

Cardiac biomarkers on admission and in-hospital mortality in COVID-19 patients with or without concomitant heart failure

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KEY WORDS

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ABSTRACT

INTRODUCTION High-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are known markers of cardiac injury. However, their role in predicting the severity of COVID-19 remains to be investigated.

OBJECTIVES We aimed to analyze the association between hs-cTnT and NT-proBNP levels and in-hospital mortality in patients with COVID-19, with emphasis on those with concomitant chronic heart failure (CHF). **PATIENTS AND METHODS** A total of 1729 consecutive patients with COVID-19 were enrolled. Demographic data, laboratory parameters, and clinical outcomes (discharge or death) were analyzed. Receiver operating characteristic (ROC) and logistic regression analyses were performed to evaluate the association between hs-cTnT and NT-proBNP values and the risk of death.

RESULTS Evaluation of hs-cTnT was performed in 1041 patients, while NT-proBNP was assessed in 715 individuals. CHF was present in 179 cases (10.4% of the cohort). Median values of hs-cTnT and NT-proBNP and in-hospital mortality were higher in CHF patients than in those without CHF. Among patients without CHF, mortality was the highest in those with hs-cTnT or NT-proBNP values in the fourth quartile. In ROC analysis, hs-cTnT equal to or above 142 ng/l and NT-proBNP equal to or above 969 pg/ml predicted in-hospital death. In patients without CHF, each 10-ng/l increase in hs-cTnT or 100-pg/ml increase in NT-proBNP was associated with a higher risk of death (odds ratio [OR], 1.01 and OR, 1.02, respectively; $P < 0.01$ for both).

CONCLUSIONS The level of hs-cTnT or NT-proBNP predicts in-hospital mortality in COVID-19 patients. Both hs-cTnT and NT-proBNP should be routinely measured on admission in all patients hospitalized due to COVID-19 for early detection of individuals with an increased risk of in-hospital death, even if they do not have concomitant heart failure.

INTRODUCTION Although COVID-19 is a viral disease in which the lungs are the primary and most severely affected organ, in some cases, it can also involve other organs, especially the heart and peripheral vessels. After the early infection stage, a severe hyperinflammation may occur, from which systemic complications are likely to result. The severity of COVID-19 depends on

many factors, the most important being age and pre-existing comorbidities.¹⁻⁴ SARS-CoV-2 can also affect the cardiovascular system in a variety of ways. In patients without a prior history of cardiovascular disease, it is likely that the extent of systemic inflammatory response is of vital importance. In individuals with a history of pre-existing cardiovascular disease or comorbidities,

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WHAT'S NEW?

The study presents results based on a large database of consecutive patients with COVID-19 treated in a single hospital according to the same standard. It shows that patients with pre-existing heart failure and COVID-19 had a particularly high risk of in-hospital death. However, abnormal values of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide (NT-proBNP) measured on admission allowed us to identify patients with a higher risk of death and prolonged hospitalization, regardless of whether they had heart failure or not. Thus, the study postulates that the markers of cardiac injury should be routinely measured on admission in all patients with COVID-19, not only in those with a history of cardiovascular disease. The results add to the growing evidence that simple-to-obtain cardiac biomarkers, such as cardiac troponin and NT-proBNP, may help in early risk stratification of patients hospitalized for SARS-CoV-2 infection.

these conditions become apparent or more complicated during COVID-19, both as a consequence of inflammation and due to the side effects of medication or secondary hospital-acquired infections or complications.⁵⁻⁷ Most patients infected with SARS-CoV-2 report to the hospital after the viremia phase, when they develop more severe symptoms of the disease: fever, weakness, dyspnea, and hypoxemia. This means that they are at least in the pulmonary phase of the disease, which can be confirmed by lung imaging. At this early stage of hospitalization, it is extremely important to identify the patients who are at an increased risk of death.

For many years, cardiac biomarkers have been used in clinical practice to identify and assess the progression of cardiovascular diseases. Among these biomarkers, high-sensitivity cardiac troponin (hs-cTn) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are the most frequently used. They are important in various cardiovascular conditions, such as chronic heart failure (CHF), ischemic heart diseases, acute coronary syndromes, or pulmonary embolism. Hs-cTn, as a marker of cardiomyocyte necrosis, and NT-proBNP, as a marker of cardiac biomechanical stress, seem to be useful for early stratification of patients hospitalized for COVID-19—both are associated with damage of the heart, and therefore, their concentration during COVID-19 indicates involvement of the cardiovascular system.^{5,8-10}

Although several studies have shown that elevated levels of hs-cTn or NT-proBNP are associated with a higher risk of complications and death in patients with COVID-19,¹¹⁻¹⁴ some aspects remain to be clarified, especially with respect to individuals with concomitant heart failure. For example, it is unclear whether troponin and/or NT-proBNP are more useful in terms of risk stratification and mortality prediction than classic inflammatory parameters, such as leukocyte count, C-reactive protein (CRP), or interleukin 6 (IL-6). Thus, the aim of this study was to investigate the association between high-sensitivity troponin T (hs-cTnT) and NT-proBNP values on

admission to the hospital and in-hospital mortality in a large cohort of patients with COVID-19, with particular emphasis on individuals with a prior history of CHF.

PATIENTS AND METHODS We analyzed medical records of all consecutive patients who were admitted between March 6, 2020 and October 15, 2020 to the University Hospital in Kraków, Poland, which was temporarily converted into an Infectious Disease Hospital designated for the treatment of patients with COVID-19. The patients were diagnosed with COVID-19 according to the World Health Organization and Polish guidelines using reverse transcription–polymerase chain reaction (rhino-oropharyngeal swab positive for SARS-CoV-2 RNA).¹⁵ The protocol used for COVID-19 treatment was in accordance with recommendations of the Polish Association of Epidemiologists and Infectiologists.^{16,17} The patient data were obtained from the electronic Hospital Information System. Cardiovascular risk factors and diseases were identified based on the medical history and/or prior treatment, and were defined according to the current European Society of Cardiology guidelines.¹⁸ Information on the demographics, symptoms, laboratory tests (hs-cTnT measured with the enzyme-linked immunoculture assay [ELICA] using a Cobas Pro device [Roche Diagnostics GmbH, Mannheim, Germany]; NT-proBNP measured with ELICA using a Cobas Pro device [Roche Diagnostics]; high-sensitivity CRP (hs-CRP) measured by nephelometry using a Siemens BN II device [Siemens Healthineers, Erlangen, Germany]; interleukin 6 (IL-6) measured with ELICA using a Cobas Pro device [Roche Diagnostics]; D-dimer measured by coagulometry using a Siemens Atellica COAG 360 device [Siemens Healthineers]), treatment options, and clinical outcomes (pneumonia, length of hospital stay, survival at discharge or death) was collected from all participants. Some data were presented in our previous paper, in which we also analyzed the association between cardiovascular drugs and mortality rates.¹⁹ Only cardiac and inflammatory biomarkers on admission (day 1 or 2) were considered. The diagnosis of pneumonia was confirmed using imaging studies such as chest X-ray or high-resolution computed tomography (CT) performed soon after admission. The data of survivors and nonsurvivors were compared, and were additionally analyzed according to the presence of previously diagnosed CHF. The study was approved by the Jagiellonian University Ethics Committee (no. 1072.6120.278.2020) and conforms to the ethical principles outlined in the Declaration of Helsinki.

Statistical analysis We used the SAS software, version 9.2 (SAS Institute, Cary, North Carolina, United States) for database management and statistical analysis. The results were expressed as numerical values and percentages for categorical variables and as mean (SD) or median and

interquartile range (IQR) for continuous variables. For the assessment of means or proportions between the study groups, we applied the *t* test or the χ^2 test, accordingly. In the case of nonparametric data, we used the Wilcoxon signed-rank test.

We analyzed the ability of hs-cTnT or NT-proBNP levels to identify participants with a higher risk of death due to COVID-19 by constructing receiver operating characteristic (ROC) curves and calculating the area under the ROC curve (AUC) using the Mann–Whitney test. Then, we estimated the optimal cutoff points for hs-cTnT and NT-proBNP to determine individuals with a higher probability of death. We calculated the closest point to (0,1) using the following formula: the square root of $([1-\text{Sensitivity}]^2 + [1-\text{Specificity}]^2)$. The test result value corresponding to the point with the shortest distance (D) was indicated as the threshold cutoff point. Independent predictors of in-hospital death were explored in logistic regression analyses. The following variables were included into the models: age above 65 years, male sex, presence of arterial hypertension, diabetes mellitus, coronary heart disease, stroke, or atrial fibrillation, a 10-mg/l increase in hs-CRP, as well as 10-ng/l and 100-pg/ml increase in hs-cTnT or NT-proBNP, respectively. In all analyses, *P* values below 0.05 indicated statistical significance.

RESULTS Study population A total of 1729 consecutive patients with COVID-19 were hospitalized from March 6, 2020 to October 15, 2020. The study population consisted of 886 men (median [IQR] age, 62 [50–74] years) and 843 women (median [IQR] age, 64 [51–77] years). Pneumonia diagnosed using chest X-ray or CT was present in 1075 patients (62.2%). On admission, 179 individuals had CHF (10.4% of the entire cohort). The proportion of patients receiving heart failure treatment identified on admission was as follows: β -blockers were used in 137 cases (76.5%), diuretics in 134 (74.9%), angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in 55 (30.7%), and mineralocorticoid receptor antagonists in 53 (29.6%). During hospitalization, the following drugs were used for COVID-19 treatment in the study population: dexamethasone in 465 patients (26.9%), remdesivir in 64 (3.7%), and tocilizumab in 5 (0.3%).

Patients with high-sensitivity cardiac troponin T assessed on admission The values of hs-cTnT were available on the first or second day after admission in 1041 patients (60.2% of the entire cohort). Elevated levels of hs-cTnT, that is, values greater than 14 ng/l (>99th percentile upper reference limit [URL]), were observed in 432 patients on admission (41.5% of all patients with known hs-cTnT). The patients with known hs-cTnT levels were older, mostly male, and had a higher body mass index as compared with the COVID-19 patients who did not have this marker assessed (TABLE 1).

Patients with N-terminal pro-B-type natriuretic peptide assessed on admission NT-proBNP values were measured on admission in 715 patients (41.4% of the entire cohort). An increased concentration of NT-proBNP (ie, >125 pg/ml; laboratory cutoff point for normal value) was found in 583 patients (81.5% of all cases with known NT-proBNP). The patients with NT-proBNP levels determined on admission were older, had a higher body mass index and were more often male than the patients with COVID-19 without available data on this parameter (TABLE 1). All comorbidities, with the exception of asthma, were more frequently observed in patients in whom hs-cTnT or NT-proBNP was assessed on admission (TABLE 1). Also, pneumonia was observed more frequently in imaging studies in this group of patients.

Patients with a history of chronic heart failure Baseline characteristics of patients with COVID-19 and a history of CHF are presented in TABLE 2. Among them, hs-cTnT values were assessed on admission in 155 individuals (86.6% of all patients with CHF), while the values of NT-proBNP were determined in 131 patients (73.2% of the group with CHF). The patients with concomitant CHF were significantly older than those without a prior history of CHF (TABLE 2). Comorbidities, except for stroke and asthma, were more common in COVID-19 patients with a history of CHF. However, no differences were found in the frequency of pneumonia, the length of hospital stay, and hs-CRP or IL-6 values between the patients with or without CHF who had the hs-TnT or NT-proBNP levels measured on admission (TABLE 2).

The median values of hs-cTnT and NT-proBNP determined on admission were significantly higher in patients with CHF than in those without a prior CHF diagnosis: 33.5 vs 9.1 ng/l; *P* < 0.001 and 2446 vs 418 pg/ml; *P* < 0.001, respectively (TABLE 3).

In-hospital course and mortality rates The median length of hospital stay was 4 days longer in those with a hs-cTnT or NT-proBNP levels determined on admission than in those without these data (*P* < 0.001). The patients who had the levels of hs-cTnT or NT-proBNP measured on admission also had higher levels of hsCRP, IL-6, and D-dimer. Moreover, pneumonia diagnosed by X-ray or CT was confirmed the most frequently in this group of patients (TABLE 1).

The overall in-hospital mortality rate was 12.9% (223 of 1729 patients). Among individuals with a known hs-cTnT value on admission, 183 patients (17.6%) died during the hospital stay, whereas the number of in-hospital deaths among patients with known NT-proBNP values was 153 (21.4%). The death rates in both abovementioned groups were significantly higher (*P* < 0.01) than in the patients who did not have hs-cTnT or NT-proBNP levels assessed on admission (TABLE 1).

In patients with a concomitant history of CHF, the mortality was higher than in those without

TABLE 1 Basic characteristics of the study participants

Characteristics on admission	hs-cTnT		<i>P</i> value ^a	NT-proBNP		<i>P</i> value ^b
	Determined (n = 1041)	Not determined (n = 688)		Determined (n = 715)	Not determined (n = 1014)	
Age, y	67.5 (14.1)	52.9 (17.7)	<0.001	67.4 (17.6)	57.6 (17.6)	<0.001
Female sex, n (%)	473 (45.44)	379 (53.78)	<0.001	307 (42.94)	536 (52.86)	<0.001
BMI ^c , kg/m ²	29.0 (5.4)	27.8 (4.4)	0.001	29.1 (5.3)	28.2 (4.8)	0.019
Pre-existing conditions, n (%)						
Arterial hypertension	708 (68.01)	262 (38.08)	<0.001	487 (68.11)	483 (47.63)	<0.001
Hyperlipidemia	385 (36.98)	88 (12.79)	<0.001	254 (35.52)	219 (21.6)	<0.001
Diabetes mellitus	329 (31.6)	116 (16.86)	<0.001	237 (33.15)	208 (20.51)	<0.001
Coronary artery disease	242 (23.25)	48 (6.98)	<0.001	168 (23.5)	122 (12.03)	<0.001
Chronic heart failure	155 (14.89)	24 (3.49)	<0.001	131 (18.32)	48 (4.73)	<0.001
Atrial fibrillation	190 (18.25)	43 (6.25)	<0.001	157 (21.96)	76 (7.50)	<0.001
Stroke	105 (10.09)	34 (4.94)	<0.001	68 (9.51)	71 (7.00)	0.06
Asthma	67 (6.44)	39 (5.67)	0.51	49 (6.85)	57 (5.62)	0.29
COPD	70 (6.72)	19 (2.76)	<0.001	57 (7.97)	32 (3.16)	<0.001
Clinical course						
hs-cTnT, ng/l	10.62 (5.19–32.87)	–	–	14.3 (6.32–48.05)	7.75 (4.33–16.82)	<0.001
NT-proBNP, pg/ml	754 (214–2843)	150 (75–895)	<0.001	594 (169–2199)	–	–
Pneumonia, n (%)	768 (73.78)	307 (44.62)	<0.001	567 (79.3)	508 (50.1)	<0.001
hs-CRP ^c , mg/l	51.5 (15–97)	18.6 (5.3–57)	<0.001	57.1 (19.3–115)	23.4 (6.16–64.7)	<0.001
D-dimer ^c , mg/l	0.86 (0.5–1.66)	0.6 (0.4–1.0)	<0.001	0.95 (0.54–1.83)	0.64 (0.41–1.18)	<0.001
IL-6 ^c , pg/ml	31.4 (10.5–76.1)	8.1 (1.5–25.1)	<0.001	32.59 (11.58–78.0)	9.38 (1.5–27.59)	<0.001
eGFR, ml/min/1.73 m ²	70 (56–90)	90 (79–90)	<0.001	77 (54–90)	90 (72–90)	<0.001
Length of hospital stay, d	18 (13–28)	14 (8–21)	<0.001	19 (13–30)	15 (10–22)	<0.001
Death, n (%)	183 (17.58)	40 (5.81)	<0.001	153 (21.4)	70 (6.9)	<0.001

Data are presented as mean (SD) or median (interquartile range) unless indicated otherwise.

a *P* < 0.05 for differences between patients with a determined vs not determined level of hs-cTnT on admission

b *P* < 0.05 for differences between patients with a determined vs not determined level of NT-proBNP on admission

c Data available in: 697 patients for BMI, 1440 patients for D-dimer, 718 patients for IL-6, and 1574 patients for hs-CRP

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; hs-cTnT, high-sensitivity cardiac troponin T; IL-6, interleukin 6; NT-proBNP, N-terminal pro-B-type natriuretic peptide

CHF; in the group with known hs-cTnT it was 32.9% vs 14.9%; *P* < 0.001 and in the group with known NT-proBNP it was 35.9% vs 18.1%, *P* < 0.001, respectively. Mortality rates by quartiles of serum hs-cTnT level in patients with COVID-19 without previously diagnosed CHF were 2.4% in the first quartile and 43.4% in the fourth quartile; *P* < 0.001 (TABLE 4), while death by quartiles of serum NT-proBNP level in patients without CHF occurred in 2.1% of patients with values in the first quartile, and 42.5% of those with values in the fourth quartile; *P* < 0.001 (TABLE 4).

Receiver operating characteristic and logistic regression analyses In the ROC curve analysis, hs-cTnT values of 142 ng/l or greater measured on admission had an 80% sensitivity and a 70% specificity for predicting in-hospital death (AUC = 0.8) (FIGURE 1). For NT-proBNP, the cutoff value of 969 pg/ml had a sensitivity and specificity of 79% and 67%, respectively, for predicting in-hospital mortality (AUC = 0.8) (FIGURE 2).

Logistic regression analysis showed that in COVID-19 patients without CHF, each 10-ng/l increase in the hs-cTnT concentration was independently associated with a higher risk of death (odds ratio [OR], 1.01; 95% CI, 1.00–1.07; *P* = 0.009), based on the model of variables described in the *Statistical analysis* section (detailed results are presented in Supplementary material, Table S1).

Similarly, in patients without CHF, logistic regression analysis of the NT-proBNP concentration on admission showed that for every 100-pg/ml increase there was a greater risk of death (OR, 1.02; 95% CI, 1.01–1.03; *P* < 0.001) (Supplementary material, Table S1).

DISCUSSION The study demonstrated that patients infected with SARS-CoV-2 who had elevated serum concentration of hs-cTnT (>142 ng/l) and/or NT-proBNP (>969 pg/ml) on admission had a markedly higher risk for in-hospital death than those with lower values of these

TABLE 2 Basic characteristics of the participants with and without a history of chronic heart failure

Characteristics on admission	All patients (n = 1729)			hs-cTnT determined (n = 1041)			NT-proBNP determined (n = 715)		
	CHF(–)	CHF(+)	P value	CHF(–)	CHF(+)	P value ^a	CHF(–)	CHF(+)	P value ^b
n (%)	1550 (89.6)	179 (10.4)	–	886 (57.2)	155 (86.6)	–	584 (37.7)	131 (73.2)	–
Age, y	60.0 (16.9)	76.0 (11.4)	<0.001	65.96 (13.9)	76.17 (11.7)	<0.001	65.4 (14.6)	76.4 (10.9)	<0.001
Female sex, n (%)	764 (49.29)	79 (44.13)	0.19	404 (45.6)	69 (44.52)	0.80	253 (43.32)	54 (41.22)	0.66
BMI ^c , kg/m ²	28.5 (4.9)	28.6 (5.8)	0.92	29.1 (5.3)	28.4 (5.8)	0.37	29.2 (5.3)	28.3 (5.3)	0.35
Pre-existing conditions, n (%)									
Arterial hypertension	816 (52.65)	154 (86.03)	<0.001	574 (64.79)	134 (86.45)	<0.001	370 (63.36)	117 (89.31)	<0.001
Hyperlipidemia	382 (24.65)	91 (50.84)	<0.001	300 (33.86)	85 (54.84)	<0.001	179 (30.65)	75 (57.25)	<0.001
Diabetes mellitus	368 (23.74)	77 (43.02)	<0.001	263 (29.68)	66 (42.58)	<0.01	175 (29.97)	62 (47.33)	0.001
Coronary artery disease	195 (12.58)	95 (53.07)	<0.001	157 (17.72)	85 (54.84)	<0.001	96 (16.44)	72 (54.96)	<0.001
Atrial fibrillation	149 (9.61)	84 (46.93)	<0.001	118 (13.32)	72 (46.45)	<0.001	92 (15.75)	65 (49.62)	<0.001
Stroke	121 (7.81)	18 (10.06)	0.29	89 (10.05)	16 (10.32)	0.91	55 (9.42)	13 (9.92)	0.85
Asthma	93 (6.0)	13 (7.26)	0.50	56 (6.32)	11 (7.10)	0.72	37 (6.34)	12 (9.16)	0.25
COPD	62 (4.0)	27 (15.08)	<0.001	48 (5.42)	22 (14.18)	<0.001	37 (6.34)	20 (15.27)	<0.001
Clinical course									
hs-cTnT, ng/ml	–	–	–	9.1 (4.83–23.82)	33.5 (11.09–96.79)	<0.001	11.86 (5.75–35.51)	38.77 (12.42–132.43)	<0.001
NT-proBNP ^c , pg/ml	–	–	–	507 (175–1726)	2446 (1103–5658)	<0.001	418 (136.5–1479.0)	2446 (1097–5635)	<0.001
Pneumonia ^d , n (%)	941 (60.71)	134 (74.86)	<0.001	652 (73.59)	116 (74.84)	0.74	466 (79.79)	101 (77.1)	0.49
hs-CRP ^c , mg/l	35.8 (9.44–83.4)	44.2 (14.3–90.90)	0.15	52.65 (15.2–98.4)	46.65 (14.5–93.98)	0.21	59.7 (22.2–123.0)	45.8 (14.3–93.8)	0.01
D-dimer ^c , mg/l	0.73 (0.45–1.42)	1.07 (0.58–1.93)	<0.001	0.82 (0.48–1.59)	1.09 (0.62–2.02)	0.002	0.91 (0.53–1.79)	1.12 (0.68–2.07)	0.04
IL-6 ^c , pg/ml	21.91 (5.7–60.14)	34.47 (15.53–70.48)	<0.001	31.32 (9.41–76.4)	34.47 (14.09–70.48)	0.15	32.31 (10.46–78.66)	33.12 (14.72–69.31)	0.26
eGFR, ml/min/1.73 m ²	88 (69–90)	56 (41–74)	<0.001	81 (61–90)	56 (41–74)	<0.001	82 (60–90)	55 (39–72)	<0.001
Length of hospital stay, d	16 (11–24)	17 (11–33)	0.017	18 (13–27)	17 (11–33)	0.39	19 (13–30)	20 (12–35)	0.30
Death, n (%)	165 (10.65)	58 (32.4)	<0.001	132 (14.9)	51 (32.9)	<0.001	106 (18.15)	47 (35.88)	<0.001

Data are presented as mean (SD), or median (interquartile range) unless indicated otherwise

a $P < 0.05$ for differences between patients with and without a diagnosis of heart failure on admission, with a determined hs-cTnT level

b $P < 0.05$ for differences between patients with and without a diagnosis of heart failure on admission, with a determined NT-proBNP level

c Data available in: 697 patients for BMI, 1440 patients for D-dimer, 718 patients for IL-6, and 1574 patients for hs-CRP

d Pneumonia was diagnosed by chest X-ray or computed tomography.

Abbreviations: CHF, chronic heart failure; others, see [TABLE 1](#)

parameters. Since hs-cTn and NT-proBNP levels were assessed on admission in about 60% and 41% of all patients, respectively, it can be assumed that the doctors ordering these tests were guided by the assessment of the general health status of their patients upon admission. This is evidenced by the fact that most comorbidities, and also pneumonia, were observed more frequently in the patients who had the hs-cTnT

or NT-proBNP levels measured. Additionally, the high percentage of patients with hs-cTnT and NT-proBNP levels evaluated on admission among individuals with CHF (87% and 73%, respectively) supports this hypothesis. Due to the fact that the frequency of myocardial injury (as defined by elevated troponin levels) among hospitalized patients with COVID-19 increases with greater severity of the disease,^{20–22} it may

TABLE 3 In-hospital mortality rate in COVID-19 patients with high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide values assessed on admission and the difference in mortality rate between patients with or without chronic heart failure

Parameter		All patients	No history of CHF on admission	CHF on admission	P value
hs-cTnT, ng/l	Patients, n (%)	1041 (100.0)	886 (85.1)	155 (14.9)	–
	Median (IQR)	10.6 (5.19–32.9)	9.1 (4.83–23.8)	33.5 (11.1–96.8)	<0.001 ^a
	Deaths, n (%)	183 (17.6)	132 (14.9)	51 (32.9)	<0.001 ^b
NT-proBNP, pg/ml	Patients, n (%)	715 (100.0)	584 (81.7)	131 (18.3)	–
	Median (IQR)	594 (169.0–2199.0)	418 (136.5–1479.0)	2446 (1097.0–5635.0)	<0.001 ^a
	Deaths, n (%)	153 (21.4)	106 (18.1)	47 (35.9)	<0.001 ^b

a P for differences in hs-cTnT or NT-proBNP levels between patients with or without CHF

b P for differences in death rate between patients with or without CHF

Abbreviations: IQR, interquartile range; others, see [TABLE 1](#)

TABLE 4 Death by quartiles of high-sensitivity cardiac troponin T and N-terminal pro-B-type natriuretic peptide values on admission in patients with COVID-19 without a history of chronic heart failure

Parameter		Quartile			
		1 (low)	2 (medium)	3 (high)	4 (very high)
hs-cTnT^a					
Value, ng/l		<5.19	≥5.19 and <10.62	≥10.62 and <32.87	≥32.87
Death	No, n (%)	242 (97.6)	224 (95.3)	181 (83.4)	103 (56.6)
	Yes, n (%)	6 (2.4)	11 (4.7)	36 (16.6)	79 (43.4)
NT-pro BNP^b					
Value, pg/ml		<136.5	≥136.5 and <418	≥418 and <1478	≥1478
Death	No, n (%)	143 (97.1)	139 (95.2)	112 (76.7)	84 (57.5)
	Yes, n (%)	3 (2.1)	7 (4.8)	34 (23.3)	62 (42.5)

a P <0.001 (χ² test)

b P <0.001 (χ² test)

Abbreviations: see [TABLE 1](#)

be concluded that the frequency of testing for cardiac markers in the present study should be higher. However, in other studies, the percentage of patients in whom these markers were assessed was similar or even lower. For example, Cunningham et al²³ performed a large analysis of over 48 000 patients with COVID-19 and found that hs-cTn and NT-proBNP were measured on admission in 34% and 25% of individuals, respectively.

The prevalence of elevated cardiac troponin levels in individuals with COVID-19 varies widely, ranging from 20% in cohorts of hospitalized patients to more than 40% in critically ill patients.²⁴⁻²⁶ Among our COVID-19 cases, cardiac injury, defined by hs-cTnT levels greater than 99th percentile URL on admission, was present in 41.5% of patients. However, considering the entire study group, regardless of the hs-cTnT levels being determined on admission, the patients with cardiac injury accounted for 25% of the total cohort (432 out of 1729). These values are therefore similar to the results presented by other authors mentioned above.²⁴⁻²⁶

In the present study, higher NT-proBNP values were observed in patients whose hs-cTnT levels were measured on admission. The reverse relationship was also observed, that is, higher hs-cTnT values were found in patients with NT-proBNP measurements performed on admission. This means that higher values of one of the cardiac markers were accompanied by higher values of the other one. Moreover, higher values of these cardiac biomarkers were seen in more severely ill patients. This finding is consistent with recent observations that myocardial injury in COVID-19 appears to be predominantly mediated by the severity of critical illness rather than direct injury of the myocardium from viral particles.²⁷ Finally, in our study, the length of hospital stay was longer by 4 days in those with hs-cTnT or NT-proBNP levels measured on admission than in those in whom these markers were not assessed. Since the exact mechanisms leading to myocardial injury in COVID-19 are still not well understood (whether cardiomyocyte damage dominates, as reflected by troponin leak, or whether heart overload is crucial,

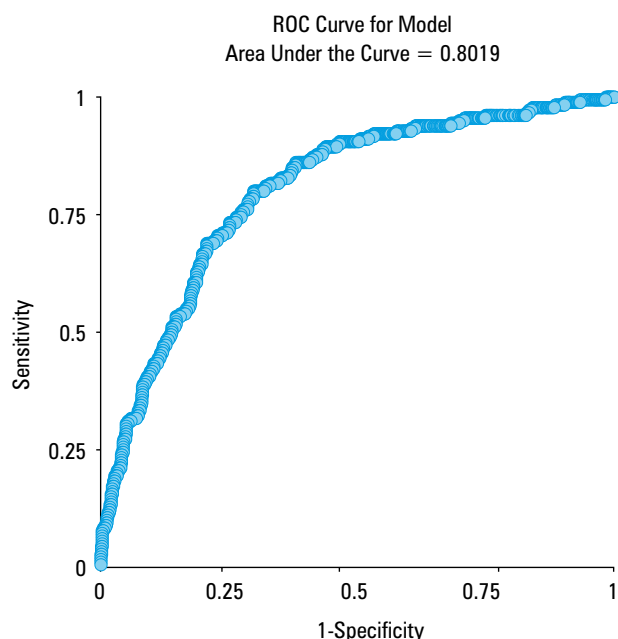


FIGURE 1 Receiver operating characteristic (ROC) curve for the association between mortality and high-sensitivity cardiac troponin T level on admission; optimal cutoff point = 141.9 ng/l with Distance to (0,1) (D) = 0.392; sensitivity, 0.80; specificity, 0.70

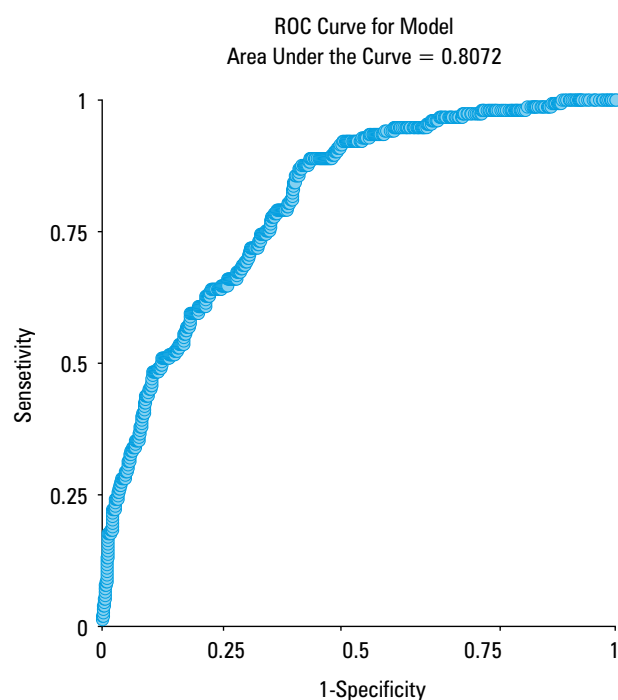


FIGURE 2 Receiver operating characteristic curve for the association between mortality and N-terminal pro-B-type natriuretic peptide levels on admission; optimal cutoff point = 969.6 pg/ml with Distance to (0,1) (D) = 0.397; sensitivity, 0.79; specificity, 0.67

as reflected by natriuretic peptide increase), it seems justified to determine both biomarkers on admission to the hospital. The relationship between the concentration of cardiac troponins on admission and mortality in mild-to-severe and critical COVID-19 patients was described by many authors.^{23,28-31} Meta-analyses published in 2020 concluded that an increased level of high-sensitivity troponin I (hs-cTnI) or

hs-cTnT is strictly associated with the most severe forms of COVID-19.^{32,33} Our observations are in line with these reports.

Another important observation from the present study is a significantly higher in-hospital mortality rate among COVID-19 patients with a history of CHF than in those without CHF. Other researchers also reported high mortality (up to 45%) in patients with CHF during hospitalization for COVID-19.³⁴ In our previous publication we found that, apart from older age and male sex, only diabetes mellitus and HF were independent predictors of in-hospital death from any cause.¹⁹ In the present study, the patients with HF had higher hs-cTnT and NT-proBNP values on admission than the remaining patients. Undoubtedly, this result was influenced by the higher age of patients with CHF and the burden of comorbidities. Unexpectedly, we did not find differences in the frequency of pneumonia, length of hospital stay, or hs-CRP and IL-6 values between patients with or without CHF who had had hs-cTnT or NT-proBNP levels measured on admission. This fact is not easy to understand. It may be hypothesized that CHF is such a serious disease that its presence could predispose to a more frequent occurrence of viral pneumonia and a higher concentration of inflammatory markers than in individuals without CHF. Unfortunately, in our database we did not collect data on the New York Heart Association functional class of the patients with CHF, which could have also elucidated their health status and better estimate the “at entry risk.” On the other hand, it should not be forgotten that before admission to the hospital, the patients with CHF had already received the usual treatment for this disease, such as ACEIs or ARBs, mineralocorticoid receptor antagonists, β -blockers, and diuretics. As shown in our previous analysis of COVID-19 patients, the use of these drugs during hospitalization was associated with a better prognosis, regardless of sex, age, and comorbidities.¹⁹ Nonetheless, there are also other observations about advantages and safety of ACEIs or ARBs used in the treatment of HF in COVID-19 cases.³⁵ A retrospective analysis recently performed in Spain showed that patients with a history of HF hospitalized for COVID-19 who continued to receive ACEI/ARB treatment had lower rates of in-hospital mortality and other adverse outcomes as compared with those in whom the therapy was stopped.³⁶ Also of note, cardiac injury is not always associated with unfavorable respiratory outcomes. For instance, in a meta-analysis published in 2021 by Bansal et al,³⁷ cardiac injury in patients with COVID-19 was associated with a higher risk of mortality (risk ratio [RR], 7.79), admission to the intensive care unit (RR, 4.06), mechanical ventilation (RR, 5.53), and coagulopathy (RR, 3.86), but was not associated with an increased risk of acute respiratory distress syndrome. It seems that the relationship between developing pneumonia and elevation of cardiac biomarkers during the SARS-CoV-2

infection needs further investigation, especially in patients with a prior history of CHF.

The importance of NT-proBNP levels on admission in patients with CHF complicated by COVID-19 was also explored before, although not as often as that of cardiac troponin. A single-center study by Belarte-Tornero et al³⁸ involved 129 patients (43 CHF and 86 non-CHF) with COVID-19. All-cause mortality was almost 2 times higher in the CHF patients than in those without CHF. A history of CHF was independently associated with 30-day mortality (hazard ratio, 2.3); however, the patients with CHF and normal hs-cTnT levels (<14 ng/l) had an excellent prognosis. In that study, an NT-proBNP level greater than 2598 pg/ml on admission was associated with a higher 30-day mortality in the patients with CHF.³⁸ Our study included slightly more individuals with CHF (179 cases); however, the cut-off point for increased mortality in patients with COVID-19 in the ROC curve analysis was lower, namely, 969 pg/ml. In a recently published meta-analysis with meta-regression, involving about 18 800 COVID-19 cases, Zinnellu et al³⁹ confirmed that BNP/NT-proBNP concentrations were significantly higher in the patients with a more severe disease or nonsurvivor status than in those with low disease severity or survivor status during follow-up.

In our hospital laboratory, the cutoff point for normal hs-cTnT value (>99th percentile URL) was 14 ng/l, and the cutoff point for normal NT-proBNP was 125 pg/ml. In the analyzed cohort of COVID-19 cases without a history of CHF, even a slightly elevated level of hs-cTnT above the reference range was associated with significantly higher mortality. As for NT-proBNP, only an increase by about 100% above the reference range was associated with a significant increase in the number of deaths in patients without a prior history of CHF. Based on this observation, blood test results showing a slight elevation in hs-cTnT and/or a relatively mild increase in NT-proBNP concentrations on admission of a patient with SARS-CoV-2 infection should warrant more stringent monitoring because the risk of in-hospital death may be greater. Other authors reported similar findings.^{5,11,22} In a multicenter, retrospective study of approximately 3200 patients with COVID-19, Qin et al⁴⁰ suggested that to evaluate the prognosis of patients with COVID-19 on admission, the cutoff threshold of abnormality for hs-cTnI, creatine kinase (CK)-myocardial band, NT-proBNP, and CK should be lower than the currently recommended laboratory range. In their dataset, cutoff values of these cardiac markers for worse prognosis were found to be much lower (ca 50%) than the upper reference limits for the general population.⁴⁰

In patients with a SARS-CoV-2 infection, several mechanisms could be involved in myocardial injury and the subsequent elevation of cardiac troponin and/or NT-proBNP levels. These include acute viral infections that may cause

myocarditis or pericarditis, hypoxia during the course of the disease, and endothelial dysfunction which may lead to ischemia of the heart and, in some cases, acute myocardial infarction type 2. Bacterial sepsis, cardiac adrenergic activation, and pulmonary embolism could also lead to troponin level elevation.^{21,41} Also, comorbidities may increase hs-cTn values.^{2,42} In our study, hypertension, diabetes, coronary artery disease, atrial fibrillation, chronic obstructive pulmonary disease, and HF occurred more frequently in the group of patients who had hs-cTnT levels measured on admission. Our results are in line with previous reports suggesting that the measurement of hs-cTn and NT-proBNP levels may improve risk stratification in patients with COVID-19 in addition to the assessment of inflammatory or thrombotic markers.⁴³⁻⁴⁵

We must acknowledge some limitations of this study. First, it was limited by its retrospective design, inducing possible bias in data collection and result interpretation (the retrospective nature of the study did not allow us to draw conclusions about the cause-effect relationship). Moreover, our results were obtained based on cases treated during the first 2 waves of the pandemic, with a similar protocol of COVID-19 in-hospital treatment. Therefore, the generalizability of our findings to asymptomatic or symptomatic COVID-19 patients who were not hospitalized may be limited. However, we presented a large, comprehensive dataset of consecutive patients and checked the data carefully. Second, hs-cTn and NT-proBNP levels were not systematically monitored during the hospital stay. Although the patients were treated in a single hospital, the assessment of cardiac troponin and NT-proBNP levels on admission was not obligatory. Third, data on concomitant diseases, including a history of HF, were obtained based on the available medical records and an interview with the patient or their relatives. Finally, echocardiography was performed on admission in a small subset of the study patients (<3%), which made it impossible to perform a reliable analysis of the heart function in relation to hs-cTn or NT-proBNP concentrations.

In conclusion, hs-cTnT or NT-proBNP predicted in-hospital mortality in all patients with COVID-19 included in our study. The patients with a history of CHF with concomitant COVID-19 who had elevated cardiac troponin or NT-proBNP levels at the time of admission to the hospital had the worst prognosis. Elevated values of hs-cTnT and NT-proBNP also enabled us to identify the patients with a higher risk of prolonged hospitalization time. For this reason, both cardiac troponin and NT-proBNP should be routinely measured on admission in all patients with COVID-19, not only in those with a history of cardiovascular disease. The results of the study support the growing evidence that simple-to-obtain cardiac biomarkers may help in early risk stratification of patients hospitalized for SARS-CoV-2 infection.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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REFERENCES

- Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020; 323: 2052-2059.
- Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J*. 2020; 41: 1821-1829.
- Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020; 395: 1054-1062.
- Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020; 323: 1574-1581.
- Khan S, Rasool ST, Ahmed SI. Role of cardiac biomarkers in COVID-19: what recent investigations tell us? *Curr Probl Cardiol*. 2021; 46: 100842.
- Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020; 5: 831-840.
- Fried JA, Ramasubbu K, Bhatt R, et al. The variety of cardiovascular presentations of COVID-19. *Circulation*. 2020; 141: 1930-1936.
- Kim CW, Aronow WS. COVID-19, cardiovascular diseases and cardiac troponins. *Future Cardiol*. 2022; 18: 135-142.
- Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020; 17: 259-260.
- Li L, Hill J, Spratt JC, Jin Z. Myocardial injury in severe COVID-19: identification and management. *Resuscitation* 2021; 160: 16-17.
- Pranata R, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. *Postgrad Med J*. 2020; 96: 387-391.
- Qin J-J, Cheng X, Zhou F, et al. Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. *Hypertension*. 2020; 76: 1104-1112.
- Stefanini GG, Chiarito M, Ferrante G, et al. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. *Heart*. 2020; 106: 1512-1518.
- Nie SF, Yu M, Xie T, et al. Cardiac troponin I is an independent predictor for mortality in hospitalized patients with COVID-19. *Circulation*. 2020; 142: 608-610.
- World Health Organization. Laboratory testing for coronavirus disease (COVID-19) in suspected human cases. Interim guidance 19 March 2020. <https://apps.who.int/iris/bitstream/handle/10665/331501/WHO-COVID-19-laboratory-2020.5-eng.pdf?sequence=1&isAllowed=y>. Accessed February 16, 2021.

- Flisiak R, Horban A, Jaroszewicz J, et al. Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of March 31, 2020. *Pol Arch Intern Med*. 2020; 130: 352-357.
- Flisiak R, Horban A, Jaroszewicz J, et al. Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists. Annex no. 1 as of June 8, 2020. *Pol Arch Intern Med*. 2020; 130: 557-558.
- European Society of Cardiology. Guidelines and Scientific Documents. www.escardio.org. Accessed February 16, 2021.
- Terlecki M, Wojciechowska W, Kłocek M, et al. Association between cardiovascular disease, cardiovascular drug therapy, and in-hospital outcomes in patients with COVID-19: data from a large single-center registry in Poland. *Kardiol Pol*. 2021; 79: 773-780.
- Aikawa T, Takagi H, Ishikawa K, Kuno T. Myocardial injury characterized by elevated cardiac troponin and in-hospital mortality of COVID-19: an insight from a meta-analysis. *J Med Virol*. 2021; 93: 51-55.
- Sandoval Y, Januzzi JL, Jaffe AS. Cardiac troponin for assessment of myocardial injury in COVID-19. *J Am Coll Cardiol*. 2020; 76: 1244-1258.
- Perrone MA, Spolaore F, Ammirabile M, et al. The assessment of high sensitivity cardiac troponin in patients with COVID-19: a multicenter study. *Int J Cardiol Heart Vasc*. 2021; 32: 100715.
- Cunningham JW, Claggett BL, Jering KS, et al. Prognostic value of natriuretic peptides and cardiac troponins in COVID-19. *Circulation*. 2021; 144: 177-179.
- Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J*. 2020; 41: 2070-2079.
- Zwaenepoel B, Dhont S, Schaumbroek H, Gevaert S. The use of cardiac troponins and B-type natriuretic peptide in COVID-19. *Acta Cardiol*. 2021 Aug 30. [Epub ahead of print].
- Wibowo A, Pranata R, Rizki Akbar M, et al. Prognostic performance of troponin in COVID-19: a diagnostic meta-analysis and meta-regression. *Intern J Infect Dis*. 2021; 105: 312-318.
- Chilazi M, Duffy EY, Thakkar A, Michos ED. COVID and cardiovascular disease: what we know in 2021. *Curr Atheroscler Rep*. 2021; 23: 10.1007.
- Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395: 497-506.
- Larcher R, Besnard N, Akouz A, et al. Admission high-sensitive cardiac troponin T level increase is independently associated with higher mortality in critically ill patients with COVID-19: a multicenter study. *J Clin Med*. 2021; 10: 10081656.
- Demir OM, Ryan M, Cirillo C, et al. Impact and determinants of high-sensitivity cardiac troponin-T concentration in patients with COVID-19 admitted to critical care. *Am J Cardiol*. 2021; 147: 129-136.
- Lala A, Johnson KW, Januzzi JL, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol*. 2020; 76: 555-546.
- Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. *Prog Cardiovasc Dis*. 2020; 63: 390-391.
- Danwang C, Endomba FT, Nkeck JR, et al. A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). *Biomark Res*. 2020; 8: 1-13.
- Salinas-Botrán A, Sanz-Cánovas J, Pérez-Somarriba J, et al. Clinical characteristics and risk factors for mortality upon admission in patients with heart failure hospitalized due to COVID-19 in Spain. *Rev Clin Esp (Barc)*. 2022; 222: 255-265.
- Savarese G, Benson L, Sundström J, Lund LH. Association between renin-angiotensin-aldosterone system inhibitor use and COVID-19 hospitalization and death: a 1.4 million patient nationwide registry analysis. *Eur J Heart Fail*. 2021; 23: 476-485.
- Pérez-Belmonte LM, Sanz-Cánovas J, Salinas A, et al. Adverse outcomes in patients with heart failure admitted for COVID-19 in association with renin-angiotensin-aldosterone system inhibitors. *Pol Arch Intern Med*. 2022; 132: 16126.
- Bansal A, Kumar A, Patel D, et al. Meta-analysis comparing outcomes in patients with and without cardiac injury and coronavirus disease 2019 (COVID 19). *Am J Cardiol*. 2021; 141: 140-146.
- Belarte-Tornero LC, Valdivielso-Moré S, Elcano MV, et al. Prognostic implications of chronic heart failure and utility of NT-proBNP levels in heart failure patients with SARS-CoV-2 infection. *J Clin Med*. 2021; 10: 10020323.
- Zinellu A, Sotgia S, Carru C, Mangoni AA. B-Type natriuretic peptide concentrations, COVID-19 severity, and mortality: a systematic review and meta-analysis with meta-regression. *Front Cardiovasc Med*. 2021; 8: 690790.
- Qin J-J, Cheng X, Zhou F, et al. Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. *Hypertension*. 2020; 76: 1104-1112.

- 41 Metkus TS, Sokoll LJ, Barth AS, et al. Myocardial injury in severe COVID-19 compared with non-COVID-19 acute respiratory distress syndrome. *Circulation*. 2021; 143: 553-565. [↗](#)
- 42 Shi S, Qin M, Cai Y, et al. Characteristics and clinical significance of myocardial injury in patients with severe coronavirus disease 2019. *Eur Heart J*. 2020; 41: 2070-2079. [↗](#)
- 43 Kim J-S, Kim M, Kim Y-J, et al. Troponin testing for assessing sepsis-induced myocardial dysfunction in patients with septic shock. *J Clin Med*. 2019; 8: 8020239. [↗](#)
- 44 Moutchia J, Pokharel P, Kerri A, et al. Clinical laboratory parameters associated with severe or critical novel coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *PLoS One*. 2020; 15: e0239802. [↗](#)
- 45 Falco de R, Vargas M, Palma D, et al. B-Type natriuretic peptides and high-sensitive troponin I as COVID-19 survival factors: which one is the best performer? *J Clin Med*. 2021; 10: 10122726. [↗](#)