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Prognostic role of ST2 biomarker in the development of adverse cardiovascular events in patients with new-onset coronavirus infection

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The aim of the study is to determine the prognostic significance of established and novel cardiovascular biomarkers (growth stimulation expressed gene 2 (ST2)) for assessing the risk of adverse cardiovascular events (ACVE) in patients with novel coronavirus infection (COVID-19) during long-term follow-up.

Methods. A non-randomized, prospective comparative study included 112 patients hospitalized with a confirmed diagnosis of COVID-19. In addition to standard laboratory tests, the levels of cardiovascular biomarkers (lactate dehydrogenase (LDH), high-sensitivity troponin I (hsTrI), high-sensitivity troponin T (hsTrT), creatine phosphokinase (CPK), creatine phosphokinase MB fraction (CPK-MB), ST2) were determined on the day of hospital admission. Patients were followed for 366 [365; 380] days.

Results. During the follow-up period, 14 (12.5%) patients developed ACVE, including 4 (3.6%) deaths from cardiovascular causes. The group of patients with developed ACVE had higher admission BMI, IL-6, D-dimer, LDH, CPK, CPK-MB and ST2 concentrations ($p<0.05$ for all parameters). Predictors of the development of ACVE were arterial hypertension (AH) (odds ratio (OR) 2.73, 95% confidence interval (CI) 1.20–6.22, χ^2 =5.3, p=0.021), obesity (OR 2.13, 95% CI 1.15–3.96; χ^2 =5.6, p=0.018), ST2 level > 36 ng/mL (OR 1.23, 95% CI 1.11–1.37; AUC 0.949, sensitivity 92.9%, specificity 33%, p=0.000).

Conclusion. The ST2 level of >36 ng/mL on the day of hospitalization as well as the presence of AH and obesity increased the likelihood of developing ACVE within 1 year of discharge in patients who had a coronavirus infection.

Keywords: ST2, cardiovascular diseases, adverse cardiovascular events, COVID-19.

Conflict of interests: none declared.

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Introduction

Approximately 24 million confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) were recorded during the pandemic of a new coronavirus infection (COVID-19) in the Russian Federation. According to the number of deaths from COVID-19, Russia ranks 4th in the world with 400 thousand deaths, and the mortality rate from COVID-19 per 100 thousand population was 276 [1].

About 80 % of infected patients have no significant symptoms of COVID-19, or the severity of the clinical picture of the disease varies from mild to moderate [2]. The severe course of COVID-19 is characterized by a "cytokine storm", acute respiratory distress syndrome, systemic inflammatory response (SIRS) and the development of multiple organ failure. In patients with severe COVID-19, pre-existing cardiovascular disease (CVD), arterial hypertension (AH) and heart failure increase the risk of poor clinical prognosis and in-hospital mortality [3]. A number of patients without a history of CVD were found to have acute myocardial injury and dysfunction during hospitalization for COVID-19, as determined by elevated high-sensitivity cardiac troponins (hsTr) above the 99th percentile [4, 5]. Considering that COVID-19 in combination with SIRS may have unfavorable effects on the cardiovascular system, biomarkers of cardiac damage such as B-type natriuretic peptide (BNP), hsTr, lactate dehydrogenase (LDH), D-dimer, along with proinflammatory markers (interleukin 6 (IL-6), C-reactive protein (CRP), ferritin) were included in the COVID-19 in-hospital mortality prediction models [3, 5].

Cardiovascular symptoms as part of COVID-19 manifestation [3, 7], destabilization of known or registration of newly detected CVD in the acute phase of the disease [3, 5, 6] are described in the works of a number of authors, however, more recent studies emphasize the importance of long-term follow-up of patients due to the possibility of development of delayed adverse cardiovascular events (ACVE) [7]. In their study, Zagidullin N. et al. found a correlation between the incidence of ACVE during long-term follow-up and the levels of traditional (high-sensitivity troponin I (hsTrI)) and promising (growth stimulation expressed gene 2 (ST2)) biomarkers at admission [7].

ST2 is a receptor protein expressed by immune cells, cardiomyocytes, fibroblasts and endotheliocytes that can exist in two isoforms, soluble (ST2) and transmembrane (ST2L). In myocardial alterations on the background of SIRS, there is a hyperproduction of interleukins, including interleukin-33 (IL-33), which binds to ST2L, realizing the cardioprotective effect of IL-33 [8]. In turn, IL-33 acts as a ligand for ST2. Myocardial stress leads to an increase in ST2 concentration, which interacts with IL-33 and blocks its antiproliferative and antiapoptotic effects [8, 9]. In the study by Pascual-Figal D.A. et al, it was shown that in patients with known heart failure, ST2 was actively produced in alveocytes and increased in cardiogenic pulmonary edema and bronchopneumonia [9]. Zeng Z. et al. found a correlation between the serum concentration of ST2 and the activity of the inflammatory response in COVID-19 [10].

Considering the possible ST2 production in lung tissue [9], activation of ST2 production by immune cells in SIRS [8] and myocardial stress [8, 9], association with inflammation in COVID-19 [10], a more detailed study of the role of plasma ST2 levels in myocardial damage in COVID-19 patients is relevant.

The aim of this study was to determine the prognostic significance of common (LDH, hsTrI, high-sensitivity troponin T (hsTrT), creatine phosphokinase (CPK), creatine phosphokinase MB fraction (CPK-MB)) and novel (ST2) cardiovascular biomarkers for assessing the risk of ACVE in COVID-19 patients during long-term follow-up.

Methods

A non-randomized, prospective comparative study included 112 patients hospitalized with a confirmed diagnosis of COVID-19. A total of 188 patients were consecutively enrolled in the initial screening. Subsequently, 76 patients withdrew from the non-randomized prospective comparative study for various reasons.

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Inclusion criteria for patients were: need for hospitalization due to COVID; positive PCR test for detection of SARS-CoV-2 RNA on admission; lung lesions of 1–4 degrees; voluntary consent of the patient to participate in the study; age 40–70 years. Exclusion criteria were: existing CVD; acute and chronic bronchial and pulmonary diseases of other etiologies; cancer; type 1 and type 2 diabetes mellitus (DM).

On the day of admission to the remodeled COVID-19 hospital, all patients underwent chest computed tomography (CT) and venous blood samples were taken for complete blood count (CBC) and biochemical blood analysis (total protein, albumin, creatinine, AST, ALT, total cholesterol, procalcitonin, LDH, CPK, CPK-MB, hsTrT, hsTrI, D-dimer, CRP, ferritin, IL-6, ST2). ST2 levels were determined using a commercially available Presage® ST2 assay kit (enzyme immunoassay kit for quantitative determination of ST2, "Biokhimmak", Russia), which is designed to quantify ST2 by enzyme-linked immunosorbent assay in 96-well microplates with monoclonal antibody coated on the bottom of the wells. Diluted plasma or serum samples were added to the appropriate wells of the microplate and incubated for the indicated time. The concentration of ST2 was detected by adding a colorimetric reagent. The threshold value of ST2 was set at 35 ng/ml [11].

Patients with COVID-19 at the hospitalization stage received drug therapy as recommended in the current "Temporary guidelines for the prevention, diagnosis, and treatment of novel coronavirus infection" [12].

The sample of 112 patients was followed up for 12 months from the moment of discharge from the hospital, while the cases of developed ACVE (myocardial infarction, pulmonary embolism, acute cerebral circulatory failure, death from cardiovascular causes) were being registered.

Statistical analysis

STATISTICA 8.0 and MedCalc 8.2.0.3 programs were used for statistical processing of the obtained results. The distribution of parameters was checked for conformity to the normality using the Shapiro-Wilk and Kolmogorov-Smirnov tests. The median, upper and lower quartiles (Me [Q1; Q3]) were indicated to represent signs with non-normal distribution. Differences between groups were analyzed by non-parametric methods using the Mann-Whitney U-test. Differences between categorical variables were analyzed using the χ^2-Pearson test. Correlations between ST2 level and clinical and laboratory parameters were established by calculation of Kendall correlation coefficient (r). Logistic regression analysis with calculation of the natural logarithm of the odds ratio (OR) with 95 % confidence interval (CI) was performed to assess the independent influence of the studied predictors on the occurrence of ACVE. ROC-curve (receiver operating characteristic) was plotted and area under the ROC-curve (AUC, Area under the ROC Curve) was calculated. In the process of ROC-analysis the cut-off point was determined with calculation of sensitivity and specificity of prognostic biomarker levels. Differences at $p<0.05$ were considered statistically significant.

The study protocol was approved by the local ethics committee of the Saratov State Medical University. Before inclusion in the study, all patients signed a voluntary informed consent for further participation.

Results

The clinical characteristics of the patients at the time of hospitalization are shown in Table 1. The majority of patients were women (57.1 %). Smoking was found in less than a quarter of patients (21.4 %), and the most common comorbidities were excess body weight (26.8 %) and dyslipidemia (45.5 %).

Table 2 shows the baseline laboratory values and Table 3 — the cardiovascular markers of the COVID-19 patients at hospital admission. Leukopenia (white blood cell count less than 4×10^9/L) was observed in 16 patients (14.3 %), leukocytosis (white blood cell count greater than 9×10^9/L) in 24 patients (21.4 %), thrombocytopenia (platelet count less than 150×10^9/L) in 22 patients (19.6 %), serum CRP greater than 10 mg/L in 103 patients (91.9 %), and IL-6 greater than 7 pg/mL in 50 patients (44.6 %).

Among cardiovascular parameters, only ST2 (in 51 (45.5 %) hospitalized patients) showed an increase above the threshold values. At the same time, no increase in hsTrT, hsTrI, CPK, CPK-MB, LDH levels was observed in any of the patients studied.

Correlation analysis revealed a direct moderate relationship between ST2 concentration and transition to non-invasive lung ventilation during hospitalization ($r=0.40$, $p<0.05$) and after discharge due to ACVE ($r=0.42$, $p<0.05$). In correlation analysis, weak direct correlations were found between ST2 and

Table 1. **Clinical characteristics of patients at the time of hospitalization**

Parameter	Patients (n=112)
Age, years	58.0 [48.5; 63.5]
Males n (%)	48 (42.9)
Females, n (%)	64 (57.1)
Body mass index, kg/m^2	25.3 [23.3; 29.4]
Hospitalization duration, days	10.0 [8.0; 14.0]
Duration of the disease at the time of hospitalization, days	7.0 [5.5; 10.0]
SpO_2, %	96.0 [94.0; 97.0]
HR, per minute	85.0 [75.0; 95.0]
Systolic BP, mmHg	125 [115.0; 130.0]
Diastolic BP, mmHg	76 [70.0; 83.0]
RR, per minute	17 [16.0; 20.0]
Severity of COVID-19 course: Moderately severe, n (%) Severe, n (%)	 77 (68.8) 35 (31.2)
CT stage at the time of hospitalization: 1, n (%) 2, n (%) 3, n (%) 4, n (%)	 63 (56.3) 31 (27.7) 16 (14.3) 2 (1.8)
Smoking, n (%)	24 (21.4)
AH at the time of hospitalization: 1 grade, n (%) 2 grade, n (%)	 13 (11.6) 6 (5.4)
Dyslipidemia, n (%)	51 (45.5)
Excess body weight, n (%)	30 (26.8)
Alimentary obesity: 1 grade, n (%) 2 grade, n (%)	 7 (6.3) 4 (3.6)

Note. CT stage at the time of hospitalization was established on the basis of the current "Temporary guidelines for prevention, diagnosis and treatment of novev coronavirus infection".

Table 2. **Laboratory parameters of patients at the time of hospitalization (Me [Q25; Q75])**

Parameter	Patients (n=112)
Leukocytes, ×10^9/l	6.7 [4.6; 9.0]
Lymphocytes, %	18 [12.0; 29.0]
Monocytes, %	5 [3; 8]
Thrombocytes, ×10^9/l	198 [150; 264]
Hemoglobin, g/l	138 [128; 151]
Erythrocytes, ×10^{12}/l	4.6 [4.3; 5.1]
Sed rate, mm/h	27 [19; 36]
CRP, mg/l	41 [17; 98]
Ferritin, ng/mL	285 [150; 601]
IL-6, pg/mL	4.1 [0.6; 28.6]
Total cholesterol, mmol/L	4.2 [3.5; 5.0]
Non-HDL-C, mmol/L	3.5 [2.7; 4.1]
Glucose, mmol/L	6.0 [5.4; 7.0]
ALT, units/l	35 [26; 60]
ACT, units/l	37 [28; 53]
D-dimer, μg/mL	0.6 [0.4; 1.0]
GFR, ml/min/m^2	84 [68; 94]

Table 3. **Concentrations of cardiovascular biomarkers in patients hospitalized with COVID-19 (Me [Q25; Q75])**

Biomarker	Patients (n=112)
LDH, units/l	175 [170; 190]
CPK, units/l	61 [57; 69]
CPK-MB, units/l	12 [9; 15]
hsTrT, ng/mL	3.5 [2; 5]
hsTrI, ng/mL	6 [4; 8.5]
ST2, ng/mL	34 [29.4; 42]

Table 4. **Structure of adverse cardiovascular events at 1-year follow-up of patients**

Study endpoints	Patients, n (%)
Adverse cardiovascular events	
MI	9 (8.0)
Stroke	3 (2.7)
PE	2 (1.8)
Deaths due to cardiovascular causes	
MI	3 (2.7)
PE	1 (0.9)

hsTrT (r=0.17, p<0.05) and LDH (r=0.14, p<0.05) levels. No correlations were found between ST2 concentration and the value of other cardiovascular (hsTrI (r=0.05, p>0.05), CPK (r=0.12, p>0.05), CPK-MB (r=0.10, p>0.05)) and inflammatory parameters (CRP (r=0.05, p>0.05), ferritin (r=0.08, p>0.05), IL-6 (r=0.05, p>0.05)).

The incidence of ACVE during the prospective follow-up is summarized in Table 4. ACVE were recorded in 14 (12.5 %) patients, including 4 (3.6 %) deaths from cardiovascular causes.

We compared the clinical and laboratory data in patients who did not reach the endpoints during the long-term follow-up (group 1) and those, who reached them (group 2) (Table 5). Table 5 shows that the patient groups did not differ in sex, age, severity of COVID-19 course, CRP, ferritin, and hsTrI levels. Significant differences were found in BMI, IL-6, D-dimer, LDH, CPK, CPK-MB, and ST2 concentrations at admission (p<0.05 for all parameters).

Using these variables as predictors of ACVE onset, we performed logistic regression analysis with OR calculation for each of the variables. Despite significant differences between the patient groups in several clinical and laboratory parameters, comorbidities were the predictors of ACVE onset: AH (OR 2.73, 95 % CI, 1.20–6.22; χ^2 =5.3, p=0.021), obesity (OR 2.13, 95 %, CI 1.15–3.96; χ^2 =5.6, p=0.018); ST2 levels (OR 1.23, 95 %, CI 1.11–1.37, p=0.000).

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Table 5. **Clinical and laboratory parameters in patients with COVID-19 depending on the development of endpoints at 1-year follow-up**

Parameter	Group 1, n=98	Group 2, n=14	p
Gender Males, n (%) Females, n (%)	 42 (42.9) 56 (57.1)	 6 (42.9) 8 (57.1)	0.563
Age, years	58 [49; 64]	57 [46; 63]	0.933
BMI, kg/m^2	24.9 [22.9; 29.0]	28.8 [25.0; 36.3]	0.018
COVID-19 course: Moderately severe, n (%) Severe, n (%)	 70 (71.4) 28 (28.6)	 7 (50) 7 (50)	0.105
CRP, mg/l	39.2 [17; 99]	72 [51; 128]	0.078
Ferritin, ng/mL	288 [156; 601]	448 [250; 898]	0.130
Total cholesterol, mmol/L	4.1 [3.5; 4.8]	5.2 [4.2; 5.8]	0.014
Non-HDL-C, mmol/L	3.3 [2.7; 4.0]	4.2 [3.5; 5.0]	0.012
D-dimer, μg/mL	0.56 [0.38; 0.92]	1.2 [0.8; 1.9]	0.001
hsTrT, ng/mL	3 [2; 5]	6 [4; 6]	0.003
hsTrI, ng/mL	6 [4; 8]	7 [5; 12]	0.150
IL-6, pg/mL	2.9 [0.6; 29.1]	15.9 [7.8; 58.5]	0.017
LDH, Units/l	175 [170; 180]	210 [195; 210]	0.000
CPK, Units/l	60 [57; 66]	71 [68; 83]	0.000
CPK-MB, Units/l	11 [9; 14]	23 [15; 33]	0.000
ST2, ng/mL	33.3 [28.5; 38]	64 [55; 84.3]	0.000

Note. The p values were obtained from the results of the non-parametric Mann-Whitney test

Based on the results of the ROC analysis, an optimal ST2 concentration of > 36 ng/mL was calculated (AUC =0.949, sensitivity 92.9%, specificity 33%, p=0.000) (Figure 1).

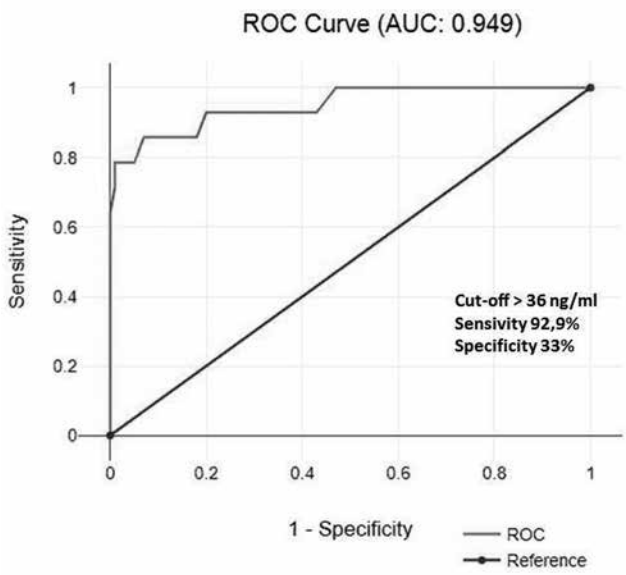

Fig. 1. Sensitivity and specificity of serum ST2 concentration in risk stratification of ACVE development in COVID-19 patients (ROC analysis)

Discussion

During the COVID-19 pandemic, the interpretation of laboratory parameters and the development of prognostic models of adverse outcomes were actively used to identify patients at high risk for adverse clinical outcomes along with chest CT [3, 5]. The most common markers of inflammation (CRP, IL-6, ferritin) and cellular damage (LDH, hsTr) have been included in these prognostic models [2, 5, 13]. These studies investigated the prognosis of various outcomes during hospitalization, and delayed outcomes were not given enough attention.

By reviewing the published works on the evaluation of ACVE development during long-term (1–2 years) follow-up of COVID-19 patients, we selected a list of cardiovascular biomarkers (LDH, hsTrI, hsTrT, CPK, CPK-MB, ST2) that were associated with the onset of ACVE [6, 7, 10]. The performed correlation analysis did not reveal significant relationships between ST2 level and the level of other laboratory parameters (including cardiovascular), which indicates the independence and standalone position of the new cardiovascular biomarker ST2. In other published works, the authors did not determine the correlation strength between ST2 level and clinical/laboratory characteristics of hospitalized patients with COVID-19.

In our study, the incidence of ACVE within 12 months was 12.5%, which is not significantly different from the incidence of ACVE in Zagidullin N. et al. (2023), which was 8.4% [7]. Reliable predictors of ACVE in this study were: hsTrI (HR 1.354, 95% CI 1.073–1.710, p=0.011) and ST2 (HR 1.002, 95% CI 1.000–1.004, p=0.017). The incidence of fatal outcomes (3.6% and 4.1%, respectively) was comparable to that observed by Motloch LJ. et al. (2023) [14]. In this large study, the predictor of mortality in the first year after discharge was the ST2 marker (HR 1.006, 95% CI 1.002–1.009, p<0.001) [14].

In our study, no significant effect of hsTrI concentration on the prognosis of patients after discharge was found, which is consistent with the data of Motloch LJ. et al. (2023) [14], but the results obtained differ from the findings of Fiedler L. et al. (2023) [7], who also analyzed the hsTrI level on the day of hospitalization. The lack of prognostic value of hsTrI may be explained by the time of blood collection from the patients (in our study and in the experiment of Motloch LJ. et al. (2002) [14], blood tests were performed on the first day of admission), and it should take at least 1–2 weeks before the myocardium is damaged by the SARS-CoV2 virus and the hsTrI level

rises [5]. The discrepancy in the results may also be due to the fact that the patients in our study had no history of CVD, and in the work of Zagidullin N. et al. (2023), 4.4 % of patients had coronary heart disease and 2.0 % had chronic heart failure.

With regard to the long-term prognosis of ACVE and mortality, the assessment of ST2 concentration has the greatest value [7, 14], which was determined in our work. We obtained significant differences between patient groups in a number of laboratory parameters (IL-6, D-dimer, LDH, CPK, CPK-MB and ST2 ($p<0.05$ for all parameters)), but only ST2 level increased the chance of ACVE (OR 1.23 [95 % CI 1.11–1.37]; AUC 0.949, sensitivity 92.9 %, specificity 33 %, $p=0.000$). The cut-off point for ST2>36 ng/mL was also determined, which is close to the cut-off points for ST2 obtained by Zhang Q. et al. (2021) [15]. The authors found that ST2 levels ⩾34.2 ng/mL (AUC 0.662, sensitivity 66.7 %, specificity 65.2 %, $p<0.001$) increased the risk of ACVE in patients with acute coronary syndrome without ST-segment elevation (HR = 10.22, 95 % CI 4.05–25.7, $p<0.001$) [15].

Conclusion

Measuring the concentrations of not only traditional but also novel biomarkers may help to stratify the development of long-term adverse events in patients with COVID-19. The study found that elevated ST2 levels in combination with traditional cardiovascular risk factors (AH, obesity) were statistically significantly associated with the development of adverse clinical outcomes in a cohort of COVID-19 patients. The likelihood of ACVE in COVID-19 patients within 1 year of hospital discharge is higher in patients with ST2 levels >36 ng/mL on the day of hospitalization. Therefore, the detection of ST2 >36 ng/mL elevation may help to predict the long-term adverse outcomes in COVID-19 patients.

Study limitations. Our study had several limitations. The study was conducted in a small sample of patients from a single institution. There was no study of cardiovascular biomarker levels in the dynamic, which could expand the list of predictive laboratory parameters.

Conflict of interests: none declared.

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