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Biomarkers for prediction of mortality in left-sided infective endocarditis

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ABSTRACT

Background: Evidence regarding biomarkers for risk prediction in patients with infective endocarditis (IE) is limited. We aimed to investigate the value of a panel of biomarkers for the prediction of in-hospital mortality in patients with IE.

Methods: Between 2016 and 2018, consecutive IE patients admitted to the emergency department were prospectively included. Blood concentrations of nine biomarkers were measured at admission (D0) and on the seventh day (D7) of antibiotic therapy: C-reactive protein (CRP), sensitive troponin I (s-cTnI), procalcitonin, B-type natriuretic peptide (BNP), neutrophil gelatinase-associated lipocalin (NGAL), interleukin 6 (IL6), tumor necrosis fator α (TNF-α), proadrenomedullin, alpha-1-acid glycoprotein, and galectin 3. The primary endpoint was in-hospital mortality.

Results: Among 97 patients, 56% underwent cardiac surgery, and in-hospital mortality was 27%. At admission, six biomarkers were independent predictors of in-hospital mortality: s-cTnI (OR 3.4; 95%CI 1.8-6.4; $P < 0.001$), BNP (OR 2.7; 95%CI 1.4-5.1; $P = 0.002$), IL-6 (OR 2.06; 95%CI 1.3-3.7; $P = 0.019$), procalcitonin (OR 1.9; 95%CI 1.1-3.2; $P = 0.018$), TNF-α (OR 1.8; 95%CI 1.1-2.9; $P = 0.019$), and CRP (OR 1.8; 95%CI 1.0-3.3; $P = 0.037$). At admission, S-cTnI provided the highest accuracy for predicting mortality (area under the ROC curve: s-cTnI 0.812, BNP 0.727, IL-6 0.734, procalcitonin 0.684, TNF-α 0.675, CRP 0.670). After 7 days of antibiotic therapy, BNP and inflammatory biomarkers improved their performance (s-cTnI 0.814, BNP 0.823, IL-6 0.695, procalcitonin 0.802, TNF-α 0.554, CRP 0.759).

Conclusion: S-cTnI concentration measured at admission had the highest accuracy for mortality prediction in patients with IE.

Introduction

Worldwide, the clinical and microbiological profile of infective endocarditis (IE) is evolving over the last decades, probably due to a higher number of patients at risk (degenerative valve disease, immunosuppression therapy, hemodialysis) and, to the higher number of invasive valve procedures [1,2]. Despite the improvements in clinical and surgical treatments, mortality is still high. Moreover, early risk stratification is still a major unmet clinical need. [2,3].

Pilot studies have suggested that biomarkers including B-type natriuretic peptide (BNP) may have clinical utility in this setting [4–9]. Biomarkers are useful for the diagnosis of and prognosis in several clinical conditions, including heart failure and sepsis, which are known complications in patients with IE. However,

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direct comparisons between different biomarkers and data on serial measurements during hospitalization are lacking. Therefore, we aimed to investigate the value of a panel of heart failure and sepsis biomarkers at admission and after 7 days of treatment, for evaluation of in-hospital mortality in patients with IE.

Methods

Study Population

In this prospective observational cohort study, we included consecutive patients with suspected left-sided IE admitted to the Heart Institute (InCor), University of São Paulo Medical School, Brazil, between 2016 and 2018. Study investigators performed daily active surveillance at the hospital to include consecutive cases.

Inclusion criteria were age > 18 years, suspected left-sided IE, and signature of informed consent. Suspected left-sided IE was defined as the presence of at least one of the following criteria: 1) Presence of risk factors for IE (mitral valve prolapse, chronic rheumatic valve disease, degenerative valve disease, valve prosthesis, congenital heart disease, history of previous IE, intravenous drug use) and fever > 37.8 °C or clinical suspicion of systemic emboli or acute heart failure due to valve dysfunction; OR 2) patients with fever > 37.8 °C and cardiac murmur or clinical suspicion of systemic emboli and no other foci for infection.

Exclusion criteria were patients who were classified as "rejected" IE, according to the Modified Duke Criteria [10] at discharge or death or use of intravenous antibiotics aimed at the IE etiology for more than 3 days before enrollment.

The ethics committee of Heart Institute (InCor) approved the study (approval number 4174150001) and all patients signed the written informed consent term.

Clinical assessment

Patients were systematically screened with blood cultures (Bactec, Becton Dickson, Heidelberg, Germany) and echocardiography. The indication for further diagnostic procedures, antibiotic treatment, and cardiac surgery were at the discretion of the treating physician, following the recommendations of the current IE guidelines [11].

Biomarker measurements

Blood samples for the determination of biomarkers were collected at inclusion (D0: when empirical or specific intravenous antibiotic for IE was started) and on the seventh day (D7) of intravenous antibiotic therapy for IE (specific or empirical treatment). After blood collection, one aliquot of the blood sample was immediately processed, from which C-reactive protein (CRP) was measured (Dimension RXL, Siemens Healthcare, Newark, USA).

Sensitive cardiac troponin I (s-cTnI, Siemens Ultra, Advia Centaur Immunoassay system, Siemens Healthcare Diagnostics, Terrytown, NY, USA), procalcitonin (VIDAS® B.R.A.H.M.S PCT™. bioMérieux, Marcy l'Etoile, France), B-type natriuretic peptide (BNP, Advia Centaur CP Immunoassay System, Siemens Diagnostics, Terrytown, NY,USA), neutrophil gelatinase-associated lipocalin (NGAL; Fine Test, Wuhan, China), interleukin 6 (IL-6; Fine Test, Wuhan, China), Tumor Necrosis Factor alpha (TNF alpha; Fine Test, Wuhan, China), proadrenomedullin (Fine Test, Wuhan, China), alpha-1-acid glycoprotein (Cobas 8000 c702, Roche-Hitachi, Switzerland), and galectin 3 (IBL, Hamburg, Germany) were measured from serum/plasma aliquots which was kept frozen at −80 °C until the day of the test.

Blood samples were collected at admission (D0) in all patients with suspected endocarditis. In patients who underwent cardiac surgery before the seventh day of antibiotics, the D7 blood sample was not performed.

Clinical endpoint

The primary endpoint was in-hospital death. All patients were followed until hospital discharge.

Statistical analysis

Categorical variables are presented as absolute values and percentages and were compared by using the Fisher exact test. Continuous variables are presented as medians and interquartile range (IQR) and were compared by using the Mann-Whitney-U test. All biomarkers had non-normal distribution and were log-transformed and standardized for the univariate and multivariate logistic regression models. We performed a multivariable logistic regression analysis for each biomarker adjusted for predefined covariables known to be associated with in-hospital mortality in IE patients (age, diabetes mellitus, heart failure NYHA III/IV at admission, and *S. aureus* infection) [2,8,11–14]. Moreover, since the overall number of events was small, we performed a sensitivity analysis of the multivariable model using dimension reduction of the covariates with principal component analysis and included only two dimensions (two variables) for each of the biomarkers, which is presented in a supplementary analysis.

Receiver operating characteristic curves (ROC) were constructed to assess the accuracy of each biomarker for prediction of the primary endpoint and compared using the de Long method. Based on the ROC curves, sensitivity and specificity of the median for each biomarker was calculated.

Additionally, accuracy of biomarkers for mortality prediction measured by the ROC curves were also performed in patients classified as IE "rejected".

The analyses were performed using Stata 11.0 (StataCorp, College Station, Texas, USA) and SPSS18.

Results

From 175 patients enrolled, 78 were excluded because of rejected IE according to the Duke criteria. Among the 97 patients included in the analysis, 84 (87%) were classified as "definite" and 13 (13%) as "possible" IE according to the modified Duke criteria at discharge/death. Blood was obtained for all 97 patients on D0, and for 74 patients on D7. Reasons for not obtaining additional blood sample at D7 were early death (6 patients), valve surgery before day 7 (15 patients), and patient refusal (2 patients). (**Supplement** Fig. 1).

Clinical and epidemiologic characteristics of the 97 patients included are shown in Table 1. The mean duration of hospital stay was 39 days (interquartile range 24 - 50 days) and the overall mortality was 27%. The univariate and multivariate analysis of biomarkers at D0 and in-hospital death are shown in Table 2. S-cTnI (OR 2.94; 95%CI 1.53-5.66; $P < 0.001$), BNP (OR 2.32; 95%CI 1.6-4.63; $P = 0.017$), and TNF-α (OR 1.82; 95%CI 1.07-3.09; $P = 0.026$) obtained at D0 were independently associated with in-hospital death. An additional multivariate analysis for in-hospital death at D0 using a principal component analysis is shown at Supplemental material (**Supplement** Table 1). Univariate analysis for all biomarkers at seventh day of antibiotic therapy (D7) reveled that s-cTnI (OR 3.16; 95%CI 1.57-6.36; $P < 0.001$), BNP (OR 3.25; 95%CI 1.36-7.76; $P = 0.008$), procalcitonin (OR 3.29; 95%CI 1.52-7.12; $P = 0.002$), CRP (OR 2.99; 95%CI 1.38-6.47; $P = 0.005$) and galectin-3

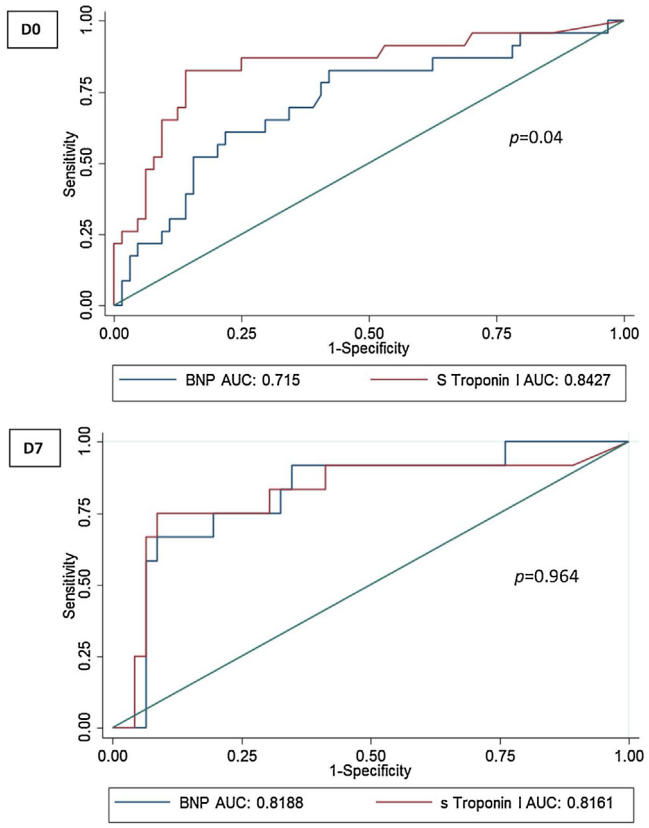

Fig. 1. Accuracy of BNP and s-Troponin I for prediction of mortality, quantified by areas under the ROC curve (AUC) at first (D0) and seventh day (D7) of therapy.

(OR 2.23; 95%CI 1.07-4.26; $P = 0.031$) were associated with in-hospital death (**Supplement** Table 2).

ROC curves at D0 and D7 for the biomarkers related to mortality are shown in Table 3. S-cTnI had the best accuracy for the prediction of in hospital mortality at D0, with an AUC 0.812 (95%CI 70-0.92), followed by IL-6 (AUC 0.734; CI95% 0.63-0.84) and BNP (AUC 0.727; CI95% 0.60-0.85). After seven days of antibiotic therapy, s-cTnI (AUC 0.814; CI95% 0.67-0.96), BNP (AUC 0.823; CI 95% 0.69-0.96), procalcitonin (AUC 0.802; CI95% 0.63-0.98) and CRP (AUC 0.759; CI95% 0.62-0.90) had good accuracy for prediction of death.

A comparative ROC curve for S-cTnI and BNP to predict in-hospital mortality reveled that S-cTnI was superior at D0 (Fig. 1).

Patients with rejected endocarditis

Patients with rejected endocarditis had overall mortality of 27% (21/78, Supplemental material Table 3). Heart failure NYHA III/IV at admission was present in 65% (51/78) of patients. The final diagnosis most frequently found were: other site of bacterial infection in 57% (pulmonary 27%, soft tissue 4%, urinary tract 4% and others sites 22%), heart failure without active infections 36% and viral infections in 10%. The ROC curves analyze of biomarkers in these patients showed that s-cTnI was the best predictor for in-hospital mortality: s-cTnI AUC 0.701 (95%CI 0.55-0.85), BNP AUC 0.698 (CI95% 0.57-0.82), IL-6 AUC 0.63 (CI95% 0.47-0.78), procalcitonin AUC 0.763 (CI95% 0.65-0.87), CRP 0.619 (CI95% 0.48-0.75) and TNF alpha AUC 0.48 (CI95% 0.34-0.61).

Discussion

The present study compares the accuracy of a pool of biomarkers for early prediction of in-hospital mortality in patients with IE. Biomarkers that indicate cardiomyocyte injury and hemodynamic cardiac stress (s-cTnI and BNP) were the most accurate for predicting mortality at admission and after 7 days of antibiotic treatment. Additionally, biomarkers that indicate uncontrolled infection, such as procalcitonin and CRP, were more accurate on after 7 days of antibiotic therapy.

Although cardiac troponins are traditionally used to diagnose myocardial infarction, [15] studies using high-sensitivity cardiac troponin assays demonstrated that it has prognostic value in several clinical conditions, such as heart failure, valve disease, sepsis, septic shock, non-cardiac surgery, and even in primary prevention patients [16–18]. Patients with IE constitute a particular population, because they may have a combination of such conditions. Though the mechanism leading to elevated s-cTnI in sepsis is still unclear,its release might be caused by an imbalance between oxygen supply and demand in patients with coronary artery disease caused by hemodynamic instability, tachycardia, and anemia, or the result of cytokine-mediated cardiac cell injury with transient loss of membrane integrity, leading to s-cTnI release [18]. Few studies have evaluated the role of troponin as an early prognostic biomarker in IE patients, suggesting that troponin may be related to worse prognosis [19–26]. However, due to the small sample size of previous studies, it was not possible to establish if troponin was an independent predictor of mortality. In the largest study [19], s-cTnI was prospectively studied in 62 patients with IE, and high levels were associated with in-hospital death. In the present study, we have expanded prior knowledge by demonstrating that s-cTnI is an independent predictor of mortality in patients with IE.

Pilot studies with other cardiac biomarkers of hemodynamic stress, have shown that BNP and NT-pro BNP obtained at admission in patients with IE are independently related to in-hospital and long-term mortality [20,24,27,28]. The present study confirms these findings and further demonstrates that BNP obtained on the seventh day of antibiotic therapy is also related to in-hospital mortality. Galactin-3, on the other hand, has not been previously studied in IE patients. Although galectin-3 is a prognostic biomarker in patients with heart failure [29], it was not associated with prognosis in our study. MR-Pro-adrenomedullin plays a role as a prognostic marker in both sepsis and heart failure [30–33]. Surprisingly, in the present study, its accuracy for prognosis was inferior to that of other biomarkers and was also not related to mortality.

Among inflammatory biomarkers, the biomarkers with the better accuracy were CRP, procalcitonin, and Il-6. CRP is one of the most-available and most-used biomarkers in clinical practice, and several studies have accessed its utility for prognosis in patients with IE [5,7,34–36]. At least 3 studies have found that a high level of CRP measured at hospital admission was independently associated with in-hospital death [5,35,37]. Additionally, Verhagen et al [7] studied the prognostic value of serial CRP measurements in 123 patients with IE for a combined end point defined as death or serious infectious complications, and they found AUC of 0.63 and 0.70 at baseline and on the seventh day after the start of antibiotics, respectively. These findings are in line with our results, highlighting that the persistence of high levels of CRP after adequate antibiotic therapy is related to a worse prognosis, and a more useful marker than early measurements of CRP.

One study evaluated procalcitonin levels at admission as a prognostic biomarker in patients with IE [4]. The authors included 50 patients in a retrospective study and found that procalcitonin levels had significantly higher discrimination than CRP for the prediction of a combination of death or serious complications due to IE. In our study, in-hospital death was used as a single end point, and we did not find an association with procalcitonin levels at admission. Few studies have been dedicated to analyzing IL-6

Table 1
Baseline characteristics and outcome of the patients.

Characteristic	All Patients (n = 97)	Discharge Alive (n = 71)	In-hospital Death (n = 26)	*P* value X^2
Baseline characteristics				
Age (median; years)	58	57	59	0.887
Male sex, n (%)	61 (63)	42 (59)	19 (73)	0.209
Comorbidities				
Chronic rheumatic valve disease, n (%)	30 (31)	25 (35)	5 (19)	0.131
Degenerative valve disease, n (%)	24 (25)	16 (22)	8 (31)	0.405
Mitral valve prolapse, n (%)	10 (10)	8 (11)	2 (7)	0.608
Congenital heart disease, n (%)	8 (8)	6 (8)	2 (8)	0.904
Prosthetic cardiac valves, n (%)	53 (55)	43 (61)	10 (39)	0.067
Hypertension, n (%)	49 (50)	36 (51)	12 (50)	0.951
Diabetes mellitus, n (%)	13 (13)	9 (13)	4 (15)	0.729
Chronic heart failure, n (%)	26 (27)	20 (28)	6 (26)	0.616
Clinical presentation				
	22	22	29	0.362
Duration of symptoms, median (days)				
History of fever, n (%)	78 (80)	60 (84)	18 (69)	0.093
Heart failure NYHA III/IV at admission, n (%)	35 (36)	24 (34)	11 (42)	0.440
Laboratory median (IQR)				
Hemoglobin g/dL	11.0 (9.5-12.4)	11.0 (9.6-12.4)	10.2 (8.7-12.1)	0.176
Creatinine mg/dL	1.19 (0.95-1.67)	1.03 (0.9-1.5)	1.53 (1.28-4.34)	0.001
Biomarkers median (IQR)				
Sensitive cardiac troponin I ng/L	59 (24-230)	45 (014-114)	629 (135-3910)	<0.001
Proadrenomedullin pmol/L	11.2 (4.9-17.6)	11.2 (3.5-15.7)	12.4 (5.9-27.3)	0.067
C-reactive protein mg/L	91 (54-157)	78 (50-140)	130 (72-206)	0.011
Tumor necrosis factor-α pg/mL	1 (1-45)	1 (1-20)	36 (1-283)	0.005
Interleukin 6 pg/mL	8.3 (1.9-26.8)	6.0 (0.7-17.1)	25.3 (7.9-40.7)	<0.001
Procalcitonin ng/mL	0.35 (0.16-1.31)	0.28 (0.15-0.68)	1.13 (0.27-4.83)	0.007
B-type natriuretic peptide pg/mL	328 (153-806)	237 (139-546)	829 (354-1194)	0.001
Neutrophil gelatinase-associated lipocalin ng/mL	2.0 (1.17-3.30)	1.9 (1.15-3.0)	2.25 (1.18-3.73)	0.329
Alpha-1-acid glycoprotein mg/dL	201 (170-240)	195 (169-233)	233 (190-246)	0.132
Galectin-3 ng/mL	20 (15-27)	20 (14-25)	20 (16-36)	0.175
Etiology				
Streptococcus spp. n (%)	38 (39)	31 (44)	7 (27)	0.135
S. aureus, n (%)	12 (12)	3 (4)	9 (35)	<0.001*
Enterococcus spp., n (%)	9 (9)	4 (6)	5 (19)	0.055*
Culture negative, n (%)	21 (22)	18 (25)	3 (12)	0.145
Echocardiography*				
	60 (62)	42 (59)	18 (69)	0.366
Valve dysfunction moderate to severe, n (%)				
Vegetation length ≥10 mm, n (%)	32 (33)	21 (30)	11 (42)	0.238
Perivalvar cardiac abscess, n (%)	12 (12)	8 (11)	4 (15)	0.602
Complications, n (%)				
	30 (31)	17 (24)	13 (50)	0.100
Systemic emboli, n (%)				
Valve surgery, n (%)	54 (56)	40 (56)	14 (54)	0.827

N = number; IQR = interquartile range; mm = millimeter; * 73% transesophageal echocardiography

Table 2
Biomarkers at inclusion (D0) and in-hospital mortality. Univariate and multivariate analysis

Biomarker	Univariate analysis				Multivariate analysis[a]			
	OR	95% CI		*P*	OR	95% CI		*P*
Sensitive cardiac troponin I	3.69	2.01	6.78	<0.001	2.94	1.53	5.66	<0.001
Proadrenomedullin	1.64	0.98	2.74	0.062	1.51	0.85	2.68	0.162
C-reactive protein	2.02	1.15	3.54	0.014	1.44	0.78	2.65	0.245
Tumor necrosis factor-α	1.94	1.22	3.07	0.005	1.82	1.07	3.09	0.026
Interleukin 6	2.23	1.23	4.03	0.008	1.84	0.95	3.55	0.070
Procalcitonin	2.01	1.23	3.30	0.005	1.46	0.81	2.64	0.204
B-type natriuretic peptide	2.40	1.34	4.33	0.003	2.32	1.16	4.63	0.017
Neutrophil gelatinase-associated lipocalin	1.18	0.75	1.86	0.468	1.18	0.70	1.99	0.532
Alpha-1-acid glycoprotein	1.86	0.67	5.18	0.233	1.24	0.41	3.79	0.703
Galectin-3	1.44	0.86	2.40	0.165	1.51	0.84	2.72	0.165

[a] Adjusted by age, diabetes mellitus, heart failure NYHA III/IV at admission, and *S. aureus* infection.

Table 3
Biomarkers accuracy to predict in-hospital mortality at admission and after 7 days of therapy in patients with endocarditis

Biomarker	At admission (n = 97) AUC (95%CI)	Sensitivity	Specificity	After 7 days of antibiotics (n = 74) AUC (95%CI)
Sensitive cardiac troponin I	0.812 (0.70-0.92)	80%	62%	0.814* (0.67-0.96)
B-type natriuretic peptide	0.727 (0.60-0.85)	79%	61%	0.823& (0.69-0.96)
Interleukin 6	0.734 (0.63-0.84)	69%	58%	0.695# (0.54-0.84)
Procalcitonin	0.684 (0.55-0.82)	66%	60%	0.802# (0.63-0.98)
Tumor necrosis factor-α	0.675 (0.55-0.80)	65%	38%	0.554# (0.40-0.71)
C-reactive protein	0.670 (0.55-0.79)	70%	44%	0.759 (0.62-0.90)

* N = 64.
& N = 60.
# n = 57.

levels in IE patients [38–40]. They describe higher levels of this cytokine at admission and its reduction during antibiotic therapy, but without a prognostic evaluation. In the present study, we show that IL-6 levels at admission were independently related to mortality. TNF- α is a proinflammatory cytokine that has increased expression in patients with septic syndrome or IE [41,42]. Also α-1-glycoprotein and NGAL, a novel biomarker of acute kidney injury, has been described with the potential for prognosis of septic patients [43–45], but in the present study these biomarkers showed a less effective discriminatory value than the other biomarkers to predict in-hospital death in IE patients.

In patients with rejected endocarditis, s-cTnI, BNP and procalcitonin had good accuracy for mortality prediction. That is in line with current literature showing that these biomarkers have prognostic impact in patients with acute heart failure and sepsis, which were the final diagnosis in this group of patients [46–50]. Therefore, our findings are not specific for endocarditis patients.

Clinical implications

The most common life-threatening complications of IE are heart failure, sepsis and embolization. Some patients with IE have overt heart failure at admission and clearly need urgent cardiac surgery. However, in most cases, heart failure presents as an indolent disease, and the measurement of BNP and s-cTnI could help in the early identification of these patients, who could benefit of early cardiac surgery. Furthermore, implementation of admission measurements of s-cTnI and BNP in patients with IE could be useful for identifying the patients at a high risk of death and improve treatment decisions, such as early transfer to a referral center that performs cardiac surgery. Additionally, maintenance of high levels of inflammatory biomarkers after 7 days of antibiotic therapy predicts death and complications during hospital-stay. Therefore, measuring CRP or procalcitonin on the seventh day of treatment seems to be a reasonable approach to monitor treatment in these patients, because the delay in reducing inflammatory biomarker levels by antibiotic therapy predicts mortality more accurately than the baseline levels do.

Limitations

This study had some limitations. First, it is a single-center study in a cardiac referral hospital. Therefore, biomarkers could perform differently in a population with a lower prevalence of previous valve disease and comorbidities. The primary endpoint was in-hospital death, without long-term follow-up, but this limitation was mitigated by the high in-hospital mortality in endocarditis patients. As the sample size is relatively small, it was not possible to perform a broader adjustment for confounding or to test the interaction or complementary role of combining biomarkers.

Conclusion

In addition to established clinical and routine laboratory variables, s-cTnI concentration measured at admission showed high accuracy for mortality prediction in patients with IE. CRP and procalcitonin additional measurements on the seventh day of therapy may be useful to identify the patients not responding to treatment.

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Conflict of interest

All author declares that they have no conflict if interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.03.009.

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