D-Dimer is a strong predictor of in-hospital mortality in patients with infective endocarditis

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Abstract

Objective: Infective endocarditis (IE) is a rare disease with a high mortality. Therefore, prognostic markers can play an important role in the follow-up. In this study, we investigated the relationship between the D-dimer (DD) level and in-hospital mortality and complications in patients with IE, because DD indicates both the fibrin turnover in vegetation and the autoimmune inflammatory response in patients with IE.
Methods: Seventy-nine patients with IE were included in the study. In-hospital death for any reason was considered to be the primary endpoint. Secondary endpoints were embolism and in-hospital death or embolism.
Results: In-hospital mortality occurred in 31 (39%) patients. The DD level was significantly higher in the group with in-hospital mortality [median (interquartile range) values 3048.0 (4911.0) vs. 556.0 (1100.2) ng/mL, p<0.001]. When the DD level was 795 ng/mL or higher, the sensitivity was 83.5%, specificity was 66.7%, the positive predictive value was 66.4%, and the negative predictive value was 94.1%, to determine in-hospital mortality. Categorically, the DD level of 795 ng/mL or higher was found to increase the risk of in-hospital mortality by 29 times (odds ratio=29; 95% confidence interval=6.13–137.11; p<0.001). In a multiple logistic regression analysis, the DD level was found to be the best independent predictor of in-hospital mortality (the AUC value only for DD was 0.86, and for the multiple logistic regression model, it was 0.89, p=0.48). A significant correlation was found between the DD level and in-hospital death or embolization [1863.0 (4914, 0) vs. 376 (607, 0) ng/mL, p<0.001]. In the multiple logistic regression analysis, DD was found to be the best independent parameter showing in-hospital mortality or embolization (the AUC value was 0.83 for DD, and 0.84 for the multiple logistic regression analysis, p=0.69).
Conclusion: These findings support that a high DD is a strong parameter predicting in-hospital mortality, and in-hospital mortality or embolic events in patients with IE. *(Anatol J Cardiol 2019; 21: 00-00)*
Keywords: infective endocarditis, embolization, D-dimer, death

Introduction

Infective endocarditis (IE) is a rare clinical condition with high mortality despite improvements in diagnostics and treatment (1-4). Therefore, prognostic markers may play an important role in the treatment approach and clinical course in IE (5). A number of clinical, echocardiographic, and biochemical markers have been investigated in terms of the prognostic value in IE (6-10).

D-dimer (DD), a product of fibrin degradation, is a diagnostic biochemical marker that has been recorded in the guidelines in acute pulmonary thromboembolism and aortic dissection, and its elevated levels are also associated with a systemic inflammatory response (11-15).

In this study, we analyzed the relationship between the DD level and in-hospital prognosis in IE patients, because DD is both an indicator of inflammation and fibrin turnover, a component of vegetation, which is the most important pathological finding in patients with IE.

Methods

Patient population

The study included 33 retrospectively and 46 prospectively followed patients, a total of 89 patients diagnosed with definite IE according to the Modified Dukes Criteria, who were hospitalized in the Ankara University Faculty of Medicine İbn-i Sina

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Hospital and Cebeci Heart Center between 2008 and 2015. Eight patients who continued their treatment in other center, and 2 other patients who refused to participate in this research were excluded from the study (Fig. 1). The study was approved by the Local Ethics Committee. It follows the principles outlined in the Declaration of Helsinki.

Echocardiographic evaluation

Echocardiographic evaluations were based on the European Society of Cardiology recommendations in echocardiography laboratories (16). Left ventricular ejection fraction, complications (abscess, cord rupture, etc.), maximal vegetation size, and valvular involvement were evaluated. In cases that needed further examination, patients were studied with trans-esophageal echocardiography. Valvular regurgitation was assessed semi-quantitatively by the color Doppler. Third- and fourth-degree valve failures were categorized as severe valve failures.

Biochemical tests

Biochemical tests (renal functions, total cholesterol, LDL), whole blood count, DD, and C-reactive protein (CRP) were studied at the Central Laboratories of İbn-i Sina and Cebeci Hospital of Ankara University.

The DD level was studied in specimens taken from the antecubital vein during hospitalization. The DD level was measured using an automated latex-enhanced immunoassay method (HemosIL D-Dimer HS 500).

Endpoints

The primary endpoint of the study was defined as in-hospital death. One of the secondary endpoints was defined as embolism, as a combination of ischemic stroke, arterial embolism, and pulmonary embolism. The other secondary endpoint was in-hospital death or embolism (Fig. 1).

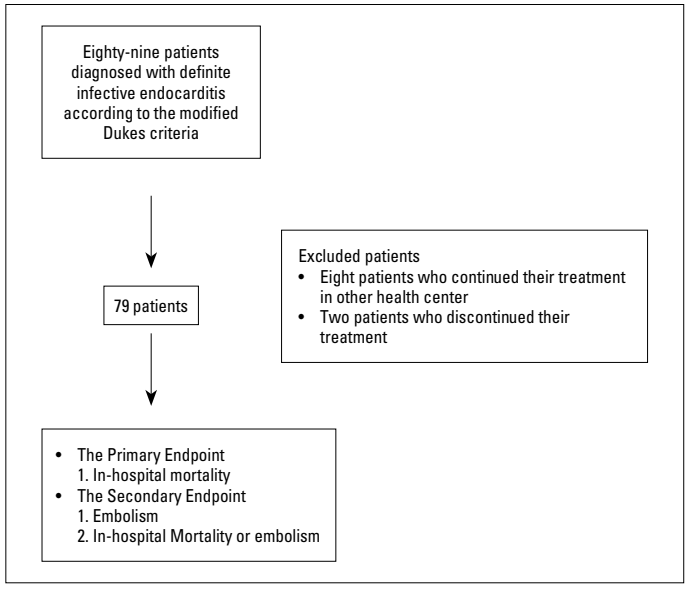

Figure 1. Study design

Sample size and power

The primary endpoint of the study was defined as in-hospital death. One of the secondary endpoints was embolism, and the other one was in-hospital death or embolism. In previous studies, the need for early surgery and death was 73% (17); the frequency of death, early surgery, and major embolic events was approximately 80% (9). Based on these findings, taking the baseline probability of 75%, and the risk increase by high DD values of 20%, alpha at 0.05, and power of 80%, we calculated that at least 49 patients had to be included in the study. A posteriori power analysis showed that this study had a power of 99% for the primary endpoint.

Statistical analysis

Categorical variables were expressed as the frequency and percentage. Continuous variables were tested for normal distribution using the Shapiro–Wilk test and graphical methods. Continuous variables with normal distribution were expressed as the mean±standard deviation (SD), and those without normal distribution were expressed as the median and interquartile range (IQR).

Categorical variables were evaluated by a chi-square test; numerical variables were assessed by Student's t-test or the Mann–Whitney U test in independent groups. A multiple logistic regression analysis was performed to assess independent effects of DD and other variables on death, embolism, and death or embolism. The goodness of fit of the model was assessed by the Hosmer–Lemeshow test. Receiver operating characteristics (ROC) curves were plotted, and the area under the curve was calculated to demonstrate the role of DD in determining the primary and secondary endpoints. A value of $p<0.05$ was considered significant.

The primary endpoint of the study was defined as in-hospital death. One of the secondary endpoints was embolism, and the other one was in-hospital death or embolism. In previous studies, the need for early surgery and death was 73% (17); the frequency of death, early surgery, and major embolic events was approximately 80% (9).

Results

Thirty-three (41.8%) of 79 patients participating in this study were female. Most of the patients were diagnosed using transthoracic or trans-esophageal echocardiography, but 2 patients were diagnosed using computed tomography. The median age of the patients was 59 (IQR=44-69), and the median duration of hospitalization was 35 days (IQR=18-56). The most common valve involvement was mitral valve endocarditis (n=32, 40.5%) (Fig. 2). Intracardiac abscess was observed in 12 patients (15%), and valve perforation was seen in 15 patients (19%).

Microbiological culture positivity was observed in 63.3% of the patients. Staphylococcus was the most common causative agent in the culture (n=18, 22.8%). In-hospital mortality rate was

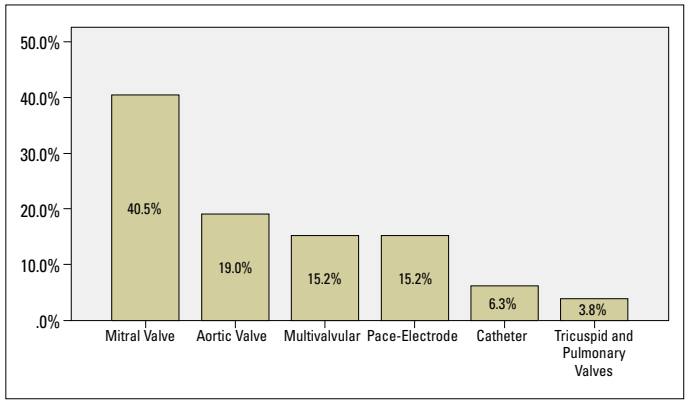

Figure 2. Distribution of the areas in which endocarditis developed

Table 1. Causes of in-hospital mortality

Causes	n (%)
Septic shock	13 (41%)
Post-operative cardiac pump failure	8 (26%)
Heart failure	5 (16%)
Stroke	4 (13%)
Major bleeding	1 (4%)

most frequently observed in staphylococcal endocarditis (n=10, 55.6%).

The most common predisposing factors for IE among study participants were the cardiac pacemaker or electrode finding (n=12, 15.2%) and degenerative valve diseases (n=11, 13.9%). These conditions were followed by rheumatic valve diseases, mitral valve prolapse, and prosthetic heart valves (n=10, 12.7%).

Only 7 patients had a previous history of IE. The primary endpoint developed in 3 of them.

Intracardiac abscess was observed in 12 patients (15%), and the valve perforation was observed in 15 patients (19%). Thirty-four patients underwent early surgical therapy. Mitral valve replacement was performed in 18 patients, aortic valve replacement in 6 patients, mitral and aortic valve replacement in 5 patients, and pacemaker excision was performed in 5 patients. When the groups who required or did not require urgent surgical treatment were compared, the DD levels were similar [1013 (1878) vs. 1022 (3335), p=0.85].

In-hospital mortality

In-hospital mortality, the primary outcome point, was found in 31 patients (39%). The most common cause of in-hospital mortality was septic shock (Table 1). Clinical features include female gender and coronary artery disease; biochemical variables such as DD, serum creatinine, mean platelet volume, and albumin levels were found to be associated with in-hospital mortality. Systolic pulmonary artery pressure and maximal vegetation size were found to be significantly higher in the group with in-hospital death observed (Table 2). Two-thirds of patients with in-hospital mortality used anticoagulant or antiplatelet therapy. Antiplatelet or anticoagulant drug use was similar between groups (p=0.100).

The median DD level was 3048 ng/mL (IQR=4911.0) in the in-hospital death group and 556 ng/mL (IQR=1100.2) in the other group (p<0.001). The area under the ROC curve plotted to dem-

Table 2. Comparison between the in-hospital mortality group and the group without mortality

	In-hospital mortality group (n=31)	Group discharged (n=48)	*P*-value
Clinical characteristics			
Age (year)			
Mean±SD	60.19±16.89	53.31±17.0	0.082
Median (IQR)	62 (23)	56 (25.75)	
Female, n (%)	18 (58.1)	15 (31.3)	0.018
DM, n (%)	6 (19)	10 (20.8)	0.873
HT, n (%)	12 (38.7)	14 (29.7)	0.370
CAD, n (%)	9 (29)	5 (10)	0.034
Heart failure, n (%)*	18 (58)	15 (31)	0.018
End stage renal disease	14 (45.2)	9 (18.8%)	0.012
Laboratory variables			
Creatinine (mg/dL)			
Mean±SD	2.0±1.6	1.7±1.8	0.045
Median (IQR)	1.3 (2.08)	0.9 (0.78)	
Albumin (g/dL)			
Mean±SD	2.7±0.7	3.3±0.7	<0.001
Median (IQR)	2.8 (0.9)	3.3 (1.1)	
Leukocyte count (x10^9/L)			
Mean±SD	15.9±19.1	10.6±3.8	0.206
Median (IQR)	12.4 (11)	10.0 (5.09)	
Hemoglobin (g/dL)			
Mean±SD	10.1±2.2	11.1±2.3	0.054
Median (IQR)	9.6 (3.3)	10.9 (2.88)	
MPV			
Mean±SD	9.09±1.31	8.28±1.09	0.004
Median (IQR)	9.1 (1.7)	8.1 (1.62)	
Sedimentation rate (mm/hour)			
Mean±SD	66.3±32.5	70.4±29.8	0.470
Median (IQR)	70.0 (54)	71.0 (52)	
CRP (mg/L)			
Mean±SD	128.4±99.4	100.9±82.8	0.318
Median (IQR)	107.0 (152.1)	80.9 (99.4)	
D-dimer (ng/mL)			
Mean±SD	4769.9±5481.4	1065.72±1518.13	<0.001
Median (IQR)	3048.0 (4911.0)	556.0 (1100.2)	

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Table 2. Cont.

	In-hospital mortality group (n=31)	Group discharged (n=48)	*P*-value
Echocardiographic variables			
Left atrium diameter (cm)			
Mean±SD	4.56±0.77	4.84±0.97	0.20
Median (IQR)	4.6 (0.7)	5.0 (0.8)	
sPAP (mm Hg)			
Mean±SD	49.51±17.39	41.26±15.12	0.043
Median (IQR)	45.0 (20.0)	40.0 (20.0)	
Left ventricular ejection fraction (%)			
Mean±SD	51.40±12.74	54.02±14.72	0.22
Median (IQR)	55 (11.25)	59 (12.0)	
Maximum vegetation size (cm)			
Mean±SD	1.7±1.1	1.2±1	0.011
Median (IQR)	1.5 (1.1)	1.0 (0.9)	
Maximum vegetation size >10 mm, n (%)	23 (72.4)	27 (56.2)	0.16
Severe valve failure, n (%)	11 (35.5%)	21 (43.8%)	0.46

*The occurrence of the New York Heart Association class 3–4 heart failure findings at the time of the IE diagnosis.
CAD - coronary artery disease; DM - diabetes mellitus; HT - hypertension; IE - infective endocarditis; IQR - interquartile range; MPV - mean platelet volume; SD – standard deviation

onstrate the effectiveness of DD in determining mortality for the hospital was 0.86 [95% confidence interval (CI): 0.78–0.94, p<0.001] (Fig. 3).

When the DD level was 795 ng/mL or higher, the sensitivity was 83.5%, specificity was 66.7%, the positive predictive value was 66.4%, and the negative predictive value was 94.1%, to determine in-hospital mortality. Categorically, the DD level 795 ng/mL or higher was found to increase the risk of in-hospital mortality by 29 times (OR=29; 95% CI=6.13–137.11; p<0.001).

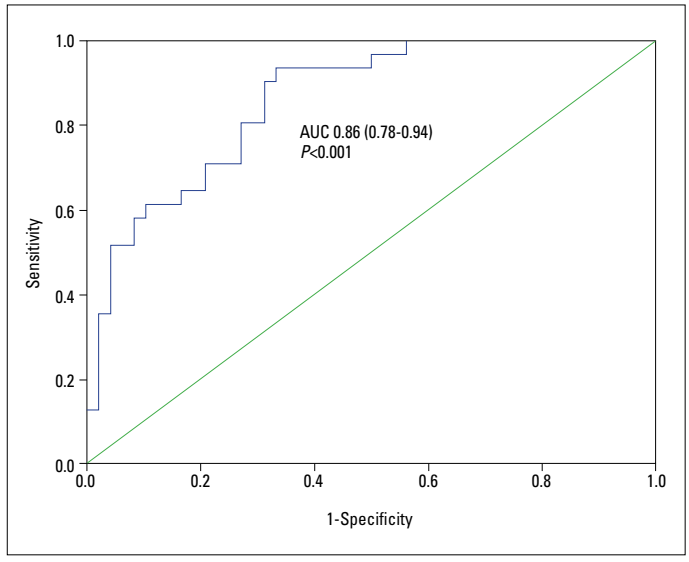

Figure 3. ROC curve representing the relationship between the DD level and in-hospital mortality

Multiple logistic regression analysis revealed that, among other factors that were significantly associated with mortality (age, coronary artery disease, heart failure, serum albumin levels, maximal vegetation size, female gender), the DD level was the most important independent factor in predicting in-hospital mortality based on the Wald statistics (Table 3).

The serum creatinine level and end stage renal disease were found to be significantly higher in the in-hospital mortality group. However, this factor was not tested in the multiple logistic regression analysis because of the small number of patients with end stage renal disease. The creatinine level did not change as a result of the addition of creatinine level to the variables found to be significant in the multiple logistic regression analysis.

When the ROC curves of the univariate analysis of DD were compared with the multiple logistic regression analysis model for

Table 3. Multiple logistic regression analysis results for in-hospital mortality

	Beta value	Wald	OR (95% CI)	*P*-value
DD (ng/mL)	0.001	12.096	1.001 (1.000-1.001)*	0.001
Gender (Male/Female)	-2.39	7.246	0.91 (0.016-0.521)	0.007
Age (year)	0.044	3.969	1.045 (1.001-1.091)	0.046
CAD	2.56	6.162	12.96 (1.714-7.992)	0.013
Heart failure**	1.11	2.56	3.03 (0.78-11.82)	0.11
Maximum vegetation size (cm)	0.53	2.44	1.7 (0.87-3.30)	0.11

Variables in the models: age, coronary artery disease, decompensated heart failure, gender, serum albumin level, maximum vegetation size, and DD
*OR for the one-unit increase
**The occurrence of the New York Heart Association class 3-4 heart failure findings at the time of the IE diagnosis
DD - D-dimer; CI – confidence interval; IE - infective endocarditis; OR - odds ratio

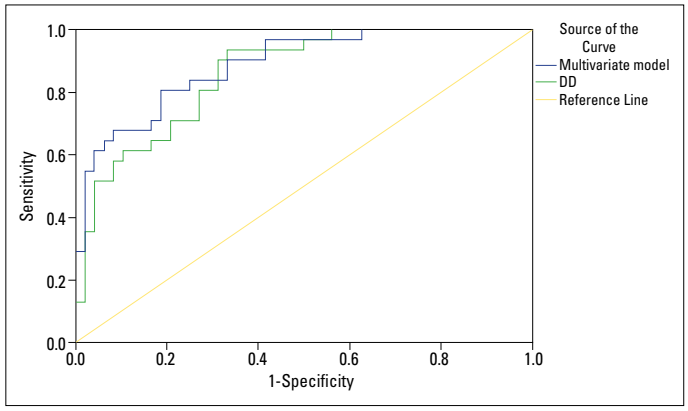

Figure 4. ROC curves of the DD level role in determining in-hospital mortality based on the multiple logistic regression model

in-hospital mortality, it was found that the curves were close to each other, and the areas under the curve were statistically similar (p=0.48). This finding suggests that the main determinant of the multiple logistic regression analysis was the DD level (Fig. 4).

In this study, when the DD limit used was 500 ng/mL or higher, which is also a traditional threshold in pulmonary embolism or deep vein thrombosis, the sensitivity of DD to in-hospital mortality was 96.8%, specificity was 50.0%, the positive predictive value was 55.6%, and the negative predictive value was 96.0%.

Embolism

Embolism, as the combination of ischemic stroke, arterial embolism, and pulmonary embolism, one of the secondary endpoints, was observed in 31 patients (39.0%). Clinical characteristics, complete blood, and inflammatory variables were similar in both the groups. The median DD level (IQR) was found to be higher but at the threshold of statistically significant in the group with embolism [1332.0 (5074.0) vs. 795.5 (2231.5) ng/mL; p=0.05]. The serum albumin level was lower in the group with embolism (p=0.03), while other biochemical variables were similar (Table 4). Echocardiographic variables were similar in both groups (Table 4). In the multiple logistic regression analysis, a low serum albumin level was associated with embolism (OR=1.001; 95% CI=1–1001; p=0.026), but no relationship was found between the DD level and embolism (p=0.694).

In-hospital death or embolism

A combination of in-hospital mortality, arterial embolism, ischemic stroke, and pulmonary embolism, which is the secondary endpoint, occurred in 49 (62.0%) patients. The serum albumin level and hemoglobin were lower, and the maximal vegetation size was significantly larger in the in-hospital mortality or embolism group [median 1.3 (IQR=1.2) cm and 1 (IQR=0.8) cm, p=0.018) (Table 5).

Median DD level was 1863 ng/mL (IQR=4914.0) in the group with in-hospital mortality or embolism and was 376 ng/mL (IQR=607.0) in the other group (p<0.001).

Table 4. Comparison of the groups with and without embolism

	Group with embolism (n=31)	Group without embolism (n=48)	*P*-value
Basic clinical characteristics			
Age (year)			
Mean±SD	58.35±17.58	54.5±16.94	0.334
Median (IQR)	61 (25)	58 (28.75)	
Female, n (%)	15 (48.4)	18 (37.5)	0.338
DM, n (%)	5 (16.7)	11 (22.9)	0.506
HT, n (%)	10 (32.3)	16 (33.3)	0.921
CAD, n (%)	6 (19.4)	8 (16.7)	0.760
Heart failure, n (%)*	9 (29)	14 (29.2)	0.990
End stage renal disease	8 (25.8)	9 (18.8)	0.456
Laboratory variables			
Creatinine (mg/dL)			
Mean±SD	1.7±1.6	1.8±1.7	0.653
Median (IQR)	1.0 (0.72)	1.0 (0.94)	
Albumin (g/dL)			
Mean±SD	2.8±0.6	3.2±0.8	0.030
Median (IQR)	2.9 (0.7)	3.2 (1.2)	
Leukocyte count (x10^9/L)			
Mean±SD	10.1±4.2	14.6±16.8	0.074
Median (IQR)	9.0 (5.6)	12.2 (6.1)	
Hemoglobin (g/dL)			
Mean±SD	10.3±2.0	11.0±2.4	0.444
Median (IQR)	10.3 (2.8)	10.9 (3.65)	
MPV			
Mean±SD	8.67±1.3	8.58±1.23	0.771
Median (IQR)	8.85 (2.05)	8.4 (1.6)	
Sedimentation rate (mm/hour)			
Mean±SD	63.9±31.4	68.5±30.2	0.693
Median (IQR)	63.0 (59.5)	71.0 (49)	
CRP (mg/L)			
Mean±SD	114.5±99.0	95.7±64.0	0.269
Median (IQR)	79.2 (104.9)	85.0 (95.1)	
D-dimer (ng/mL)			
Mean±SD	3206.9±4107.8	2075.1±3962.0	0.050
Median (IQR)	1332.0 (5074.0)	795.5 (2231.5)	
Echocardiographic variables			
Left atrium diameter (cm)			
Mean±SD	4.7±0.5	4.7±0.9	0.781
Median (IQR)	4.8 (0.7)	4.9 (0.9)	
sPAP (mm Hg)			
Mean±SD	47.0±17.8	42.6±15.4	0.482
Median (IQR)	40.0 (20.0)	40.0 (15.0)	

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Table 4. Cont.

	Group with embolism (n=31)	Group without embolism (n=48)	*P*-value
Left ventricular ejection fraction (%)			
Mean±SD	56.1±12.7	50.6±14.7	0.052
Median (IQR)	60.0 (10.0)	55.0 (12.5)	
Maximum vegetation size (cm)			
Mean±SD	1.42±0.9	1.4±1.3	0.318
Median (IQR)	1.2 (1.2)	1.0 (1.4)	
Maximum vegetation size >10 mm, n (%)	21 (67.7)	29 (60.4)	0.670
Moderate–severe valve failure, n (%)	22 (44.9)	10 (33.3)	0.106

*The occurrence of the New York Heart Association class 3-4 heart failure findings at the time of the IE diagnosis
CAD - coronary artery disease; DM - diabetes mellitus; HT - hypertension; IE - infective endocarditis; IQR - interquartile range; MPV - mean platelet volume; SD – standard deviation

Table 5. Comparison of the groups with and without in-hospital mortality or embolism

	Groups with in-hospital mortality or embolism (n=49)	Groups without in-hospital mortality or embolism (n=30)	*P*-value
Clinical characteristics			
Age (year)			
Mean±SD	57.9±16.7	52.9±17.8	0.220
Median (IQR)	61.0 (23.5)	57.5 (34.0)	
Female, n (%)	24 (49%)	9 (30%)	0.097
DM, n (%)	9 (18.8%)	7 (23.3%)	0.616
HT, n (%)	10 (33.3%)	16 (32.7%)	0.950
CAD, n (%)	10 (20.4%)	4 (13.3%)	0.424
Heart failure, n (%)*	6 (20%)	17 (34.7%)	0.163
End stage renal disease	14 (28.6%)	3 (10%)	0.051
Laboratory variables			
Creatinine (mg/dL)			
Mean±SD	1.8±1.6	1.7±1.8	0.692
Median (IQR)	1.1 (0.9)	1.0 (0.9)	
Albumin (g/dL)			
Mean±SD	2.8±0.6	3.4±0.9	0.003
Median (IQR)	2.8 (0.8)	3.4 (1.2)	
Leukocyte count (x10^9/L)			
Mean±SD	13.7±15.5	11.0±3.92	0.832
Median (IQR)	11.4 (6.6)	10.9 (5.2)	

Table 5. Cont

	Groups with in-hospital mortality or embolism (n=49)	Groups without in-hospital mortality or embolism (n=30)	*P*-value
Hemoglobin (g/dL)			
Mean±SD	10.2±2.2	11.5±2.4	0.023
Median (IQR)	9.8 (3.1)	11.1 (3.1)	
MPV			
Mean±SD	8.74±1.76	8.37±1.2	0.192
Median (IQR)	8.8 (1.75)	8.1 (1.58)	
Sedimentation rate (mm/hour)			
Mean±SD	65.4±31.4	74.4±29.3	0.217
Median (IQR)	70.0 (59.0)	71.0 (43)	
CRP (mg/L)			
Mean±SD	123.3±101.5	90.0±61.3	0.287
Median (IQR)	103.8 (115.5)	80.2	
D-dimer (ng/mL)			
Mean±SD	3627.3±4768.7	709.23±791.0	<0.001
Median (IQR)	1863.0 (4914.0)	376.0 (607.0)	
Echocardiographic variables			
Left atrium diameter (cm)			
Mean±SD	4.6±0.7	4.9±1.1	0.119
Median (IQR)	4.7 (0.7)	5 (0.8)	
sPAP (mm Hg)			
Mean±SD	46.4±16.8	41.4±15.7	0.369
Median (IQR)	40.0 (22.5)	40.0 (15.0)	
Left ventricular ejection fraction (%)			
Mean±SD	54.9±12.1	49.9±16.2	0.233
Median (IQR)	60.0 (10.0)	55.0 (20.0)	
Maximum vegetation size (cm)			
Mean±SD	1.6±1.0	1.2±1.1	0.018
Median (IQR)	1.3 (1.2)	1.0 (0.8)	
Maximum vegetation size >10 mm, n (%)	34 (69.4%)	16 (53.3)	0.233
Moderate–severe valve failure, n (%)	22 (44.9%)	10 (33.3%)	0.313

*The occurrence of the New York Heart Association class 3-4 heart failure findings at the time of the IE diagnosis
CAD - coronary artery disease; DM - diabetes mellitus; HT - hypertension; IE - infective endocarditis; IQR - interquartile range; MPV - mean platelet volume; SD – standard deviation

The area under the ROC curve was 0.83 (95% CI=0.74–0.92; p<0.001) (Fig. 5). The sensitivity for DD within 722 ng/mL and above for in-hospital mortality or embolic events was 81.6%; specificity was 73.3%; positive predictive value was 83.3%, and the negative predictive value was 71%. Categorically, the DD level of 722 ng/mL or higher was found to increase the risk of in-hospital mortality or embolism by 12.2 times.

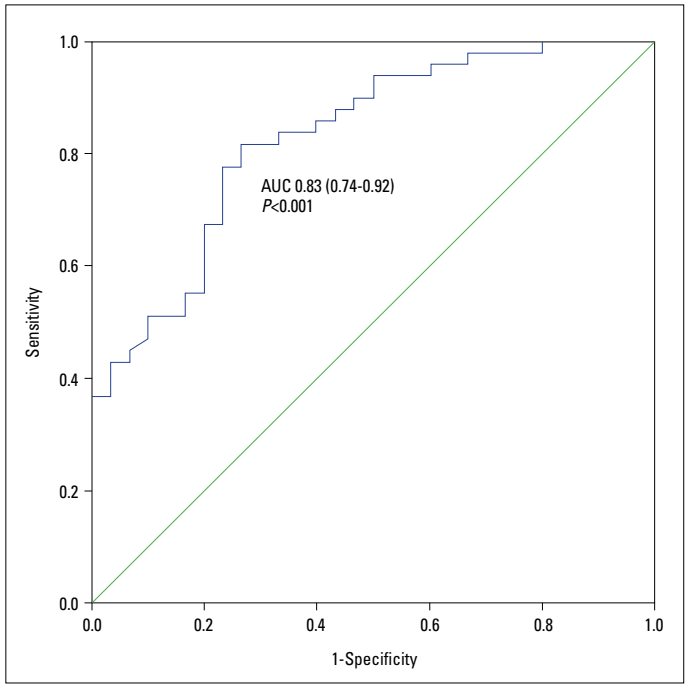

Figure 5. ROC curve presenting the relationship between the DD level and in-hospital mortality and embolism

In the multiple logistic regression analysis, the DD level was found to be an independent predictor of in-hospital mortality or embolism (combination of in-hospital mortality, arterial embolism, ischemic stroke, and pulmonary embolism) in patients with IE (OR=1.001; 95% CI=1–1001; p<0.001). In addition, low serum albumin levels were associated with in-hospital mortality or embolism (Table 6).

Comparing the ROC curves for in-hospital mortality or embolism in a multiple logistic regression analysis and for the DD level in a univariate analysis, it was found that the curves were close to each other and that the areas under the curves were statistically similar (Fig. 6). This finding suggests that the determinants of the multiple logistic regression mainly depend on the DD level.

Discussion

In this study, we found a strong association between the DD level and in-hospital death, and in-hospital death or embolism.

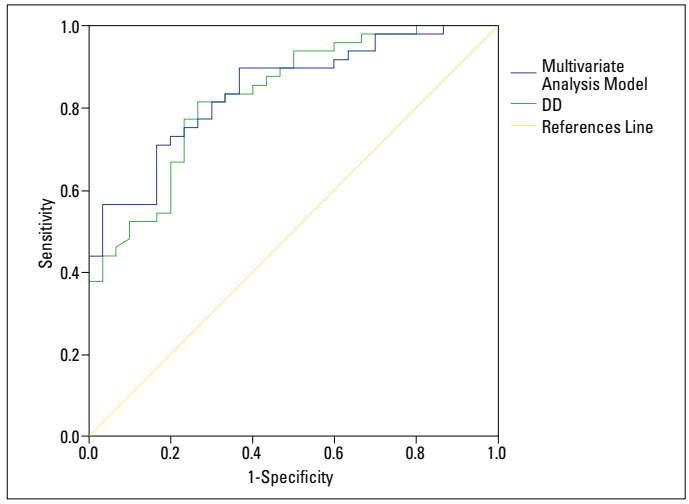

Figure 6. ROC curves of the DD level role in determining in-hospital mortality based on the multiple logistic regression model

In addition, a significant relationship was also found between the old age, female gender, coronary arterial disease and mortality, and between the low serum albumin level and in-hospital mortality or embolism. In a multiple logistic regression analysis, a high DD level was found to be a strong and best predictor of in-hospital mortality or the combination of in-hospital mortality and embolism.

In spite of all the advancements in medical diagnostics and treatment, IE is a disease with a high mortality rate (1, 2). Identification of high-risk patients may provide guidance for an early surgical and more aggressive pharmacologic treatment (18). Therefore, new markers are needed to identify high-risk patients.

DD is a fibrin degradation product that indicates the coagulation level and fibrin turnover in circulation, which is part of the diagnostic approach in acute pulmonary thromboembolism and aortic dissection guidelines (11, 12). In addition, DD is also a marker of an inflammatory response (15) so that it is probably related to death and complications in various clinical conditions such as cancer and sepsis (19). In this study, we investigated the relationship between the DD level and in-hospital mortality and complications in IE patients because DD indicates both the fibrin turnover in vegetation and the septic and autoimmune inflammatory response.

There are only a few studies exploring the relationship between the DD level and in-hospital mortality and embolism in pa-

Table 6. Multiple logistic regression analysis results for in-hospital mortality or embolism

	Beta value	Wald	OR (95% CI)	*P*-value
DD	0.001	7.941	1.001 (1.000-1.001)*	0.005
Serum albumin	-0.876	4.761	0.417 (0.19-0.915)	0.029
Maximum vegetation size	0.449	2.476	1.567 (0.896-2.741)	0.116

Variables in the models: serum albumin level, maximum vegetation size, and DD
*OR for the one-unit increase
DD - D-dimer value; OR - odds ratio

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tients with IE (7, 20). Turak et al. (20), similar to our study, found that there was an association between a high DD level and in-hospital mortality in patients with IE. In our study, this relationship was also shown by a multiple logistic regression analysis, and the DD level was found to be the strongest predictor of the multiple logistic regression analysis. In addition, it is indicated that the predictive value of DD alone was as strong as the multiple logistic regression analysis in our study.

In IE, fibrin is created as a result of the tissue damage, and vegetation formation occurs as a result of the microorganism and platelet accumulation; then, cytokines such as IL-1, IL-6, IL-8, IFNγ, and TNFα are released, and coagulation cascade is activated (14, 21). Activation of the coagulation cascade increases fibrin turnover. Since the amount of released cytokine increases because of severe inflammation, fibrin turnover might accelerate, and the DD level might increase as well (14, 22, 23). This situation can be a marker of a poor clinical outcome. Indeed, high levels of DD were predictive of a poor clinical outcome in sepsis (19). Similarly, higher DD levels may be considered as a biomarker of in-hospital mortality or embolism in patients with IE as a consequence of an increased fibrin cycle.

The vegetation size can also be considered to be an echocardiographic parameter that can reflect the fibrin cycle. A correlation between the DD level and vegetation size can be expected. However, there was no correlation between the size of the vegetation and the DD level found in this study (p=0.135; r=0.17). In this study, 2D echocardiography can only be used to measure the maximum length of the vegetation, and the vegetation volume could not be measured by 3D echocardiography. Additionally, an increase in the fibrin turnover can occur without a visible thrombus, and even in this case, the DD level might be high (24). For these reasons, there may not be a strong correlation between the DD level and vegetation size, and DD may provide a better idea of in-hospital mortality and complications, as it can better reflect the dynamic fibrin turnover. DD is an indicator of increased inflammatory response, as well as fibrin turnover. Indeed, in studies investigating DD levels in aortic dissection, it was concluded that high DD levels are a consequence of an extreme systemic inflammatory response rather than the thrombus volume (13, 25, 26). Similarly, high levels of DD in IE may be associated with an increased systemic inflammatory response, as well as fibrin turnover. Thus, the DD levels can be associated with in-hospital mortality and embolism in IE without a correlation with the vegetation size or platelet count.

In a study (n=42) conducted by Bakal et al. (7), the DD level of 425ng/dl or higher was seen to predict embolic incidents with a 77.0% sensitivity and 62.0% specificity. In this study, only left heart endocarditis was included, and systemic embolic events were investigated. In our study, no statistically significant relationship was found between embolism and the DD level. Right heart endocarditis was present in a significant proportion of patients included in our study (25.3%), so pulmonary embolisms, which may cause silent or non-specific symptoms rather than systemic embolism leading to clinical manifestations, may be more likely in our study. This might lead to different findings in both studies. In clinical situations where deep venous thrombosis is used as a diagnostic tool for DD, such as pulmonary embolism, the DD level increases after thromboembolism symptoms, and symptoms develop (12). In our study, this relationship could not be determined since the baseline DD level was used.

There are some studies investigating the relationship between in-hospital adverse events and laboratory variables in patients with IE. At the time of diagnosis or follow-up, the CRP level was correlated with in-hospital mortality (9, 27). In our study, no significant relationship was found between CRP levels at the time of IE diagnosis and intra-hospital death, but the CRP follow-up was not investigated. Such a result may have been obtained because some of the patients included in our study received antibiotics before the study. There is also a study that revealed the association between a high mean platelet volume (MPV) with in-hospital mortality (28). Similarly, in our study, there was a relationship between the high MPV level and in-hospital mortality; but this association was not detected in embolism, in-hospital death, or embolism.

In our study, a significant correlation was found between a low serum albumin level and embolism, and in-hospital mortality or embolism. Albumin is a negative acute phase reactant, so low serum levels are seen in severe infective and inflammatory conditions (29). A low serum albumin level is associated with an increase in in-hospital complications as an indirect indicator of severe infection and sepsis.

In our study, septic shock was the most common cause of in-hospital death. This finding is consistent with the previous study in our country (30).

Study limitations

This study has several limitations. First, the study is a single-center study with a limited number of participants. Second, a limited number of patients with echocardiographic abscess formation were observed, and we did not find microbiological factors in all patients. Therefore, these clinical situations could not be evaluated. Third, in this exploratory analysis, we first used the backward elimination method, and then we also tested the most important variables using the forced entry method to get a parsimonious model. We acknowledge that the number of the variables included in the model is relatively high compared to the general rule of thumb, which may lead to bias. On the other hand, posterior power was found to be substantial. Finally, we couldn't perform 3D echocardiography.

Despite these limitations, our study has put forward that the DD level is a strong predictor of in-hospital mortality in patients with IE. In fact, the AUC value of the CHA2DS2-VASC score, which is one of the risk determinants that we use most frequently in daily cardiology practice, is 0.606, which determines the stroke risk in AF patients, whereas the AUC value of DD level is 0.86, which determines the mortality risk in patients with IE in our study (31).

Similarly, the negative predictive value of BNP in terms of determining heart failure was between 71% and 88% (32, 33), while the predictive value of the DD level for mortality was 94.1% in our study. Although these comparisons are used to predict different clinical entities, it is suggested that the value of DD in predicting mortality is better than other commonly used clinical scores or markers in predicting clinical events.

Conclusion

Our study findings suggest that the DD level is an easy, fast, and cheap method that can be used as a strong predictor of in-hospital mortality in patients with IE.

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