chronic health failure: implication on interpretation of test results. *Am Heart J.* 2013; **165(6)**: 995-999 [DOI: 10.1016/j.ahj.2013.02.029]
33. Berezin AE. The Biomarker Utility in Risk Stratification in an Ambulatory Heart Failure: ST2 or Galectin-3? *Journal of Cardiol. Ther.* 2016; **3(1)**: 456-458 [DOI: 10.17554/j.issn.2309-6861.2016.03.105]
34. Maisel AS, Richards AM, Pascual-Figal D, Mueller C. Serial ST2 testing in hospitalized patients with acute heart failure. *Am J Cardiol.* 2015; **105(7) Suppl**: 32B-37B [DOI: 10.1016/j.amjcard.2015.01.038]
35. Berezin AE. Up-to-date clinical approaches of biomarkers' use in heart failure. *Biomed Res Ther* 2017, **4(6)**: 1341-1370. [DOI: 10.15419/bmrat.v4i06.178]
36. Januzzi JL, Pascual-Figal D, Daniels LB. ST2 testing for chronic heart failure therapy monitoring: the International ST2 Consensus Panel. *Am J Cardiol.* 2015; **115(7 Suppl)**: 70B-5B. [DOI: 10.1016/j.amjcard.2015.01.044]
37. Manzano-Fernández S, Januzzi JL, Pastor-Pérez FJ, Bonaque-González JC, Boronat-García M, Pascual-Figal DA, Montalban-Larrea S, Navarro-Peñalver M, Andreu-Cayuelas JM, Valdés M. Serial monitoring of soluble interleukin family member ST2 in patients with acutely decompensated heart failure. *Cardiology.* 2012; **122(3)**: 158-66. [DOI: 10.1159/000338800]
38. Najjar E, Faxén UL, Hage C, Donal E, Daubert JC, Linde C, Lund LH. ST2 in heart failure with preserved and reduced ejection fraction. *Scand Cardiovasc J.* 2019; **53(1)**: 21-27. [DOI: 10.1080/14017431.2019.1583363]
39. Sugano A, Seo Y, Ishizu T, Sai S, Yamamoto M, Hamada-Harimura Y, Machino-Ohtsuka T, Obara K, Nishi I, Aonuma K, Nogami A. Soluble ST2 and brain natriuretic peptide predict different mode of death in patients with heart failure and preserved ejection fraction. *J Cardiol.* 2019; **73(4)**: 326-332. [DOI: 10.1016/j.jjcc.2018.10.012]