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SST2 and NT-proBNP biomarkers in prediction of COVID-19

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Abstract. ***Background.*** *COVID-19 may cause or worsen cardiac dysfunction and patients with pre-existing cardiovascular disease, including heart failure (HF), who have an increased risk of severe and fatal outcomes of COVID-19. The study aimed to determine the role of soluble suppression of tumorigenesis-2 protein (sST2) and natriuretic peptide test (NT-proBNP) in predicting the severe course and in-hospital mortality of patients with COVID-19 and hypertension.* ***Materials and methods.*** *One hundred and fifteen patients with COVID-19 and hypertension were examined. The determination of sST2 and NT-proBNP in blood serum were done using the enzyme-linked immunosorbent assay. The clinical endpoint was assessed during the hospitalization period (death, hospitalization in the intensive care unit, prolonged hospitalization). The risk of the final event development was calculated for the patients who reached the threshold sST2 concentrations, and, separately, based on the diagnostic values of the NT-proBNP.* ***Results.*** *The cut-off values of sST2 recommended for the diagnosis of HF in our study were reached in 7 (28 %) cases. The risk of final clinical points development in these patients was as follows: OR = 10.67; 95% CI: 1.31–86.9; p = 0.0270. The level of NT-proBNP, which meets the criteria for the diagnosis of HF, was constant in only 10 (11.1 %) individuals (p = 0.0461) and the risk of clinical events developing was equal to OR = 7.0; 95% CI: 1.72–28.6; p = 0.0067.* ***Conclusions.*** *Stratification of patients based on sST2 values, in addition to NT-proBNP parameters, may provide further prognostic value compared to NT-proBNP levels in patients with COVID-19 and HF.*

Keywords: *sST2; NT-proBNP; coronavirus disease; heart failure*

Introduction

Cardiovascular disease and cardiovascular risk factors (hypertension and diabetes) are strongly associated with mortality in COVID-19 patients, regardless of their age. Recent research suggests that patients hospitalized with COVID-19 may be exposed to an increased risk of developing heart failure (HF), even in the absence of a cardiovascular disease history or cardiovascular disease risk factors [1]. Assessment of HF biomarkers such as sST2 and NT-proBNP may be useful in predicting the COVID-19 adverse course.

Currently, the most widely used HF biomarkers are natriuretic peptides (NP). In response to pressure overload or a ventricular volume increase, left ventricular cardiomyocytes stretch and secrete B-type natriuretic peptides (BNP) through a whole cascade of transformations from the 134 amino acid precursors of BNP (pre-proBNP), to the cleavage of the inactive 76-amino acid NT-proBNP and the formation of the active 32-amino acid BNP [2, 3]. Both biologically active BNP and NT-proBNP can be measured in plasma [4]. BNP accurately diagnoses HF in patients with dyspnoea and predicts future events in these patients using a 100 ng/ml cutoff [5]. The NT-proBNP threshold value of 300 pg/ml has a 98% predictive value for excluding acute HF and 125 pg/ml for excluding heart failure in outpatients [6]. At the same time, the NT-proBNP value is highly age-dependent. Therefore, in patients under 50 years of age, it is recommended to use > 450 pg/ml as a diagnostic level of NT-proBNP for acute HF; in patients from 50 to 75 years — > 900 pg/ml, and in patients older than 75 years — > 1800 pg/ml [7]. NPs are also helpful in assessing HF severity and prognosis. These biomarkers alone or in combination play an important role in the HF treatment dynamic assessment, but their accuracy is limited by several factors, including renal impairment, obesity, and/or atrial fibrillation [7].

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A novel investigational biomarker — soluble (s) ST2 — is a circulating soluble isoform of the interleukin-33 (IL-33) receptor released by cardiomyocytes and fibroblasts in response to cellular injury. Experimental models manifested that under normal conditions, IL-33 interacts with the transmembrane cellular isoform of the ST2L receptor, showing cardioprotective properties: it reduces myocardial fibrosis, hypertrophy, and cardiomyocyte apoptosis, which in turn improves cardiac function. Unlike the transmembrane ST2L form, the soluble sST2 isoform competitively binds to IL-33. The interaction of sST2ɜIL with IL-33 acts as a decoy for IL-33, blocks the IL-33/ST2L system, and, consequently, eliminates the cardioprotective effects described above. Therefore, the ST2 system acts not only as a mediator of IL-33 function in its transmembrane isoform ST2L but also as an IL-33 inhibitor through its soluble isoform sST2. All clinical conditions that increase wall stress, inflammation, and macrophage activation increase sST2 and thus may lead to deteriorating cardiac fibrosis [8]. The current threshold level indicating a good outcome in HF patients is 35 ng/mL. The higher the sST2 level in HF, the higher the mortality rate. Biaggi P. research demonstrates that the combination of higher sST2 levels and NP produces the most accurate mortality predictions within one year, whereas isolated high NP levels failed to predict mortality in patients with low sST2 levels [8, 9].

The study **aimed** to compare the prognostic value of heart failure biomarkers NT-proBNP and sST2 in COVID-19.

Materials and methods

A cross-sectional analysis was based on a sample of 115 patients with COVID-19 pneumonia hospitalized at the Lviv Clinical Emergency Medical Hospital. All the patients were over 18 years of age and gave their consent to participate in the research. The criteria for including patients in the study were the diagnosis of pneumonia, verified on the basis of laboratory and instrumental research methods, the detection of the SARS-CoV-2 genome in swabs from the nasopharynx and oropharynx by the polymerase chain reaction method and/or the detection of the SARS-CoV-2 IgM antibodies and the level of COVID-19 infection suspicion according to the CO-RADS scale, which corresponds to 5 points; heavy epidemiological anamnesis.

Patients without a confirmed pneumonia diagnosis, suspected of being infected with COVID-19 according to the CO-RADS scale of 1–4 points, persons with other pneumonia etiological variants (bacterial, hypostatic), pulmonary tuberculosis accompanied by severe diabetes, patients with immunosuppressive conditions, severe chronic patients with respiratory system pathology, end-stage renal failure, recently experienced acute coronary syndrome, aortocoronary bypass, heart failure, liver cirrhosis, as well as patients with sepsis were not taken into account.

Patients were randomized into two groups — group I (25 people) and group II (90 people). The groups were comparable in terms of age and sex. In group I patients, we explored the sST2 level determined by the immunoenzymatic method, and in 90 patients of group II, we analyzed the NT-proBNP indicator determined by the immunofluorescence method in the biochemical laboratory of the Lviv Clinical Hospital of Emergency Medical Care. The following parameters were assessed: patients' age, sex, treatment results (discharge/death) and length of the treatment course. We studied complaints, medical history, results of physical examination, additional laboratory, and instrumental methods of examination during hospitalization.

The risk of final event development was calculated for both groups. The clinical endpoint was defined as cardiovascular death or death from all causes, hospitalization in the emergency department, and/or long-term hospitalization (over 30 days). The clinical endpoint was assessed in patients who achieved NT-proBNP cut-off values of > 450 pg/ml in patients under 50 years of age, > 900 pg/ml in patients 50 to 75 years of age, and > 1800 pg/ml in patients over 75 years of age and sST2 value over 35 ng/ml at the time of hospitalization.

The study was conducted after the approval of the Ethical Commission for Experimental Development and Research at Danylo Halytsky Lviv National Medical University (No. 10 dated 16.12.2019). All patients signed an informed consent to participate in the study. The study complies with the principles of the Declaration of Helsinki.

Statistical analysis. Categorical variables are presented as frequencies and percentages and while continuous variables as mean ± standard deviation (SD) or median and interquartile range (IQR), respectively. We compared means for continuous variables using independent group t-tests when data were distributed normally; otherwise, the Mann-Whitney test was performed. The distribution normality was assessed using the Shapiro-Wilk test. Categorical variables' proportions were compared using the chi-square test or Fisher's exact test, as appropriate. All data were analyzed using Statistica 6.0. A two-tailed P value of < 0.05 was considered an indicator of differences of statistical significance in all analyses.

Table 1. Baseline characteristics and concomitant diseases in patients with COVID-19

Parameters	sST2 group	n = 25	NT-proBNP group	n = 90	P
Age, years	69.20 ± 13.37	25	67.52 ± 8.80	90	0.4566
Male, %	40	10	53.3	48	0.2393
Body mass index, kg/m^2	30.09 ± 5.40	25	29.90 ± 7.63	90	0.9075
Hypertension, %	84	21	90	81	0.3745
Diabetes, %	28	7	38.9	35	0.3167
Sepsis, %	0	0	0	0	0
Creatinine, μmol/L	122.00 ± 40.52	17	121.16 ± 50.83	88	0.9489
C-reactive protein, mg/L	56.33 ± 40.51	7	69.67 ± 51.34	66	0.5086

Results

In total, 115 patients with coronavirus disease participated in the study. The participants' average age was 69.20 ± 13.37 years and 67.52 ± 8.80 years in group I and II, respectively. With the same prevalence in patients hospitalized for COVID-19 pneumonia, concomitant diseases were noted — hypertension (p = 0.3745) and diabetes (p = 0.3167) (Table 1).

There were no differences in key indicators that can affect the interpretation of cardiac biomarkers, such as renal dysfunction, sepsis, BMI in patients of both groups (p > 0.05).

The sST2 values distribution in the patients' blood plasma is presented in Fig. 1, 2.

The NT-proBNP values distribution in the patients' blood plasma is presented in Fig. 3, 4.

The sST2 cut-off levels recommended for the HF diagnosis in our study amounted to 28 % of patients (n = 7), while the NT-proBNP level, which meets the criteria for the HF diagnosis, was constant only in 11.1 % (n = 10; p = 0.0461).

In both groups of patients who reached the diagnostic threshold values for the HF diagnosis, the risk of developing clinical endpoints was revealed: OR = 10.67; 95% CI: 1.31–86.9; p = 0.0270 and OR = 7.0; 95% CI: 1.72–28.6; p = 0.0067 in group I and II, respectively.

The correlation analysis showed the correlation between the creatinine and NT-proBNP indicators (r = 0.6031; p = 0.000), but not for sST2.

Discussion

Our study established the prognostic value of assessment of cardiac NT-proBNP and sST2 biomarkers in the development of adverse events in hospitalized patients with coronavirus pneumonia. Natriuretic peptides are known as useful biomarkers for diagnosis, severity assessment, and prognostic assessment of HF end-point events. However, the NT-proBNP level is affected by many additional factors, such as age, renal failure, obesity, which often lead to false results and incorrect clinical interpretation. When dividing patients into groups, we made sure that the patients were comparable in terms of age, sex, and comorbidities to avoid the unwanted influence of these additional factors on the study of the interpretation of the results. No differences were detected in key indicators, such as renal dysfunction, sepsis, and BMI in patients of both groups. At the same time, ac-

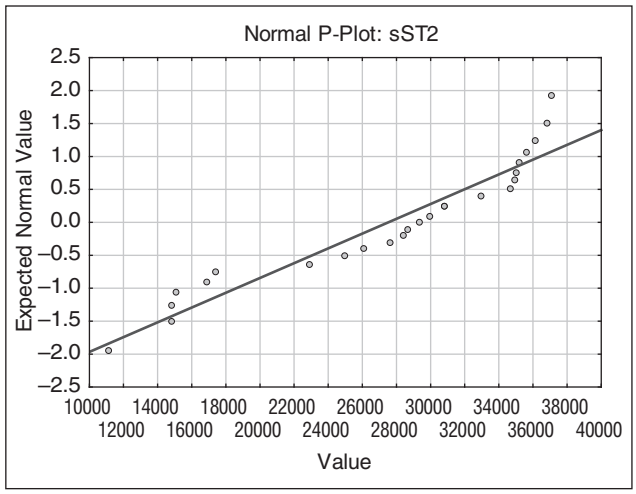

Figure 1. Distribution of sST2 values in blood plasma of patients with COVID-19 (P-Plot)

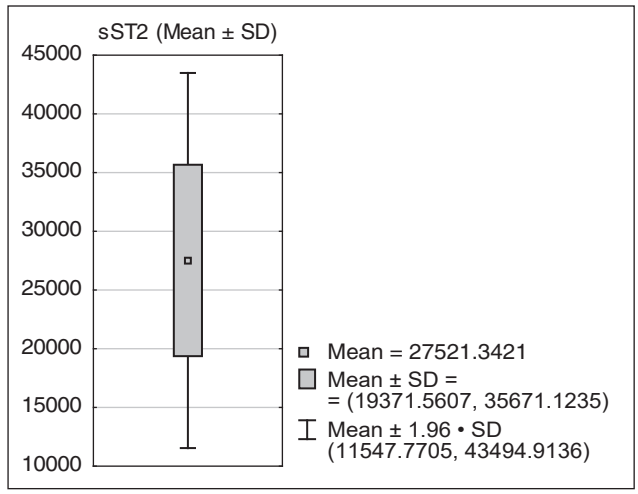

Figure 2. Distribution of sST2 values in blood plasma of patients with COVID-19 (Mean ± SD)

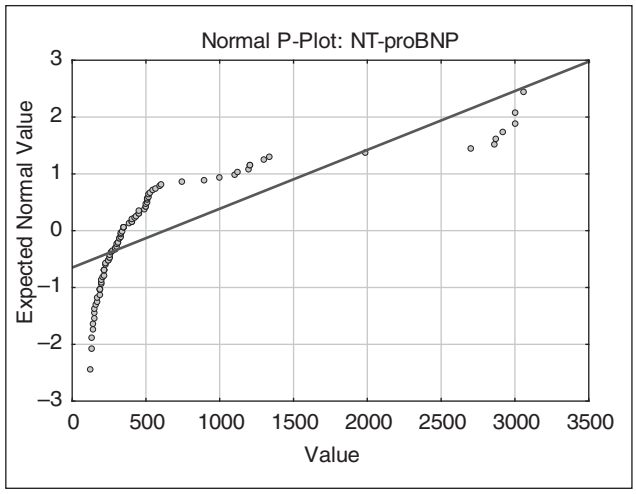

Figure 3. Distribution of NT-proBNP values in blood plasma of patients with COVID-19 (P-Plot)

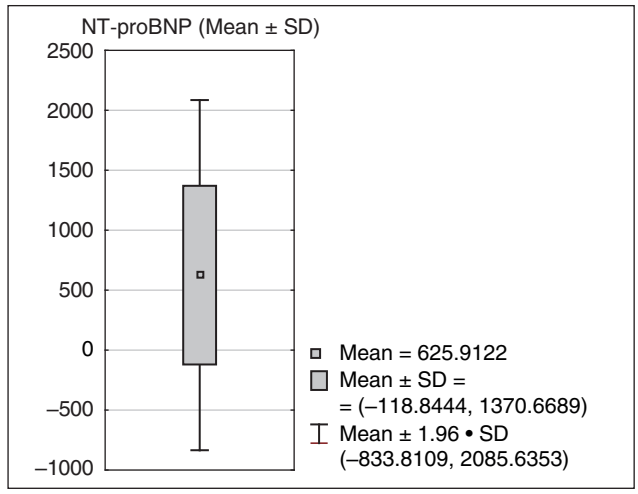

Figure 4. Distribution of NT-proBNP values in blood plasma of patients with COVID-19 (Mean ± SD)

Table 2. Clinical outcomes (death, ICU hospitalization, hospitalization for over 30 days) in patients with COVID-19 depending on the level of sST2 and NT-proBNP

Parameters	sST2 group		NT-proBNP group	
	n = 7	n = 18	n = 10	n = 80
Endpoint, % (n)	4	2	5	10
Death	2	1	2	3
ICU hospitalization	1	1	2	5
Hospitalization for over 30 days	1	0	1	4

cording to our observations, the limit values of sST2 recommended for the HF diagnosis in our study reached significantly more patients — 28 %, while the NT-proBNP level, which meets the criteria for the HF diagnosis, was constant only in 11.1 % of patients (p = 0.0461). Yet, the risk of the final event development is equally high in both groups of patients. Correlation analysis showed a relationship between NT-proBNP and creatinine values (r = 0.6031; p = 0.000) but not for sST2. We believe that the NT-proBNP dependence on additional factors may have influenced the results interpretation and the adverse prognosis assessment; it is also possible that the established concentration threshold for both biomarkers played its role.

The IL-33/ST2 axis probably plays a certain role in the systemic COVID-19 manifestations [9, 10]. Previous studies have shown that the IL-33/ST2 axis is involved in inflammatory responses in several viral infections: flu, herpes simplex viruses, coxsackie B, lymphocytic choriomeningitis, and metapneumovirus [11]. Accumulated scientific evidence supports the argument that sST2 levels increase early in SARS-CoV-2 infection and that such changes are an independent risk factor for worse outcomes. They outperform other biomarkers that have been used to guide treatment so far [9]. In a Zhikun Zeng's study, for example, in eighty COVID-19 patients who were hospitalized at Sun Yat-sen University, Guangzhou, China, sST2 levels were persistently high during disease progression in the serum of severe cases and patients who subsequently died [10]. We assume that the sST2 release may occur through additional mechanisms mediated by the SARS-CoV-2, unrelated to the HF development mechanisms.

For example, a rare but severe pediatric COVID-19 presentation has been described as one closely resembling Kawasaki disease. sST2 has been shown to be elevated in Kawasaki disease patients, which, in addition, correlated with a worse clinical course [12]. Pascual-Figal et al. demonstrated the pulmonary origin of sST2 in acute decompensated HF, revealing a correlation between their concentration and alveolar wall thickness. It requires further investigation to determine whether elevated sST2 levels in COVID-19 are associated with comorbid cardiac disease in these patients, and so do the possible cardiovascular implications of potentially persistent elevated sST2 levels in convalescents [13]. Given the well-established association of sST2 levels with other pulmonary and cardiovascular diseases, it is imperative to explore whether such sST2 levels reflect a certain inflammation memory with a long-term effect.

The identification of sST2 as an early predictor of the worst prognosis in COVID-19 patients has important clinical implications. sST2 is a readily available biomarker that can be continuously determined in blood samples. Pharmacological modulators for this axis are available and are currently being tested for other pathologies that could be evaluated for the treatment or prevention of severe COVID-19 cases.

Our research has several limitations. The study was conducted in a single center and on a small sample, prompted by the urgent need to deepen our knowledge of the disease. Nevertheless, the clinical characteristics in our cohort were consistent with the published data of other studies carried out both around the world and in Ukraine [9, 10, 13].

Conclusions

Patients' stratification based on sST2 values, along with the NT-proBNP parameters assessment, may provide additional prognostic value in COVID-19 patients. Among patients suffering from COVID-19 infection, sST2 measurement after hospitalization may be a useful biomarker for the early identification of those at higher risk of severe complications or death and for the implementation of more aggressive therapy at the initial stage of the disease.

References

1. Bashir H, Yildiz M, Cafardi J, et al. A Review of Heart Failure in Patients with COVID-19. Heart Fail Clin. 2023 Apr;19(2S):e1-e8. doi: 10.1016/j.hfc.2023.03.002.

2. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart. 2006 Jun;92(6):843-9. doi: 10.1136/hrt.2005.071233.

3. Maalouf R, Bailey S. A review on B-type natriuretic peptide monitoring: assays and biosensors. Heart Fail Rev. 2016 Sep;21(5):567-78. doi: 10.1007/s10741-016-9544-9.

4. Cao Z, Jia Y, Zhu B. BNP and NT-proBNP as Diagnostic Biomarkers for Cardiac Dysfunction in Both Clinical and Forensic Medicine. Int J Mol Sci. 2019 Apr 12;20(8):1820. doi: 10.3390/ijms20081820.

5. Plichart M, Orvoën G, Jourdain P, et al. Brain natriuretic peptide usefulness in very elderly dyspnoeic patients: the BED study. Eur J Heart Fail. 2017 Apr;19(4):540-548. doi: 10.1002/ejhf.699.

6. Pan Y, Li D, Ma J, Shan L, Wei M. NT-proBNP test with improved accuracy for the diagnosis of chronic heart failure. Medicine (Baltimore). 2017 Dec;96(51):e9181. doi: 10.1097/MD.0000000000009181.

7. Mueller C, McDonald K, de Boer RA, et al; Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019 Jun;21(6):715-731. doi: 10.1002/ejhf.1494.

8. Biaggi P, Ammann C, Imperiali M, et al. ST2 – a new biomarker in heart failure. Cardiovasc Med. 2019;22:w02008. doi: 10.4414/cvm.2019.02008.

9. Sánchez-Marteles M, Rubio-Gracia J, Peña-Fresneda N, et al. Early Measurement of Blood sST2 Is a Good Predictor of Death and Poor Outcomes in Patients Admitted for COVID-19 Infection. J Clin Med. 2021 Aug 11;10(16):3534. doi: 10.3390/jcm10163534.

10. Zeng Z, Hong XY, Li Y, Chen W, Ye G, Li Y, Luo Y. Serum-soluble ST2 as a novel biomarker reflecting inflammatory status

and illness severity in patients with COVID-19. Biomark Med. 2020 Dec;14(17):1619-1629. doi: 10.2217/bmm-2020-0410.

11. Murdaca G, Paladin F, Tonacci A, et al. Involvement of Il-33 in the Pathogenesis and Prognosis of Major Respiratory Viral Infections: Future Perspectives for Personalized Therapy. Biomedicines. 2022 Mar 19;10(3):715. doi: 10.3390/biomedicines10030715.

12. Sato YZ, Molkara DP, Daniels LB, et al. Cardiovascular biomarkers in acute Kawasaki disease. Int J Cardiol. 2013 Mar 20;164(1):58-63. doi: 10.1016/j.ijcard.2011.06.065.

13. Pascual-Figal DA, Pérez-Martínez MT, Asensio-Lopez MC, et al. Pulmonary Production of Soluble ST2 in Heart Failure. Circ Heart Fail. 2018 Dec;11(12):e005488. doi: 10.1161/CIRCHEARTFAILURE.118.005488.

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Роль sST2 та NT-proBNP у прогнозуванні перебігу COVID-19

Резюме. ***Актуальність.*** Результати останніх досліджень показують, що пацієнти, госпіталізовані з COVID-19, можуть мати підвищений ризик розвитку серцевої недостатності (СН), навіть за відсутності в анамнезі серцево-судинних захворювань або факторів їх ризику. ***Мета:*** порівняти прогностичну цінність біомаркерів серцевої недостатності NT-proBNP та sST2 при COVID-19. ***Матеріали та методи.*** Обстежено 115 пацієнтів із COVID-19, які були госпіталізовані у Львівську клінічну лікарню швидкої медичної допомоги. Їм визначали показники sST2 та NT-proBNP в сироватці крові методом імуноферментного аналізу. Кінцеву клінічну точку оцінювали впродовж періоду госпіталізації (серцево-судинна смерть або смерть від усіх причин, госпіталізація у відділення реанімації та інтенсивної терапії та/або тривала госпіталізація). Ризик розвитку кінцевої події розраховували для групи пацієнтів, які досягли граничних концентрацій sST2 відповідно до критеріїв діагностики СН ACC/AHA, та окремо на основі діагностичних значень NT-proBNP. ***Результати.*** Граничні рівні sST2 у нашому дослідженні відзначено в 7 (28 %) пацієнтів, у той час як лише в 10 (11,1 %) випадках (p = 0,0461) уміст NT-proBNP відповідав критеріям діагностики СН. В обох групах пацієнтів, які досягли порогових для діагностики СН значень, виявлено ризик розвитку кінцевих клінічних точок: OR = 10,67; 95% ДІ: 1,31–86,9; p = 0,0270 та OR = 7,0; 95% ДІ: 1,72–28,6; p = 0,0067 відповідно в першій та другій групах. За допомогою кореляційного аналізу виявлено зв'язок між показниками креатиніну та NT-proBNP (r = 0,6031; p = 0,000), але не sST2. ***Висновки.*** Стратифікація пацієнтів на основі значень sST2 разом із оцінкою параметрів NT-proBNP може забезпечити додаткову прогностичну цінність порівняно з умістом NT-proBNP у хворих на COVID-19 та СН.

Ключові слова: sST2; NT-proBNP; коронавірусна хвороба; серцева недостатність