Prognostic Value of Cardiac and Noncardiac Biomarkers in Infective Endocarditis: A Prospective Cross-sectional Study

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Abstract

Background and Aims: Infective endocarditis (IE) is associated with several morbidities and high rate of mortality. Predicting these morbidities can be helpful in managing patients and can prevent possible complications, result from IE. In this study, we aimed to evaluate the association between C-reactive protein (CRP), N-terminal pro brain natriuretic peptide (BNP), monocyte to high density lipoprotein (HDL) ratio Charlson comorbidity index, and European System for Cardiac Operative Risk Evaluation (Euro SCORE) in complicated cases of IE. **Materials and Methods:** This prospective study was conducted on a referral center from January 2017 to December 2020. Patients with definite or possible diagnosis of IE based on the modified Duke criteria were included in this study. Demographic information and serum levels of N-terminal pro BNP, D-Dimer, CRP were evaluated in patients. In addition, we used Charlson comorbidity index and The Euro SCORE for subjective assessment. **Results:** One hundred and four patients (64 males, median age: 58) included in the final analysis. Intracardiac involvement, central nervous system (CNS) complications and systemic complications were observed in nine patients (9.7%), 16 patients (15.4%), and eight patients (7.7%) respectively. The mortality rate was 14.4%. D-dimer ($P = 0.008$), pro-BNP ($P = 0.008$), and Charlson criteria ($P = 0.012$) were higher in patients with systematic complications. In addition, NT pro-BNP was significantly associated with CNS complications ($P = 0.04$) and D-Dimer level was significantly associated with in-hospital mortality ($P = 0.008$). **Conclusion:** Serum biomarkers such as pro-BNP and D-dimer, and comorbidity indices can be used for risk stratification of patients with IE. The level of pro-BNP is significantly associated with CNS complications and the level of D-dimer is significantly with mortality in patients with IE.

Keywords: Biomarkers, endocarditis, heart failure, morbidity, mortality

Introduction

Infective endocarditis (IE) is a rare infectious disease caused by bacteria, fungi, or germs affecting the endocardium of the heart, which has an increasing trend during the last 30-years.[1] This disease is usually occurred in 1.4 out of 100,000 people annually with a mortality of 1.2 per 1000 among the adult population.[2] Also, IE is associated with several in-hospital major events including thromboembolic events, septic shock, heart failure, and prolonged intensive care unit stay.[3,4] Therefore, addressing the likelihood of possible morbidities and mortality can help to better manage this disease and its complications. Addressing the in-hospital morbidities and mortality can be conducted by several ways, including the echocardiographic evaluation,[5] blood culture,[6] and laboratory tests.[7]

There are several types of biomarkers, associated with adverse outcomes in IE, including C-reactive protein (CRP), serum level of N-terminal pro brain natriuretic peptide (BNP), cardiac troponin, and inflammatory cytokines.[8] In addition, some unspecific scoring system such as European System for Cardiac Operative Risk Evaluation (Euro SCORE), the Costa score, De Feo-Cotrufo score or specific scoring systems like

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PALSUSE score can be used for the prediction of outcomes in IE.[9]

In the current study, we are aimed to investigate the predictive values of biomarkers and indices of inflammation (i.e., CRP, pro-BNP, D-dimer and monocyte to high density lipoprotein [HDL] ratio), Charlson comorbidity index and Euro SCORE in patients who presented to a referral center in Iran.

Materials and Methods

Study design

This prospective cross-sectional study was conducted on patients who were presented in Rajaie cardiovascular medical center from January 2017 to December 2020 and admitted due to IE. Convenience sampling was used for patient selection and the sample size was calculated to be about 100 patients based on the Cochrane formula with a confidence level of 95%, the margin of error of 10%, and a population portion of 50%. The inclusion criteria for this study assume age > 18 and definite or possible diagnosis of IE based on the modified Duke criteria.[10] In addition, patients who did not fill out the informed consent form, were excluded from the study.

Data collection

After the inclusion, recording baseline information such as age, gender, underlying diseases and before starting the antibiotic therapy, a blood sample was collected to perform biochemical tests. Serum N-terminal pro BNP (NT-proBNP) (Human NT-proBNP ELISA Kit, Abcam®, UK), serum D-Dimer (Human D-Dimer ELISA Kit, Abcam®, UK), and CRP (Human C Reactive Protein ELISA Kit, Abcam®, UK) were assessed in patients. In addition, serum HDL was requested for evaluating the monocyte to HDL ratio, which considers an accessible cardiovascular prognostic marker for the inflammation and oxidative stress.[11] The outcomes of patients during hospitalization were classified as systemic complications, including heart failure, cardiogenic shock, septic shock, central nervous system (CNS) complications, including ischemic cerebrovascular events, hemorrhagic cerebrovascular events, intracardiac involvement such as cardiac abscess and atrioventricular block and in-hospital mortality. Moreover, Charlson comorbidity index[12] and The Euro SCORE[13] were used as subjective assessment method.

Statistical analysis

The data were entered into SPSS software (IBM, Inc., Armonk, NY) version 26 for the statistical analysis. The normality of data was evaluated by the Kolmogorov–Smirnov test and due to the lack of normality, nonparametric statistical tests were used. The qualitative variables were reported as number (percentage) data and quantitative variables were reported as median (Q1, Q3). The bivariate associations between data were assessed by the Man–Whitney *U*-test. In addition, logistic regression analysis was used for evaluating the likelihood of morbidities and mortality based on the assessed parameters.

Ethical consideration

This study was conducted under the consideration of medical ethics committee of Shahid Rajaie cardiovascular center with the registration number of: IR.RHC.REC.1396.34. Informed consent form was filled by all patients before including in the study. In addition, we assure that the data will remain secure by the researchers.

Results

Demographics and underlying diseases

One-hundred and four patients entered this study. There were 64 males (61.5%) and the median age of patients was 58 years (interquartile range: 44–64, range: 32–76). In terms of underlying diseases, thirty patients had diabetes mellitus (28.9%), 24 patients (23%) had hypertension, and 16 patients had dyslipidemia (15.4%). There were no differences in terms of demographics and underlying disease between patients who suffered different complications.

Biomarkers and complications

Eight patients (7.7%) had systemic complications, 16 patients (15.4%) had CNS complications, nine patients (9.7%) had intracardiac involvement, 15 patients (14.4%) had mortality, and 34 patients (32.7%) had at least one morbidity or mortality. The results of laboratory tests and Euro SCORE (presented based on median (Q1, Q3)) are presented in Table 1. As seen, the values of D-dimer (P = 0.008), pro-BNP (P = 0.008), and Charlson criteria (P = 0.012) were significantly higher in patients with systematic complications. In addition, in patients with mortality, the level of D-dimer (P = 0.000), pro-BNP (P = 0.003), and Charlson score (P = 0.005) were significantly higher than patients who remained alive. It was revealed that the level of D-dimer (P = 0.001) and pro-BNP (P = 0.006) were significantly higher in the composite group (those who had at least one morbidity/mortality). There were no differences in CRP level, monocyte/HDL ratio and Euro SCORE in different complications of patients (P > 0.05). In order to assess the multivariate association between the variables, logistic regression analysis was conducted. It was suggested that pro-BNP level is significantly associated with CNS complications (odds ratio [OR]: 1; 95% confidence interval [CI]: 1–1; P = 0.04); in addition, the mortality was significantly associated with the D-Dimer level (OR: 1.001; 95% CI: 1–1.001; P = 0.008) [Table 2].

Discussion

In the current study, the association between some laboratory and subjective variables with morbidities and short-term mortality in patients with IE was evaluated. We observed that the values of D-dimer, pro-BNP, and Charlson criteria were significantly higher in patients with IE, with systemic complications, including heart failure, cardiogenic shock, and septic shock, and in-hospital mortality. It was revealed that the level of pro-BNP was significantly associated with CNS related complications and the level of D-dimer was significantly associated with in-hospital mortality.

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Table 1: The values of laboratory variables based on the complication in the studied patients

Complications	Monocyte/HDL	*P**	D-dimer	*P**	Pro-BNP	*P**	CRP	*P**	Charlson criteria	*P**	Euro SCORE	*P**
Systemic												
Yes	90.5 (61.9–109.45)	0.22	3843 (1980–8219)	0.008	22,081 (3757–35,000)	0.008	42.4 (21.8–65.7)	0.62	4 (2.2–5.7)	0.012	10.5 (7–16.2)	0.916
No	108.01 (83.66–172.60)		1684 (791–3221)		2151 (680–9384)		35.8 (12.2–67)		1 (0–3)		10.8 (5.2–24)	
CNS												
Yes	129.16 (75.38–188.98)	0.57	2246 (1235–3388)	0.24	5918 (1608–19,589)	0.15	49 (11.2–75)	0.56	0 (0–2)	0.27	10.7 (5–17.7)	0.91
No	106.3 (82.8–162.06)		1684 (712–3285)		2151 (809–9384)		35.8 (13.2–67)		1 (0–3)		10.7 (5.2–22.7)	
Intracardiac												
Yes	84 (75.3–94.88)	0.10	2605 (812–7875)	0.21	5708 (1500–30,000)	0.16	22.7 (12.9–105.5)	0.79	2 (0–5.5)	0.53	13.1 (10.7–16.3)	0.46
No	108.4 (84.52–172.6)		1692 (832–3258)		2370 (766–10,112)		36.8 (13–66.9)		1 (0–3)		9.9 (5.2–24.7)	
Mortality												
Yes	105.7 (79.6–140.3)	0.65	3943 (3198–6794)	0.000	12,518 (2538–33,882)	0.003	20.9 (10.1–59.6)	0.29	4 (1–6)	0.005	10.7 (5–20.5)	0.52
No	107.7 (83.4–171.87)		1556 (715–2821)		1915 (628–6407)		40 (13.5–69.9)		1 (0–3)		10.5 (7.9–21.6)	
Composite												
Yes	106.9 (84–173.4)	0.9	3213 (1320–4611)	0.001	5713 (1746–21,165)	0.006	27.2 (16–70.3)	0.77	2 (0–4.2)	0.34	10.7 (7–16.3)	0.7
No	107.3 (80–168.2)		1490 (674–2501)		1896 (600–5754)		38.8 (11.8–66.9)		1 (0–3)		10 (5–26.2)	

*Values are presented based on Mann–Whitney *U*-test. Systemic complications include heart failure, cardiogenic shock and septic shock; CNS complications include ischemic and hemorrhagic cerebrovascular events; intracardiac complications include cardiac abscess and atrioventricular block. Values of D-dimer, pro-BNP and CRP are presented as ng/mL, pg/mL and mg/L respectively. BNP: Brain natriuretic peptide, CRP: C-reactive protein, HDL: High density lipoprotein, CNS: Central nervous system, Euro SCORE: European System for Cardiac Operative Risk Evaluation

The assessment of monocyte to HDL ratio in IE was one of the aims of this study. The monocyte is known as a source for cytokines secretion, which interacts with platelets and endothelial cells, resulting in the platelet aggregation and the activation of pro-thrombotic pathways.[14] In addition, monocytes are a known source for inflammatory cytokines secretion, which can play a major role in the pathophysiology of IE.[15] It was suggested that HDL cholesterol can ameliorate these effects of monocytes by its anti-inflammatory and anti-oxidant effects.[16] Therefore, novel markers such as monocyte to HDL count can reveal the inflammatory status and can predict the cardio-vascular events.[17] In a study in 2017, it was revealed that patients with IE at the lowest tertile of monocyte/HDL ratio experienced significantly less mortality and major cardiac events.[18] How-ever, our study showed that there are no differences in monocyte/HDL ratio in terms of morbidities and mortality in patients with IE. In fact, it seems that more studies are needed to find the value of monocyte/HDL ratio as a prognostic parameter in the IE.

Evaluating the pro-BNP level and its association with morbidities and mortality was another goal of this study. It has been demonstrated that the pro-BNP is a prognostic marker for cardiovascular diseases such as heart failure, cardiogenic shock, septic shock, and postoperative events after major surgeries.[19,20] Also, the prognostic role of pro-BNP in IE was evaluated in recent years. In a study by Kahveci *et al*. in 2007 on 45 patients, high levels (>1500 pg/mL) of pro-BNP were related with in-hospital mortality in patients with IE.[21] In another study on 703 patients with IE, higher quartiles of pro-BNP had higher prognostic value for in-hospital mortality than CRP.[22] Our study demonstrated that the values of pro-BNP in patients with IE are significantly higher in the context of heart failure, cardiogenic shock, septic shock or in hospital mortality. In addition, it was significantly associated with CNS complication in patients with IE; however, the pro-BNP level was not associated with in hospital mortality, intracardiac events or systemic complications. It seems that higher levels of pro-BNP should be consider as an alert for possible morbidities or mortality in IE, but further studies are needed to confirm this.

We evaluated the levels of D-dimer in patients with IE to assess its prognostic value for morbidities and mortality. D-dimer, a fibrin-degradation product associated with possible thrombosis, is a valuable marker for predicting thromboembolic events such as ischemic cerebrovascular events, pulmonary thromboembolism, and myocardial infarction.[23] The prognostic value of D-dimer in predicting morbidities and mortality in IE patients has been discussed in recent years. In a study by Bakal *et al*. in 2013 on 42 patients with IE, the systemic embolism was seen in 13 patients, which was associated with D-dimer more than 425 ng/dL.[24] In another study by Turak *et al*. on 157 patients, increased level of D-dimer ≥4.2 mg/L was assumed as an independent risk factor for in-hospital mortality in patients with IE.[25] Similar results for in hospital mortality was observed by Barış *et al*.[26] and Lin *et al*.[27] In the current

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Table 2: Multivariate logistic regression analysis

Variables	OR	95% CI	*P*
Systemic complications			
Monocyte/HDL	1.003	0.99–1.01	0.64
D-dimer	1	1–1.001	0.49
Pro-BNP	1	1–1	0.23
CRP	0.99	0.96–1.03	0.94
Charlson criteria	0.99	0.91–1.07	0.87
Euro SCORE	0.96	0.86–1.07	0.49
CNS complications			
Monocyte/HDL	0.99	0.98–1.01	0.86
D-dimer	1	1–1	0.85
Pro-BNP	1	1–1	0.04
CRP	1	0.98–1.03	0.66
Charlson criteria	1.01	0.98–1.05	0.31
Euro SCORE	0.99	0.93–1.06	0.91
Intracardiac complications			
Monocyte/HDL	0.98	0.96–1.01	0.35
D-dimer	1	0.99–1	0.52
Pro-BNP	1	1–1	0.73
CRP	1	0.97–1.03	0.9
Charlson criteria	0.98	0.89–1.09	0.77
Euro SCORE	0.98	0.91–1.05	0.62
Mortality			
Monocyte/HDL	1	0.98–1.01	0.99
D-dimer	1.001	1–1.001	0.008
Pro-BNP	1	1–1	0.18
CRP	0.98	0.94–1.02	0.51
Charlson criteria	0.99	0.89–1.10	0.87
Euro SCORE	1.02	0.95–1.08	0.55
Composite			
Monocyte/HDL	0.99	0.98–1.008	0.77
D-dimer	1	1–1.001	0.06
Pro-BNP	1	1–1	0.1
CRP	0.97	0.98–1.02	0.97
Charlson criteria	1	0.97–1.03	0.6
Euro SCORE	0.98	0.93–1.03	0.52

Euro SCORE: European System for Cardiac Operative Risk Evaluation, HDL: High density lipoprotein, BNP: Brain natriuretic peptide, CRP: C-reactive protein, OR: Odds ratio, CI: Confidence interval, CNS: Central nervous system

study, the levels of D-dimer in IE patients with heart failure, septic shock, cardiogenic shock and in-hospital mortality were significantly than the other patients. It seems that this factor can be administered as a valuable tool for risk stratification in IE.

In the current study, the level of CRP was not associated with morbidities and mortality related to the IE. Previous studies observed that the serial measurement of CRP can be helpful in the follow-up of patients with IE; while its baseline assessment may fail to predict morbidities and mortality.[28] However, in a study by Mohanan *et al*. in 2018 on 101 patients with IE, the baseline level of CRP was significantly associated with mortality, major cardiovascular events, and need for surgery.[29]

Due to the significant effects of comorbidities in the outcomes of IE,[30,31] we administered the Charlson comorbidity index to represent its association with morbidities and mortality in IE. The use of Charlson comorbidity index was also observed in some similar studies. In the study of Lu *et al*. in 2013 on 148 patients with IE, age adjusted Charlson comorbidity index more than three was significantly associated with all-cause mortality.[32] In another study by Kim *et al*. on more than 400 patients with IE, the in-hospital mortality rate was significantly associated with Charlson comorbidity index.[33] We found no association between Charlson comorbidity index and morbidities/mortality in patients with IE. It seems that existing comorbidities may influence the long-term outcomes in IE;[34] however, more studies are needed to evaluate its prognostic value for in-hospital events.

In this study, we also used Euro SCORE, which is a valuable tool for the risk assessment in cardiac surgery.[35] We applied this score for assessing outcomes in patients with IE, which was one of the positive points of this study. There are limited data in this regard. In the study of Komuttarin and Poolthananant in 2021 on 43 patients with IE, Euro SCORE II ≥12% was significantly associated with mortality.[36] Although, we administered the logistic Euro SCORE system, which has stronger prognostic value than Euro SCORE II, based on the study of Urso *et al*. on 111 patients with IE. In the mentioned study, the value of APORTEI risk score was significantly higher than logistic Euro SCORE or Euro SCORE II.[37] We found no associations between the Euro SCORE and morbidities/mortality in patients with IE. However, the prognostic value of this factor should be evaluated especially in IE cases who need surgical interventions.

The levels of biomarkers can be used as valuable tools for risk stratifications in patients with IE during in-hospital period in order to recognize high-risk patients who need intensive monitoring and early treatment. This study was associated with some limitations. First, our sample size was small and larger sample size may alter the results. In addition, due to high number of variables, it was hard for us to implement the type of bacteria in the analysis. Furthermore, we did not classify patients who needed surgical intervention. It would be better for future studies to conduct as multicentric studies to have a larger sample, and evaluate the type of bacteria, or the infected heart valve, to have a better insight about the prognostic values of laboratory tests.

Conclusion

The levels of pro-BNP and D-dimer, in addition to the comorbidity index are higher in complicated patients with IE. The level of pro-BNP is significantly associated with CNS complications and the level of D-dimer is significantly with mortality in patients with IE. These factors can be used as valuable tools for risk stratifications in patients with IE during in-hospital period in order to recognize high-risk patients who need intensive monitoring and early treatment. In this study the prognostic values of CRP and monocyte/HDL were not

associated with morbidity and mortality although, further studies are needed to approve these results.

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Conflicts of interest

There are no conflicts of interest.

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