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Original article

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Pentraxin 3: possibilities and prospects for using a biomarker in patients with COVID-19

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Abstract:
Objective: to determine the potential predictive value of serum biomarkers for adverse cardiovascular events in post-COVID-19 patients.
Materials and Methods. The prospective study included 114 patients hospitalized with confirmed COVID-19. In addition to standard examinations, blood samples were collected on the day of admission to determine levels of serum cardiovascular biomarkers, including pentraxin 3 (PTX3). Patients were monitored for 366 [365; 380] days after discharge from the COVID-19 hospital with registration of all major adverse cardiovascular events (MACE) that developed.
Results. During follow-up, we observed MACE in 19 patients (16.7%), including 2 deaths (1.8%) from cardiovascular causes. The incidence of MACE was higher in patients with higher concentrations of PTX3 (OR 1.28, 95% CI 1.13-1.45; p<0.001), interleukin 6 (OR 1.01, 95 % CI 1.0-1.02; p=0.048), D-dimer (OR 2.05, 95% CI 1.16-3.6; p=0.019), lactate dehydrogenase (OR 1.08, 95% CI 1.03-1.13; p<0.001), and MB fraction of creatine kinase (OR 1.19, 95% CI 1.02-1.39; p=0.001). PTX3>3.1 ng/mL predicted the development of MACE with a sensitivity of 94.0% and specificity of 82.1% (AUC 0.885; p<0.001).
Conclusion. Serum biomarkers, in particular PTX3, can be used to predict the development of MACE in the long-term follow-up of post-COVID-19 patients.

Keywords: pentraxin 3 (PTX3), cardiovascular diseases, major adverse cardiovascular events, COVID-19.

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Introduction

Similar to most viruses, when severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the body, it activates the innate component of the immune response, manifested by hyperproduction of proinflammatory cytokines, such as interleukin (IL) 1, IL-6 and tumor necrosis factor α (TNF-α) [1].

Pentraxins are proteins of innate immunity. They destroy microbes, activate complement, and recruit lymphocytes. Under experimental conditions, it has been proven that proinflammatory cytokines (TNF-α, IL-1), toll-like receptors (TLRs), microorganisms (including viruses) and microbial groups stimulate the secretion of long pentraxins, such as pentraxin 3 (PTX3), by polymorphonuclear neutrophils, macrophages, endothelial and smooth muscle cells, adipocytes, and alveolar epithelium [2]. In turn, C-reactive protein (CRP), which represents short pentraxins, is synthesized by hepatocytes, and its release is also induced by proinflammatory cytokines (mainly IL-6, IL-1 and TNF-α) [3]. Therefore, the main features distinguishing PTX3 from CRP are its local formation in the site of inflammation (vascular wall, heart, lungs, etc.) by several types of cells and a rapid increase of its concentration during inflammatory or infectious process.

The damage to the cardiovascular system (CVS) by the SARS-CoV-2 virus has been actively discussed since the beginning of the COVID-19 pandemic. The basis for this was created by autopsy studies confirming myocardial damage in patients with COVID-19 [4, 5]. Increases in concentrations of high -sensitivity cardiac troponin (hs-Tn) were reported in patients who developed myocarditis, acute right ventricular failure, thromboembolism, cardiac arrhythmias and asystole during hospitalization for COVID-19 [6, 7]. Serum markers of myocardial damage, along with hs-Tn, include creatine kinase (CK), MB fraction of creatine kinase (CK-MB), myoglobin and PTX3 [8].

Several studies confirmed that PTX3 plays a prognostic role in many diseases, such as fungal, bacterial and viral infections, sepsis, cardiovascular disease (CVD) and acute respiratory distress syndrome [9]. In 2021, E. Brunetta et al. and A. Schirinzi et al. considered PTX3 as a prognostic marker for adverse outcomes in patients with COVID-19 [10, 11].

From the above, it follows that PTX3 can be used as a prognostic marker of both the intensity of the body's inflammatory response and damage to the CVS in patients with COVID-19.

Objective – to determine the prognostic value of PTX3 and other serum biomarkers regarding the development of

major adverse cardiovascular events (MACE) in patients with a new coronavirus infection during their long-term follow-up.

Materials and Methods

Our open-label prospective nonrandomized comparative trial initially included 144 patients who were admitted to the hospital and complied with both inclusion and exclusion criteria. The former criteria were as follows: admission to a COVID-19 hospital; positive PCR test for detection of SARS-CoV-2 RNA; grades 1-4 lung damage at hospital admission; voluntary consent of the patient to participate in the study; and age of 18-70 years. Exclusion criteria were: existing CVD; acute and chronic diseases of the bronchi and lungs of other etiologies; oncological diseases; and types 1 and 2 diabetes mellitus. Subsequently, for various reasons, 30 patients dropped out of the study, including 3 patients who developed MACE during the inpatient treatment phase.

The study was approved by the Ethics Committee at Razumovsky Saratov State Medical University of the Russian Ministry of Healthcare. Upon admission to the COVID-19 hospital, all patients were subjected to computed tomography of the chest (CTC), venous blood samples for a complete blood count (CBC) and blood biochemistry test. The latter identified concentrations of total protein, albumin, creatinine, aspartate aminotransferase, alanine aminotransferase, total cholesterol, procalcitonin, lactate dehydrogenase (LDH), CK, CK-MB, hs-TnT, hs-TnI, D-dimer, CRP, ferritin and IL-6. In addition to CBC and standard biochemistry, blood samples were collected from patients within 24 hours of admission to determine PTX3 levels. To identify the concentration of PTX3, we employed a commercial kit designed for the quantitative determination of human PTX3 via enzyme-linked immunosorbent assay (ELISA) in samples of serum, blood plasma, and cell culture supernatants. According to the instructions included with the kit, the threshold value for PTX3 was 2 ng/mL.

During inpatient treatment, study subjects received pharmacotherapy prescribed in the Interim Guidelines on Prevention, Diagnosis and Treatment of New Coronavirus Infection (COVID-19), Version 16 (18 August 2022) [12].

The patient cohort was monitored for a year from the moment of discharge from the hospital. During the observation period, we assessed the development of the following study endpoints regarding MACE: acute coronary syndrome, pulmonary embolism, acute cerebrovascular accident, arrhythmia (paroxysmal supraventricular/ventricular tachycardia, atrial fibrillation) and deaths from cardiovascular causes (DCC).

Statistical data processing was carried out using the STATISTICA 8 software (StatSoft Inc., USA) and MedCalc 8.2.0.3. The distributions of analyzed variables were tested for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests. To describe variables with a distribution other than normal, the median, and upper and lower quartiles (Me [Q1; Q3]) were presented. Differences between groups were analyzed using the nonparametric Mann–Whitney U test. Differences between categorical variables were analyzed using the Pearson's $\chi 2$ test. To predict the development of MACE depending on the values of clinical and laboratory parameters, we employed logistic regression analysis with calculation of natural logarithms of the odds ratios (OR) with a 95% confidence intervals (CI). To identify the prognostic value of promising biomarkers (PTX3), the area under the ROC curve (AUC) was calculated. In the course of ROC analysis, we determined the cut-off point with the calculation of sensitivity and specificity. Differences were considered statistically significant at $p<0.05$.

Results

Clinical and laboratory characteristics of patients at hospital admission are presented in *Tables 1-3*.

Table 1 clarifies that women prevailed among hospitalized patients (57.9%), smoking history was noted in less than one-fourth of patients, and the length of hospital stay was 10.0 [8.0; 14.0] days. In 31 (27.2%) patients in the hospital, we observed an increase in respiratory failure and the volume of lung damage according to CTC results. Just 9 (7.9%) patients required noninvasive/invasive ventilation. The most common concomitant pathology was overweight (27.2%) and class 1 exogenous obesity (15%).

Table 2 presents the initial values of laboratory parameters, and Table 3 summarizes data on cardiovascular biomarkers of patients with COVID-19 at hospital admission. Leukopenia (less than 4×109/L leukocytes) was observed in 16 (14%) patients, leukocytosis (more than 9×109/L leukocytes) was detected in 24 (21.1%) individuals, thrombocytopenia (less than 150×109/L platelets) was established in 22 (19.3%) study subjects, serum CRP exceeding 10 mg/L was noted in 103 (90.4%) patients, IL-6 exceeding 7 pg/ml was typical for 50 (43.9%) individuals, procalcitonin of more 0.5 μg/L was found in 2 (1.8%) study subjects, and PTX3 exceeding 2 ng/mL was detected in 109 (95.6%) patients. We noted no increase in the concentrations of CK, CK-MB, and hs-Tn at hospital admission.

Patients were monitored for 366 [365; 380] days after discharge from the COVID-19 hospital. During this period, we detected MACE in 19 (16.7%) patients, including 2 (1.8%) DCC (*Table 4*).

Next, to determine statistically significant differences in the development of MACE, patients were distributed among two groups: group 0 included study subjects without the development of endpoints during long-term follow-up; group 1 encompassed individuals with the development of endpoints during long-term follow-up (*Table 5*).

The data presented in Table 5 imply that patients who developed MACE during the one-year follow-up had higher values of body mass index, stayed longer in hospital treatment, and also had a higher risk of cardiovascular events according to the European Systematic Coronary Risk Evaluation 2 scale (17.3% [6; 33] and 11.7% [2; 27], respectively; p=0.006). These patients also had significantly higher concentrations of IL-6, D-dimer, LDH, CK, CK-MB and PTX3 ($p<0.05$) upon admission to the COVID-19 hospital. There were no statistically significant differences between the groups depending on the severity of COVID-19 (p=0.052), the volume of lung tissue damage according to CTC scan (p=0.418), and initial values of SpO2 (p=0.134).

Among the studied parameters, increased levels of PTX3 (OR 1.28, 95% CI 1.13-1.45; $p<0.001$), IL-6 (OR 1.01, 95% CI 1, 0-1.02; p=0.048), D-dimer (OR 2.05, 95% CI 1.16-3.6; p=0.019), LDH (OR 1.08, 95% CI 1.03- 1.13; $p<0.001$), CK MB (OR 1.19, 95% CI 1.02-1.39; p=0.001), and smoking

(OR 4.05, 95% CI 1.1-14 .95; p=0.001) were associated statistically significantly with MACE.

Table 1. Clinical characteristics of patients at hospital admission

Parameter	Patients (*n*=114)
Male, count (%)	48 (42.1)
Female, count (%)	66 (57.9)
Age, years	57 [46; 63]
Body mass index, kg/m^2	25.0 [22.7; 29.4]
Severity grade of COVID-19 course, count (%): Moderate Severe	 81 (71.1) 33 (28.9)
Severity grade of CT at hospital admission, count (%): 1 2 3 4	 66 (57.9) 31 (27.2) 15 (13.1) 2 (1.8)
SpO_2, %	96.0 [94.0; 97.0]
Heart rate, per min	85.0 [75.0; 95.5]
Respiratory rate, per min	17.0 [16.0; 20.0]
Oxygen therapy, count (%)	45 (39.5)
Smoking, count (%)	27 (23.7)
SCORE2, risk at the time of hospitalization, count (%): Low Moderate High	 4 (3.5) 55 (48.2) 41 (36)
Excess body weight, count (%)	31 (27.2)
Obesity, count (%): Class I Class II	 17 (15) 5 (4.4)
Arterial hypertension, count (%): Grade 1 Grade 2	 7 (6.1) 3 (2.6)

CT, computed tomography; SCORE2, The European Systematic Coronary Risk Evaluation 2 score.

Table 2. Laboratory parameters of patients at hospital admission

Parameter	Patients (*n*=114)
Leukocytes, ×109/L	6.9 [4.8; 9.0]
Lymphocytes, %	19 [13.0; 27.0]
Monocytes, %	5 [3; 8]
Platelets, ×109/L	199 [151; 264]
Hemoglobin, g/L	139 [128; 151]
Red blood cells, ×1012/L	4.6 [4.3; 5.1]
Erythrocyte sedimentation rate, mm/h	27 [19; 36]
CRP, mg/L	41 [17; 98]
Ferritin, ng/mL	285 [150; 601]
Interleukin 6, pg/mL	4.1 [0.6; 28.6]
Total cholesterol, mmol/L	4.2 [3.5; 5.0]
D-dimer, μg/mL	0.6 [0.4; 1.0]
Vitamin D, ng/mL	35 [31.0; 38.0]
Glomerular filtration rate, mL/min/m^2	84 [68; 94]

CRP, C-reactive protein.

Table 3. Cardiovascular biomarkers of patients at hospital admission

Parameter	Patients (*n*=114)
LDH, IU/L	175 [170; 190]
CK, IU/L	61 [57; 68]
CK-MB, IU/L	12 [9; 15]
hs-TnT, ng/mL	0.03 [0.01; 0.05]
hs-TnI, ng/mL	0.22 [0.2; 0.25]
PTX3, ng/mL	5.7 [3.6; 8.9]

LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, MB fraction of creatine kinase; hs-TnT, high-sensitivity troponin T; hs-TnI, high-sensitivity troponin I; PTX3, pentraxin 3.

Table 4. Structure of adverse cardiovascular events during one-year follow-up of patients

Study endpoints	Patients, count (%)
MACE	
Acute coronary syndrome	5 (4.4)
Arrhythmias	10 (8.8)
Acute cerebrovascular accident	4 (3.5)
Pulmonary embolism	1 (0.9)
DCC	
Acute coronary syndrome	1 (0.9)
Pulmonary embolism	1 (0.9)

MACE, major adverse cardiovascular events; DCC, deaths from cardiovascular causes.

Table 5. Clinical and laboratory parameters in patients with COVID-19 depending on the advance of clinical endpoints

Parameter	Groups		*p*
	0, *n*=95 (83.3%)	1, *n*=19 (16.7%)	
Age, years	52.4 [18; 70]	57.6 [32; 69]	0.151
Body mass index, kg/m^2	26.0 [19.6; 40.8]	28.4 [21.6; 40.1]	0.040
Length of hospital stay, days	11.4 [6; 41]	14.8 [8; 49]	0.015
Leukocytes, ×10^9/L	7.3 [1.5; 19.4]	7.1 [2.1; 13.1]	0.822
Lymphocytes, %	21 [6; 53]	22 [5; 51]	0.888
Monocytes, %	6.1 [1; 16]	3.6 [1; 7]	0.001
Platelets, ×10^9/L	218.1 [100; 475]	192.4 [97; 358]	0.233
Hemoglobin, g/L	140 [99; 176]	141 [115; 185]	0.689
Red blood cells, ×10^{12}/L	4.7 [3.4; 6.1]	4.5 [3.8; 5.7]	0.054
Glomerular filtration rate, mL/min/m^2	83.9 [44; 127]	74.3[50; 105]	0.048
CRP, mg/L	65.1 [2; 465]	69.8 [3; 196]	0.422
Ferritin, ng/mL	395 [18; 1560]	416.5 [98; 1009]	0.565
Interleukin 6, pg/mL	18.7 [0; 254.7]	33.2 [0; 184]	0.019
Total cholesterol, mmol/L	4.2 [1.9; 6.9]	4.6 [2; 7.5]	0.209
D-dimer, μg/mL	0.7 [0.05; 3.8]	1.6 [0.2; 7.7]	0.003
LDH, IU/L	174.9 [160; 215]	200 [170; 230]	0.000
CK, IU/L	61.5 [34; 95]	77.7 [58; 150]	0.001
CK-MB, IU/L	11.4 [5; 28]	21 [11; 48]	0.000
hs-TnT, ng/mL	0.03 [0.01; 0.05]	0.04 [0.01; 0.05]	0.290
hs-TnI, ng/mL	0.22 [0.2; 0.25]	0.23 [0.2; 0.3]	0.392
PTX3, ng/mL	5.3 [3.5; 8.1]	9.6 [4.4; 12.4]	0.015

p-values were obtained from the results of the nonparametric Mann–Whitney U test; CRP, C-reactive protein; LDH, lactate dehydrogenase; CK, creatine kinase; hs-TnT, high-sensitivity troponin T; hs-TnI, high-sensitivity troponin I; PTX3, pentraxin 3.

Since there are currently no generally accepted threshold values for PTX3 as a promising biomarker of damage to CVS, we performed the ROC analysis to determine the cut-off point value. The concentration of PTX3>3.1 ng/mL predicted the development of MACE in the long term in post-COVID-19 patients (sensitivity 94.0%, specificity 82.1%; AUC 0.885; p<0.001) (*Figure*).

Discussion

The concentration of PTX3 in the blood plasma of healthy people is negligible and amounts to less than 2 ng/mL, whereas an increase in the PTX3 content was noted in older female patients. In a multiethnic study by N.S. Jenny et al. (2014), which included 2,838 patients without a history of CVD, after adjustments for gender, age, and ethnicity, an increase in PTX3 levels of 1.62 ng/mL was associated with the presence of coronary calcification (OR 1.05, 95% CI 1.01-1.08), and with increased risks of myocardial infarction (OR 1.51, 95% CI 1.16-1.97), combined CVD (OR 1.23, 95% CI 1.05-1.45) or coronary artery disease (OR 1 .33, 95% CI 1.10–1.60), but not with stroke, DCC or total all-cause mortality [13]. Serum PTX3 levels at admission were significantly higher in the group of patients with acute myocardial infarction (AMI) than in the control group without it (2.27±0.81 and 0.86±0.50 ng/mL, respectively; p<0.001). In multivariate analysis, PTX3 was a significant independent predictor of long-term DCC after adjusting for other risk factors (OR=1.12, 95% CI 1.04-1.20; p=0.001) [13].

According to the results of large-sample randomized clinical trials, CORONA (1,457 patients) and GISSI-HF (1,233 patients), an increase in PTX3 concentration was a prognostic marker of hospital admission due to decompensation of chronic heart failure, DCC and combined mortality from other causes [14].

In our study, PTX3 levels at hospital admission were significantly higher in patients who developed MACE during one-year follow-up vs. patients without adverse outcomes (9.6 [4.4; 12.4] and 5.3 [3.5; 8.1] ng/mL, respectively; p=0.015).

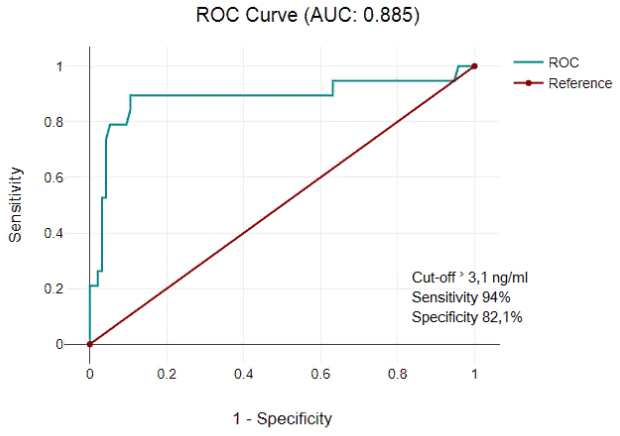

Figure. Determining the cut-off point based on PTX3 concentration to predict major adverse cardiovascular events within a year after COVID-19

The prognostic value of new biomarkers in the stratification of long-term MACE during two-year follow-up of patients who suffered ST-segment elevation AMI was highest in the multiple marker model with three biomarkers: NT-proBNP (OR 1.19, 95% CI 1.018-1.32; p<0.001); sST2 (OR 1.000013, 95% CI 1.00-1.001; p=0.007); PTX3 (OR 1.178, 95% CI 0.798-1.73; p=0.434) vs. the single marker or two-marker models (LR=12.45; p=0.033) [15]. A 2020 prospective study by N. Zagidullin et al. involving 147 patients with ST-segment elevation AMI showed that the best predictor of DCC within two years after discharge was PTX3 (OR 3.1, 95% CI 1 .63-5.39; p<0.001). In ROC analysis, PTX3 concentration of 169 ng/mL predicted DCC (sensitivity 68.4%, specificity 82.0%; AUC 0.804; p=0.063) [16]. In that study, PTX3>3.1 ng/mL was prognostically significant for MACE (sensitivity 94.0%, specificity 82.1%; AUC 0.885; p<0.001). The differences in the study results were mainly due to the presence of a history of CVD (AMI) in the study by N. Zagidullin [16] vs. the absence of established CVD in patients at the time of inclusion in our study.

COVID-19 exhibits a wide range of clinical manifestations and a varied course of infection ranging from asymptomatic stage to critical conditions. It is currently known that patient characteristics such as old age, immunodeficiency, and concomitant diseases (CVD, diabetes mellitus, heart failure, malignant neoplasms) are associated with severe COVID-19 [17, 18]. However, there are no generally accepted markers for predicting adverse outcomes when monitoring patients during their hospital stay and after discharge. Such markers would be useful for risk stratification of early and late cardiovascular events in patients hospitalized with COVID-19. Based on these data, we hypothesized the possibility of using PTX3 as a biomarker linking the activity of the inflammatory process with the risk of developing MACE in post- COVID-19 patients.

In international publications, the initial level of PTX3, together with other inflammatory markers (IL-6, CRP), was a reliable parameter that determined not only the severity, but also the progression of COVID-19 (p<0.001) [4-6, 17, 18]. The latter study assessed the significance of generally accepted markers of inflammatory activity (CRP, ferritin, IL-6), markers of cardiovascular damage (LDH, CK, CK-MB, hs-TnT, hs-TnI) and the promising biomarker PTX3 for predicting the development of adverse outcomes in patients within a year after their discharge from hospital [18].

The presence of a connection between the level of PTX3 and various factors (severity of COVID-19, long hospital stay, high values of D-dimer, hs-TnT, hs-TnI, thrombotic complications during hospitalization) were described in studies by M. Tong et al. [18], A. Genç et al. [19], and A. Protti et al. [20].

Our study had several limitations. We carried it out on a small sample of patients from one of the departments for the treatment of patients with COVID-19. The value of other potential markers for predicting the development of MACE (such as sST-2, NT-proBNP and VCAM-1), were not explored in the course of our research.

Conclusion

Serum biomarkers (PTX3 and CPK-MB) can probably be used to predict the development of MACE in long-term follow-up of patients after COVID-19. Integration of PTX3

determination into routine clinical practice may improve cardiovascular risk stratification in patients after COVID-19.

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Conflict of interest: none declared by the authors.

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