The Prognostic Value of Cardiac Biomarkers and Echocardiography in Critical COVID-19

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Abstract

Background Early risk stratification is crucial in critically ill COVID-19 patients. Myocardial injury is associated with worse outcome. This study aimed to evaluate cardiac biomarkers and echocardiographic findings in critically ill COVID-19 patients and to assess their association with 30-day mortality in comparison to other biomarkers, risk factors and clinical severity scores.

Methods Prospective, single-center, cohort study in patients with PCR-confirmed, critical COVID-19. Laboratory assessment included high sensitive troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) on admission to ICU: a hs-cTnT ≥ 14 pg/mL and a NT-proBNP ≥ 450 pg/mL were considered as elevated. Transthoracic echocardiographic evaluation was performed within the first 48 hours of ICU admission. The primary outcome was 30-day all-cause mortality. Predictive markers for mortality were assessed by ROC analysis and cut-off values by the Youden Index.

Results A total of 100 patients were included. The median age was 63.5 years, the population was predominantly male (66%). At the time of ICU admission, 47% of patients had elevated hs-cTnT and 39% had elevated NT-proBNP. Left ventricular ejection fraction was below 50% in 19.1%. Elevated cardiac biomarkers (hs-cTnT P-value < 0.001, NT-proBNP P-value = 0.001) and impaired left ventricular function (P-value 0.011) were significantly associated with mortality, while other biomarkers (D-dimers, ferritin, C-reactive protein) and clinical scores (SOFA) did not differ significantly between survivors and non-survivors. An optimal cut-off value to predict increased risk for 30-day all-cause mortality was 16.5 pg/mL for hs-cTnT (OR 8.5, 95% CI: 2.9, 25.0) and 415.5 pg/ml for NT-proBNP (OR 5.1, 95% CI: 1.8, 14.7).

Conclusion Myocardial injury in COVID-19 is common. Early detection of elevated hs-cTnT and NT-proBNP are predictive for 30-day mortality in patients with critical COVID-19. These markers outperform other routinely used biomarkers, as well as clinical indices of disease severity in ICU. The additive value of routine transthoracic echocardiography is disputable and should only be considered if it is likely to impact therapeutic management.

Background

Currently, SARS-CoV-2 has infected over 190 million people, resulting in more than 4 million registered deaths (1). Based upon the severity of illness, the National Institutes of Health (NIH) proposes five categories: asymptomatic, mild, moderate, severe and critical. The latter contains individuals with respiratory failure, septic shock, and/or multiple organ dysfunction requiring intensive care (2).

Myocardial injury is common in Coronavirus Disease 2019 (COVID-19). The prevalence of values above the upper reference limit (URL) for high sensitive troponin (hs-cTnT) in COVID-19 patients varies widely, ranging from 20% in cohorts of hospitalized patients to more than 50% in critically ill patients (3–6). Data about natriuretic peptides are more scarce, though up to 48% of critical COVID-19 patients present with elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) (7). Echocardiographic abnormalities are observed in up to half of all COVID-19 patients undergoing echocardiography (8–10).

Elevated cardiac biomarkers and echocardiographic abnormalities, especially reduced ventricular contractility, are associated with worse clinical outcome including mortality in COVID-19 patients (7, 10–15). As most of the published reports are retrospective studies, the current role of cardiac biomarkers and/or echocardiography in the prognostication of COVID-19 patients is still unclear. Different cardiac societies therefore have recommended against the routine use of these parameters for prognostic purposes (16, 17).

The purpose of this study was to prospectively evaluate the presence of elevated cardiac biomarkers and echocardiographic abnormalities in critical COVID-19 patients at the time of admission to the intensive care unit (ICU), to assess their association with 30-day all-cause mortality and to compare their prognostic performance to that of other biomarkers, risk scores and risk factors.

Methods

Study design, data collection and study outcome

This prospective, single-center, cohort study was carried out at the ICU of the Ghent University Hospital in Belgium, a 1.061-beds tertiary care center, between April 2020 and April 2021. The study was approved by the local ethical committee (BC-07568, April 1st, 2020). Inclusion criteria were: age 18 years or older, ICU admission, severe COVID-19 as diagnosed by real-time reverse-transcriptase polymerase chain reaction assays, and informed consent of the patient or legal representative. Patients were included within 48 hours after ICU admission. Patients were excluded when informed consent for this study was not obtained or when they were transferred from other ICUs of surrounding hospitals. Given the fact that COVID-19 is a new disease and the explorative character of the study, we decided to limit the number of included patients to a convenience sample of 100 patients.

Demographics, pre-existing comorbidities and clinical risk-scores and ratios (total and respiratory sequential organ failure assessment score (SOFA) and PaO2/FiO2-ratio (P/F ratio)) on admission were automatically abstracted from the electronic health record on the moment of admission. Laboratory assessment included hs-cTnT (Roche Diagnostics International Ltd.), NT-proBNP, C-reactive protein (CRP), ferritin and D-dimers. The first value upon admission was withheld when several blood samples were taken within one day. The cut-off for hs-cTnT was 14 pg/ml (corresponding with levels above the 99th percentile of a normal reference population) and for NT-proBNP 450 pg/mL.

During follow-up, the use of vasopressors, mechanical ventilation and/or venovenous extracorporeal membrane oxygenation was recorded. Transthoracic echocardiography was performed within the first 48 hours of inclusion, using a portable ultrasound machine CX50 (Philips Medical Systems, Andover, MA). The following parameters were evaluated: the global left ventricular (LV) function, left ventricular ejection fraction with eyeball-method (LVEF) (normal, midrange and reduced), LV end diastolic diameter (LVEDD), diastolic function (E/A ratio and E/e' septal), tricuspid annular plane systolic excursion (TAPSE), estimate systolic pulmonary arterial pressure (SPAP) using the maximal tricuspid regurgitation velocity with CW

Doppler, valvular function and presence of pericardial fluid. Diastolic function was dichotomized according to indices of diastolic dysfunction and increased left atrial pressure (E/A > 1.5 and/or E/e' septal > 14). Echocardiography was performed by six skilled sonographers, all images were stored in the Picture Archiving and Communication System (PACS) of the hospital. The primary outcome of the study was all-cause 30-day mortality.

Data analysis

The statistical analysis was performed using SPSS statistics (Version 27.0, IBM Corp, Armonk, NY). Normality of the distribution of continuous variables was tested by the Shapiro Wilk test. Categorical variables are shown as frequencies, and continuous variables as mean (standard deviation) or median (interquartile range) based upon normality of distribution. Comparison of categorical variables was performed using Chi-squared tests and for comparison of continuous variables Mann-Whitney U tests was used. Predictive markers for mortality were assessed by receiver operating characteristic (ROC) analysis and cut-off values by the Youden Index. The latter is a frequently used summary measure of the ROC curve. It represents the effectiveness of a diagnostic marker and enables the selection of an optimal threshold value (18). All tests were 2-sided with $P < 0.05$ considered statistically significant.

Results

Patient characteristics and outcomes

A total of 100 patients were included within 48 hours of ICU admission. Baseline characteristics are presented in Table 1. Median age was 63.5 years, and the population was predominantly male (66%). The mean body mass index (BMI) was 28.7 kg/m², 28% had type 2 diabetes mellitus and 42% was known with arterial hypertension. On admission the median total SOFA-score was 3.0, with a respiratory SOFA-score of 2.0. The median P/F-ratio on admission was 96.3 mmHg. The median length of stay in ICU was 10 days. Within the first 30 days after inclusion 21 patients died (21%). Non-survivors were significantly older and more often male. Respiratory SOFA, total SOFA and P/F ratio did not differ significantly between survivors and non-survivors.

Biomarkers

Biomarkers of inflammation (CRP, ferritin, D-dimer) did not differ significantly among survivors and non-survivors. Cardiac biomarkers were elevated in almost half of all included patients: hs-cTnT ≥ 14 pg/ml in 47%, and NT-proBNP ≥ 450 pg/ml in 39%. The level of these biomarkers was significantly higher in non-survivors (Table 2). Figure 1 shows a ROC-curve for all 5 biomarkers with their respective area under the curve (AUC). The biomarkers for inflammation were not associated with mortality, while the association of hs-cTnT (AUC: 0.79) and NT-proBNP (AUC: 0.71) was fair. Based on our data, we explored an optimal cut-off value for risk prediction for hs-cTnT and NT-proBNP. A value of 16.5 pg/ml for hs-cTnT corresponded with sensitivity and specificity for mortality of resp. 71.4 % and 48.6 %. The univariable odds ratio for 30-day all-cause mortality in patients with hs-cTnT ≥ 16.5 pg/ml was 8.5 (95% CI 2.9, 25.0).

For NT-proBNP, an optimal cut-off value of 415.5 pg/ml corresponded with sensitivity and specificity for mortality of resp. 71.4 % and 38.5 %. The univariable odds ratio for 30-day all-cause mortality in patients with NT-proBNP ≥ 415.5 pg/ml was 5.1 (95% CI 1.8, 14.7). Survival analysis curves are shown in Fig. 2. Unadjusted odds ratio's (OR) for 30-day all-cause mortality for cardiac biomarkers is in Fig. 3.

Echocardiography

Transthoracic echocardiography was not feasible in 11 patients (11%) due to poor visualization or prone ventilation. LVEF was reduced in 19.1% of patients (Table 1). LVEF was significantly lower in those who ultimately died (Table 2). Levels of hs-cTnT and NT-proBNP were elevated in up to respectively 38.9% and 34.7% of patients with normal LVEF. Right ventricular function, evaluated by TAPSE, was normal (> 14mm) in 94.8% of our cohort. After dichotomization between normal and abnormal TAPSE (≥ vs < 14 mm), patients with an abnormal RV function had higher mortality but this increase was not significant. There was no significant difference between survivors and non-survivors concerning diastolic function. The presence of moderate to severe valvular regurgitation (aortic, mitral, and tricuspid) or pericardial effusion did not differ significantly between the two groups. Unadjusted OR's for 30-day all-cause mortality for echocardiographic findings are shown in Fig. 3.

Discussion

This prospective study in critically ill COVID-19 patients has six important findings: (I) elevated levels of hs-cTnT and NT-proBNP upon admission are common and were found in respectively 47% and 39% of patients, (II) Elevated cardiac biomarkers are not necessarily linked to ventricular dysfunction as around 40% of patients with normal ejection fraction had either elevated levels of hs-cTnT and/or NT-proBNP, (III) Elevated levels of hs-cTnT, and to a lesser extent, NT-proBNP were associated with mortality, (IV) Serum levels of frequently used markers of inflammation (C-reactive protein, D-dimers and ferritin) and other clinical parameters of disease-severity (total SOFA, respiratory SOFA and P/F ratio) were not predictive for mortality, (V) Decreased LV function was associated with worse prognosis, whereas diastolic dysfunction and impaired RV function were not, (VI) cardiac ultrasound was not possible for various reasons in as much as 11% of this cohort of critical COVID-19 patients.

Whether cardiac biomarkers should be systematically measured as part of the workup for every hospitalized COVID-19 patient remains subject of debate. Currently, the European Society of Cardiology (ESC) and the American College of Cardiology (ACC) recommend against their routine use, while awaiting more evidence, as they warn for unnecessary diagnostic investigations, risk exposure and medical overuse (16, 17). Another reason to not currently recommend the routine use of cardiac biomarkers in prognostication is the belief that these markers would only be of limited incremental prognostic value to other markers of disease-severity (19), which is in contrast with the findings in our study and previous research. In an early report of 191 patients with COVID-19 in Wuhan, the univariable odds ratio for mortality when hs-cTnT was above the 99th percentile upper reference limit was 80.1 (95% CI, 10.3–620.4; P < 0.0001) regardless of underlying cardiovascular disease. This was higher than for all other biomarkers or scores tested, including D-dimers, ferritin and SOFA-score (20). Another study by Manocha

et al. showed that hs-cTnT was the only independent predictor of mortality among the same five biomarkers (i.e. CRP, ferritin, D-dimers, NT-proBNP and hs-cTnT), whereas Shi *et al.* found statistical significance for both hs-cTnT and NT-proBNP (21, 22). Our results are in line with these findings and support the statement of Sandoval *et al.* that the use of cardiac biomarkers for prognostic purposes may help in risk-stratification (23). We furthermore agree that this should not necessarily lead to unnecessary diagnostic testing when it is accompanied by clear education about the goals and implications of potentially elevated biomarkers (23).

We observed a reduced left and right ventricular function in respectively 17% and 5.2% of our patients. Previous large-scale research found similar results concerning reduced left ventricular function (20%), whereas right ventricular function was reduced in about 30% (10). Based on our data, reduced left ventricular systolic function was associated with mortality. However, right ventricular function, assessed with TAPSE, was not. Due to the low number of patients with reduced right ventricular contractility one should interpret this finding with caution. In previous research, left- and right ventricular function, analyzed with strain measurements, were both correlated with poor outcome (10, 14, 24). Diastolic dysfunction, based upon E/A and E/e' measurement, was not associated with higher odds for 30-day all-cause mortality. A prospective study of Szekely *et al.* showed similar results for E/A, though elevated E/e' in their cohort was associated with a higher hazard ratio for death. However, this result just narrowly met statistical significance (HR 1.08, 95% CI: 1.001, 1.2) (9). Overall, comparison of echocardiographic findings in COVID-19 subjects is difficult given the large heterogeneity in study populations and measurement approaches (24).

The fact that patients with elevated cardiac biomarkers did not necessarily have a reduced LVEF underlines the hypothesis that cardiac injury in COVID-19 may be due to a myriad of causes including direct myocardial injury of SARS-CoV-2 and indirect myocardial stress due to respiratory failure, thrombogenicity, sympathetic stimulation, cytokine release and endothelial dysfunction (19, 25, 26). As such, elevated cardiac biomarkers may represent disease severity in a more complete way than routine echocardiography. Moreover, routine echocardiography is not always possible in real-world practice due to practical (poor visualization and prone ventilation) or logistic problems, which limits its use even more. In the present cohort echocardiography was not feasible in about one tenth of patients. Furthermore, it exposes health care personnel to contagious risks and may be more time-consuming due to disinfection protocols. Taken together, the additive value of routine echocardiography on top of the measurement of cardiac biomarkers is questionable, even though reduced left ventricular function may predict worse outcome. This is in line with the ESC guidance, which currently recommends against performing echocardiography in COVID-19 patients, unless it is likely to alter the management strategy (16).

The current study has some important strengths. First, the study population was critically ill and prospectively evaluated, which contrasts with most studies evaluating all hospitalized patients retrospectively. Second, the combination of a prospective assessment of biomarkers and echocardiographic in the same study population is rather unique. To our knowledge, only two smaller similar series were previously published (27, 28). In these studies, LV dysfunction was common in

patients with elevated serum levels of hs-cTnT, though also present in 12% of patients without elevated levels of hs-cTnT (27, 28). However, possible relationships between the levels of cardiac biomarkers or echocardiographic findings and outcome parameters were not studied.

Five study limitations should also be addressed. First, no serial data of cardiac biomarkers was obtained, although this could be of interest as dynamic changes may add additive value in prognostication (23, 29). Second, extrapolation of these results should be done with caution as this was a single-center study in critical COVID-19 patients and criteria for admission to ICU may differ between hospitals. For instance, COVID-19 patients with mono-organ failure requiring high flow nasal cannula, as well as patients with established do-not-resuscitate orders were admitted to dedicated mid-care units and thus not included in the present study. Third, our study has a relatively small sample size and results must be validated in larger cohorts. Fourth, echocardiographic evaluation of LVEF was performed using eye-balling methodology and no strain-based measurements were obtained. Finally, the extent of preexisting cardiovascular disease was largely unknown and therefore no difference could be made between established cardiovascular disease and new COVID-19 induced cardiovascular abnormalities.

Conclusion

This study highlights the strong predictive value of the cardiac biomarkers hs-cTnT and NT-proBNP taken upon ICU admission in critically ill COVID-19 patients. They outperform other routinely used biomarkers, as well as clinical indices of disease severity in ICU in this specific cohort. Transthoracic echocardiography has several limitations and should therefore only be considered if it is likely to impact therapeutic management.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethical committee (BC-07568, April 1st, 2020).

Consent for publication

Informed consent of every patient or the legal representative was obtained prior to inclusion.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

N/A

Funding

N/A

Authors' contributions

HS, SG and EH conceived the principal idea. BZ, SD, HS and SG performed the echocardiography. BZ and SD were major contributors in data analysis and writing the manuscript. EH was prime investigator of the project and was a major contributor in the data analysis. HS, SG and EH critically revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1

Baseline demographics, disease severity, laboratory assessments and echocardiographic parameters of patients on admission to the intensive care unit.

Demographics (n = 100)	
Age (y)	63.5 (IQR 57.0–71.0)
Gender	
Male	66 (66.0 %)
Female	34 (34.0 %)
BMI (kg/m²)	28.7 (IQR 25.1–33.6)
Diabetes mellitus	28 (28.0 %)
Arterial hypertension	42 (42.0 %)
Severity of illness (n = 100)	
Total SOFA-score on admission	3.0 (IQR 2.0–8.0)
Respiratory SOFA-score on admission	2.0 (IQR 2.0–3.0)
P/F ratio (IQR) on admission	96.3 (IQR 71.6–124.7)
Use of vasopressors during admission	54 (54.0 %)
Use of mechanical ventilation during admission	60 (60.0 %)
Use of vv-ECMO during admission	7 (7.0 %)
Inflammatory markers at time of inclusion (n = 100)	
CRP (mg/L)	136.5 (IQR 67.0–201.3)
D-dimers (ng/mL)	1020.0 (IQR 660.0–1795.0)
Ferritin (µg/L)	1139.0 (IQR 640.8–2346.8)
Cardiac biomarkers at time of inclusion (n = 100)	
hs-cTnT (µg/L)	
≥ 14 µg/L	47 (47.0 %)
< 14 µg/L	53 (53.0 %)
NT-proBNP (pg/mL)	
≥ 450 pg/mL	39 (39.0 %)
< 450 pg/mL	61 (61.0 %)
Echocardiography parameters at time of inclusion	
LVEF (%) (n = 89)	
Normal (> 50%)	72 (80.9 %)

Demographics (n = 100)	
Midrange (40–50%)	16 (18.0 %)
Reduced (< 40%)	1 (1.1 %)
LVEDD (mm) (n = 83)	46.0 (IQR 43.0–51.0)
Diastolic function	
E/A (n = 79)	
< 1.5	85 (85.0 %)
≥ 1.5	15 (15.0 %)
E/e' septal (n = 72)	
< 14	60 (83.3 %)
≥ 14	12 (16.7 %)
Right ventricular function	
TAPSE > 14mm (n = 77)	73 (94.8 %)
Pulmonary artery pressure (mmHg) (n = 51)	24.0 (IQR 15.0–31.0)
Moderate to severe valvular dysfunction (n = 87)	7 (8.0 %)
Pericardial effusion (n = 89)	4.5 (4.5 %)

BMI: body mass index. vv-ECMO: venovenous extracorporeal membrane oxygenation. SOFA: Sequential Organ Failure Assessment. CRP: c-reactive protein. NT-proBNP: N-terminal pro-brain natriuretic peptide. hs-cTnT: high sensitive troponin T. LVEDD: left ventricular end diastolic diameter. DT: deceleration time. TAPSE: tricuspid annular plane systolic excursion. LVEF: left ventricular ejection fraction. MR: mitral regurgitation. AR: aortic regurgitation. TR: tricuspid regurgitation. ICU: intensive care unit.

Table 2

Distribution of baseline demographics, disease severity, laboratory assessments and echocardiographic parameters of patients between survivors and non-survivors.

	Survivors (n = 79)	Non-survivors (n = 21)	P-value
Demographics			
Age (y)	61.0 (IQR 52.0–71.0)	69.0 (IQR 66.5–72.0)	0.008
Gender			
Male	48 (60.8 %)	18 (85.7 %)	0.032
Female	31 (39.2 %)	3 (14.3 %)	
BMI (kg/m²)	28.9 (IQR 25.7–33.9)	25.8 (IQR 22.4–31.4)	0.034
Diabetes mellitus	22 (27.8 %)	6 (28.6 %)	0.948
Arterial hypertension	33 (41.8 %)	9 (42.9 %)	0.929
Length of stay ICU (d)	10.0 (IQR 5.0–16.0)	15.0 (IQR 6.5–24.0)	0.085
Severity of illness at time of inclusion			
Use of vasopressors	36 (45.6 %)	18 (85.7 %)	0.001
Use of mechanical ventilation	42 (53.2 %)	18 (85.7 %)	0.007
Use of vv-ECMO	4 (5.1 %)	3 (14.3 %)	0.141
Total SOFA-score	3.0 (IQR 2.0–8.0)	4.0 (IQR 2.0–11.5)	0.342
Respiratory SOFA-score	2.0 (IQR 2.0–3.0)	2.0 (IQR 2.0–3.0)	0.784
P/F ratio (IQR)	96.3 (IQR 70.2–120.6)	92.9 (IQR 74.5–153.5)	0.375
Inflammatory markers at time of inclusion			
CRP (mg/L)	137.1 (IQR 69.0–208.0)	125.5 (IQR 56.5–200.5)	0.496
D-dimers (ng/mL)	1025.0 (IQR 640.0–1740.0)	965.0 (IQR 625.0–2885.0)	0.912
Ferritin (µg/L)	1079.0 (IQR 661.0–2271.0)	1492.0 (IQR 603.0–3072.0)	0.469
Cardiac biomarkers at time of inclusion			
hs-cTnT (µg/L)			
≥ 16.5 µg/L	18 (22.8 %)	15 (71.4 %)	< 0.001
< 16.5 µg/L	61 (77.2 %)	6 (28.6 %)	
NT-proBNP (pg/mL)			

	Survivors (n = 79)	Non-survivors (n = 21)	P-value
≥ 415.5 pg/mL	26 (32.9 %)	15 (71.4 %)	0.001
< 415.5 pg/mL	53 (67.1 %)	6 (28.6 %)	
Echocardiography parameters at time of inclusion			
LVEF (%)			
Normal (> 50%)	62 (86.1 %)	10 (58.8 %)	0.011
Midrange (40–50%)	10 (13.9 %)	6 (35.3 %)	
Reduced (< 40%)	0 (0.0 %)	1 (5.9 %)	
LVEDD (mm)	47.0 (IQR 43.0–51.0)	46.0 (IQR 40.0–54.0)	1.000
Diastolic function			
E/A			
< 1.5	55 (83.3 %)	12 (92.3 %)	0.410
≥ 1.5	11 (16.7 %)	1 (7.7 %)	
E/e' septal			
< 14	52 (86.7 %)	8 (66.7 %)	0.090
≥ 14	8 (13.3 %)	4 (33.3 %)	
Right ventricular function			
TAPSE > 14mm	62 (96.9 %)	11 (84.6 %)	0.069
Pulmonary artery pressure (mmHg)	22.0 (IQR 11.8–30.0)	29.0 (IQR 26.0–37.0)	0.043
Moderate to severe valvular dysfunction	4 (5.6 %)	3 (18.8 %)	0.081
Pericardial effusion	3 (4.2 %)	1 (5.9 %)	0.759

BMI: body mass index. vv-ECMO: venovenous extracorporeal membrane oxygenation. SOFA: Sequential Organ Failure Assessment. CRP: c-reactive protein. NT-proBNP: N-terminal pro-brain natriuretic peptide. hs-cTnT: high sensitive troponin T. LVEDD: left ventricular end diastolic diameter. TAPSE: tricuspid annular plane systolic excursion. LVEF: left ventricular ejection fraction. MR: mitral regurgitation. AR: aortic regurgitation. TR: tricuspid regurgitation. ICU: intensive care unit.

Figures

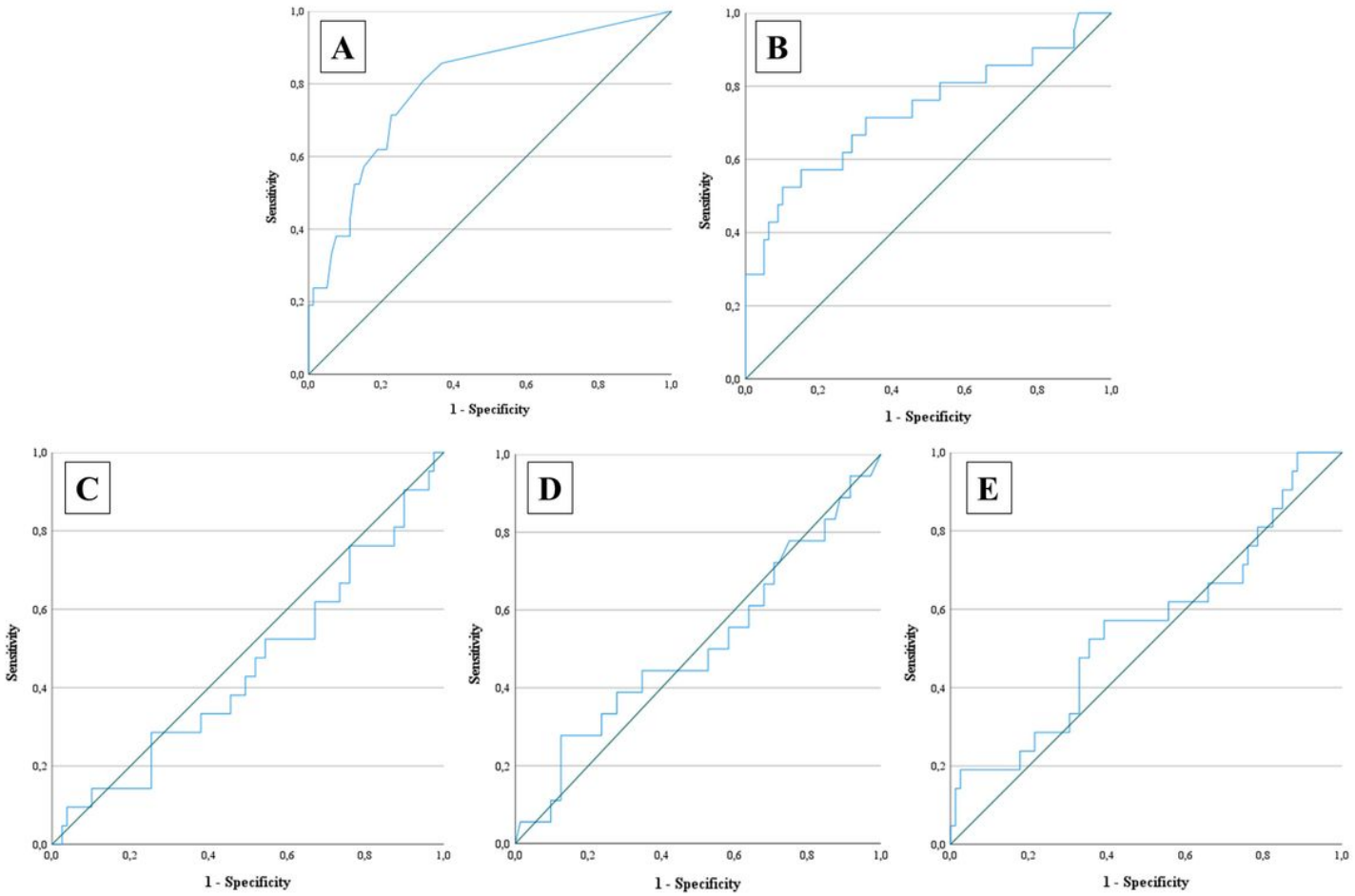

Figure 1

Receiver operating characteristic curve Receiver operating characteristic (ROC) curves for five biochemical markers: high-sensitive troponin T (panel A), N-terminal pro-brain natriuretic peptide (panel B), C-reactive protein (panel C), D-dimers (panel D) and ferritin (panel E). hs-cTnT: high-sensitive troponin T. NT-proBNP: N-terminal pro-brain natriuretic peptide. Area under the curve (AUC) 95% confidence interval P-value hs-cTnT 0.797 0.687 – 0.907 < 0.001 NT-proBNP 0.732 0.594 – 0.870 0.001 CRP 0.451 0.309 – 0.594 0.496 D-dimers 0.508 0.349 – 0.668 0.912 Ferritin 0.552 0.406 – 0.697 0.469

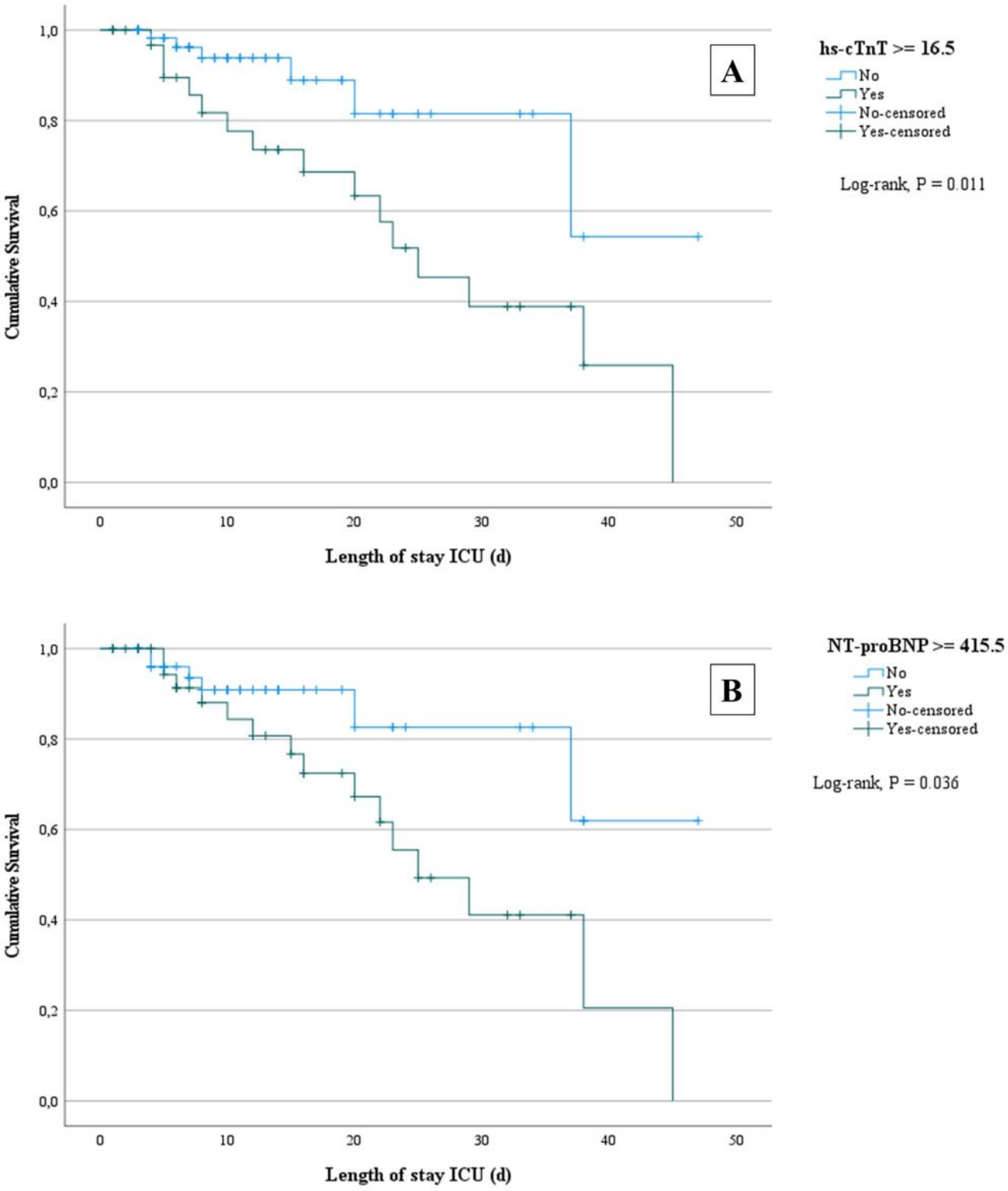

Figure 2

Survival analysis based upon the level of hs-cTnT and NT-proBNP on admission to ICU Survival analysis based upon both levels of high sensitive troponin T (panel A) and N-terminal pro-brain natriuretic peptide (panel B) on admission to ICU. hs-cTnT: high-sensitive troponin T. NT-proBNP: N-terminal pro-brain natriuretic peptide.

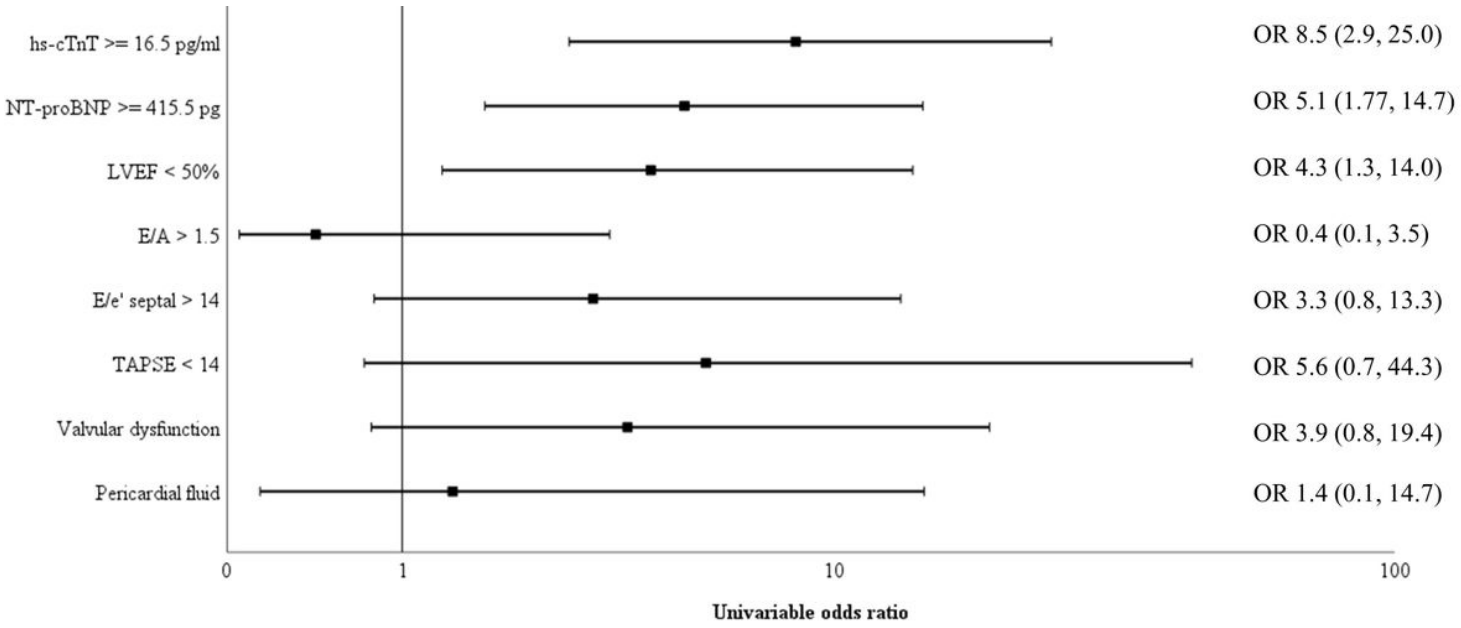

Figure 3

Univariable odds ratio for 30-day all-cause mortality Univariable odds ratio for 30-day all-cause mortality for cardiac biomarkers hs-cTnT and NT-proBNP as well as several echocardiographic measurements (reduced left ventricular ejection fraction (LVEF), increased E/e', increased E/A, decreased tricuspid annular plane systolic excursion (TAPSE), valvular dysfunction and pericardial fluid). Both elevated cardiac biomarkers above their respective cut-off value and a reduced LVEF had a significant higher odds ratios for 30-day all-cause mortality. NT-proBNP: N-terminal pro-brain natriuretic peptide. hs-cTnT: high sensitive troponin T. TAPSE: tricuspid annular plane systolic excursion. LVEF: left ventricular ejection fraction. OR: odds ratio.