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Relationship between D-dimer and systemic embolism in patients with infective endocarditis

Dr. Ruken Bengi Bakal, Dr. Süleyman Karakoyun,# Dr. Gökhan Kahveci, Dr. Olcay Özveren,* Dr. Onur Omaygenç, Dr. Suzan Hatipoğlu Akpınar, Dr. Taylan Akgün, Dr. Nihal Özdemir

Cardiology Clinics, Kartal Koşuyolu Higher Specialization Training and Research Hospital, Istanbul
Assoc. Prof. Dr. Yaşar Eryılmaz, MD, PhD; Cardiology Clinic, Doğubeyazıt State Hospital, Ağrı
* Department of Cardiology, Yeditepe University Hospital, İstanbul

ÖZET

Amaç: Çalışmanın amacı, enfektif endokarditli (EE) hastalarda plazma D-dimer (DD) düzeylerinin klinik bulgu veren sistemik embolik olayları öngörmedeki değerini araştırmaktır.

Çalışma planı: Çalışmaya EE tanısı konulan 42 (ortalama yaş: 45±16, %78'i erkek) hasta dahil edildi. Hastaların klinik, laboratuvar ve ekokardiyografik bulguları değerlendirildi.

Bulgular: Sistemik emboli olan 13 hastada plazma DD düzeyi, olmayanlara göre daha yüksek tespit edildi (p=0.016). Ayrıca hastalar DD >500 ng/dL ve <500 ng/dL olmak üzere iki gruba ayrıldığında, DD >500 ng/dL olan grupta klinik emboli oranı daha yüksek saptandı (p=0.036). ROC eğrisi (receiver operating curve) analizinde DD >425 ng/dL değerinde eğri altında kalan alan 0.735 olarak hesaplandı (%95 GA 0.560-0.909, p=0.016). DD >425 ng/dL değeri, %77 duyarlılık ve %62 özgüllükle klinik emboliyi öngörmektedir. Hematokrit (r=-0.31, p=0.045), trombosit (r=-0.40, p=0.009), albümin (r=-0.37, p=0.026) ve globülin (r=0.38, p=0.028) düzeyleri ile DD düzeyi arasında anlamlı korelasyon saptandı.

Sonuç: Enfektif endokarditli hastalardan embolik olay gelişenlerde DD seviyeleri yüksek bulundu. Plazma DD düzeylerinin sessiz embolileri öngörmedeki yerini belirlemek için yeni çalışmalara ihtiyaç vardır.

ABSTRACT

Objectives: The aim of this study was to investigate the value of plasma D-dimer (DD) levels for predicting systemic embolism in patients with infective endocarditis (IE).

Study design: A total of 42 patients (mean age: 46±16 years; 78% males) with IE were included. Clinical, laboratory and echocardiographic findings of the patients were evaluated.

Results: Increased plasma DD levels were determined in 13 patients with systemic embolism (p=0.016). Moreover, when patients were divided in two groups as DD >500 ng/dl, and DD <500 ng/dl, the rate of clinical embolism was found to be increased in the DD >500 ng/dl group (p=0.036). Receiver operating characteristics (ROC) curve analysis was performed to detect the best cut-off value of DD in the prediction of systemic embolism. DD >425 ng/dl yielded an area under the curve (AUC) value of 0.735 (95% CI 0.560-0.909, p=0.016). DD >425 ng/dl demonstrated a sensitivity of 77% and specificity of 62% for the prediction of clinical embolism. Hematocrit (r=-0.31, p=0.045), platelet counts (r=-0.40, p=0.009), albumin (r=-0.37, p=0.026), and globulin (r=0.38, p=0.028) levels were correlated significantly with DD levels.

Conclusion: Plasma DD levels were found to be increased in patients with IE who developed clinically significant systemic embolism. Further studies are needed to determine the predictive value of DD levels for clinically silent systemic embolism.

Address of correspondence: Dr. Ruken Bengi Bakal. Denizer Cad., Cevizli Kavşağı, No: 2, Cevizli, Kartal 34865 İstanbul.
Phone: +90 216 - 500 15 00 e-mail: ruken_bakal@yahoo.com

Abbreviations:

DD *D-dimer*
EE *infective endocarditis*
TTE *Transthoracic echocardiography*

Since D-dimer (DD) is a common indicator of fibrinolysis, and activation of coagulation, it is used as an indirect marker of thrombotic activity. Plasma DD is a cross-linked fibrin derivative formed as an outcome of fibrin degradation by endogenous fibrinolytic system.[1] In addition to its role as a predictive factor of prothrombotic state, it can indicate the presence of a thromboembolic risk. Increased levels of DD can be rarely detected in healthy individuals. In every case where formation, and degradation of fibrin are accelerated including acute coronary syndromes, peripheral vascular diseases, pulmonary embolism, acute stroke, pregnancy, sickle cell anemia, hemolytic crisis, malign diseases, postoperative period, congestive heart failure, DD levels increase.[2,3]

In infective endocarditis (IE) risk of embolism is very high, and it is seen in 20-50 % of the patients.[4] In this study we aimed to investigate the relationship between plasma DD levels, and systemic embolism.

PATIENTS AND METHOD

Selection of patients

Fifty-seven consecutive patients followed up between January 2004, and December 2004 with the indication of suspect IE were retrospectively enrolled in the study. All patients underwent echocardiographic examinations, and their blood cultures were obtained. The patients were evaluated as for clinical risk factors potentially predisposing to IE. Fifteen patients who didn't meet modified Duke criteria [4] with a lower probability of having IE were excluded from the study, and a total of 42 patients (9 females, and 33 males) were included in the study. Plasma DD levels, clinical, echocardiographic, and other laboratory findings were evaluated. Written informed consent forms were obtained from all participants, and the study was approved by the local ethics committee.

Echocardiographic examination

All patients underwent standard transthoracic echocardiographic (TTE) assessments using Vivid 5 (GE, Vingmed Ultrasound, Horten, Norway) echocardiography devices. Images obtained from parasternal long, and short axis, apical 4-5, and 2 chamber views were recorded. Transesophageal echocardiograms were obtained from 17 (64.3 %) patients with unsatisfactory TTE imaging quality, and negative TTE findings despite higher degree of clinically suspect IE. All measurements were performed in compliance with the criteria of American Society of Echocardiography [5]

All intracardiac mass lesions with or without demonstrable oscillatory movements located on endocardial structures, valves or intracardiac implants with or without oscillation were evaluated as vegetations. Non-homogenous, thickened, echodense or echoluscent perivalvular areas were evaluated as abscesses. Pulsatile perivalvular nonechogenic areas as revealed by colour Doppler flow signals were assessed as pseudoaneurysms. Paravalvular regurgitation with or without associated oscillatory prosthetic valve movements was determined as prosthetic valve detachment. Demonstration of disruption of endocardial tissue integrity by colour Doppler US was appraised as perforration. Communication between two adjacent cavities as revealed by colour Doppler US was indicative of the presence of a fistula.

Plasma DD level

For the measurement of plasma DD levels, blood samples of all patients were drawn in the mornings from antecubital vein after 12 hours of fasting, but within the first 24 hours of referral. For quantitative evaluations microparticle agglutination test with polystyrene microspheres ((AMAX AUTO D-Dimer analyzer) was used. One unit sodium citrate was mixed with nine units of venous blood sample, and centrifuged at 3500 rpm for 10 minutes. Separated supernatant plasma was left at + 15^{o}C, and measurements were performed within 8 hours.

Sampling for blood culture

From every patient 10 ml blood samples were drawn thrice from different peripheral veins on admission at 30-minute intervals using a sterile technique to obtain at least one aerobic, and one anaerobic blood culture.

Medical, and surgical treatment

After withdrawal of blood samples from all patients for blood cultures, appropriate empirical antibotherapy was initiated. Afterwards, antibiotics effective on the susceptible microorganism were selected, and antibiotherapy was maintained with that antibacterial agent. Early indications for surgery were determined as congestive heart failure secondary to acute aortic and /or mitral valve regurgitation, echocardiographically detected valvular perforation, rupture of chordae tendinae, parafistulous or paravalvular abscess and/or pseudoaneurysm, mechanical valve detachment, advanced paravalvular insufficiency, a large (> 10 mm) vegetation leading to systemic embolization, a big mobile vegetation localized on anterior leaflet of the mitral valve, and right heart failure associated with a big vegetation.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation, and categorical variables as percentages. In the comparison of continuous variables Student t-test, Mann-Whitney U-test, and for the comparison of categorical variables *chi*-square test were used. For the determination of relevant parametres, Spearman and Pearson correlation analyses were performed. The results were evaluated within 95 % confidence interval and at a significance level of $p<0.05$. For statistical analysis SPSS (Statistical Package for Social Sciences) for Windows 20.0 programı was used.

RESULTS

Mean age of 9 female (22%) , and 33 male (78 %) patients was 45±16 years As predisposing cardiac entities, rheumatismal valve (9.5%), senile degenerative valve (19%), bicuspid aortic valve (19%), and prosthetic valve (19%), Fallot tetralogy (2.4%), ventricular septal defect (2.4%) , and mitral valve prolapse (2.4%) were detected. A predisposing heart disease was not found in two (4.8 %) patients. Involvement of aortic (n=19; 45.5 %), mitral (n=15; 35.5 %) valves or both valves (n=8; 19 %) was detected. Acute valvular damage (valvular perforation and/or rupture of chorda tendinea) (n=18; 42.9 %), annular invasion (abscess and/or pseudoaneurysm) (n=12; 28.6 %), paravalvular regurgitation (n=2; 4.8 %), and detachment of prosthetic valve (n=3; 7.1 %) were detected. Twenty-eight (66.7 %) patients had advanced valvular regurgitation

On admission, atrial fibrillation (n=13; 31 %), and symptoms of class 3-4 heart failure (n=25; 55.9 %) based on New York Heart Association (NYHA) were detected.

Clinically manifest embolism was detected in 13 (31 %) patients. These embolisms affected cerebral (n=8; 19 %), and peripheral (n=4; 9.5 %) vascular systems or both of them (n=1; 2.4 %). A total of 9 (21.4 %) patients died because of congestive heart failure (n=3), sepsis (n=2), cerebral bleeding (n=2), sepsis secondary to prolonged decubitus (n=1), and acute abdomen (n=1). A total of 31 (73.8 %) patients with active endocarditis underwent surgical intervention within the first 24 hours (n=6; 14.3 %) (emergency surgery), between 1.-7. (n=6; 14.3 %), 7.-30. (n=15; 35.7 %), and 31. -60. days after their referrals.

In blood culture media of the patients methicilline-resistant (n=3, 7.1%) or sensitive (n=6; 14.3 %) *Staphylococcus Aureus*, streptococci (n=6; 14.3 %) , brucella spp. (n=2; 4.8%), enterecocci (n=2; 4.8%) , and coagulase-negative *Staphylococcus Aureus* grew. Any bacterial growth was not detected in blood cultures of 22 (52.4 %) patients.

Table 1. Demographic, clinical, and laboratory data according to the presence or absence of systemic embolism

Variable	Systemic embolism (+) (n=13)		Systemic embolism (–) (n=29)		*p*
	%	Mean.±SD	%	Mean.±SD	
Age		47.6±17		44.3±16.5	0.56
Gender (Male)	77		79		0.86
Hypertension	31		10		0.10
Diabetes mellitus	8		14		0.57
NYHA 3-4	62		59		0.86
D-dimer (ng/dL)		1084 (133-8818)		301 (81-3758)	0.016*
D-dimer >500 ng/dL (%)	69		35		0.036*
Size of the vegetation (cm)		15.6±7.9		15±6.9	0.80
Left atrium (cm)		4.5±0.9		5.2±1.6	0.15
LV end-diastolic diameter (cm)		5.9±0.7		6±1.1	0.61
LV end-systolic diameter (cm)		3.7±0.7		3.8±1	0.67
Ejection fraction		60.5±10.8		63.6±13.5	0.62
WBC (10^3/mL)		10.4±4.9		13.8±8.8	0.20
Hemoglobin (g/dL)		10.3±3.3		10.6±1.6	0.70
Platelet (10^3/mL)		220.6±125.7		297.1±188.2	0.19
Creatinine (mg/dL)		1.5±1		1.7±1.6	0.67

Variables were expressed as %, median (interquartile interval) or mean ± SD.
. *p<0.05. SD: Standard deviation ; NYHA: New York Heart Association functional class; LV: Left ventricle.

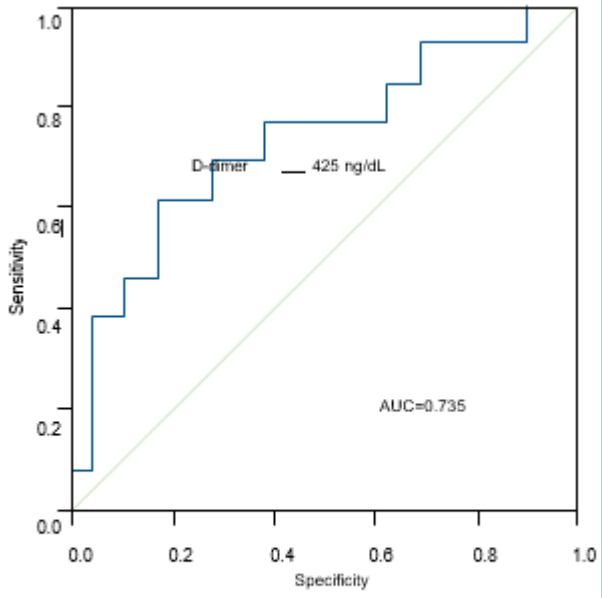

Figure 1. ROC curve for D-dimer in the prediction of systemic embolism in patients with infective endocarditis (n=42). Sensitivity (77%), and specificity (62%) for a cut-off value of 425 ng/dL (AUC,area under curve).

Clinical, echocardiographic, and laboratory values of the patients with or without systemic embolism are summarized in Table 1. Mean DD level of the patients was estimated as 1001±1543 ng/dL (range, 81-8818 ng/dL). Mean DD levels were significantly higher in the group with clinically manifest embolism (1084 ng/dL [133-8818] vs 301 ng/dL [81-3758], respectively; p=0.016). When the patients were divided in groups with DD >500 ng/dL or <500 ng/dL, clinically manifest embolism was more frequently encountered in the former group (47.4, and 17.4%, respectively (p=0.036).

Receiver operating characteristics (ROC) curve analysis was performed to determine the best cut-off value in the prediction of embolism in the patient group with clinically manifest embolism. Area under the curve (AUC) for DD >425 ng/dL was calculated as 0.735 (95 % CI, 0.560-0.909, p=0.016). DD values above 425 ng/dL predicts clinically manifest embolism with 77 % sensitivity, and 62 % specificity (Figure 1).

Besides, a correlation was found between levels of DD, and .hematocrit (r=-0.31, p=0.045), platelet counts (r=-0.40, p=0.009), serum albumin (r=-0.37, p=0.026) and serum globulin (r=0.38, p=0.028) values.

Despite lack of any correlation between levels of D-dimer and creatinine, in the group with DD >500 ng/dL, higher creatinine levels were detected relative to the other group (2.1±1.8 mg/dL *vs* 1.2±0.8 mg/dL, p=0.045). Although, patients who had embolism had higher levels of DD, their creatinine levels were relatively lower (1.7±1.6 mg/dL *vs* 1.5±1 mg/dL , p=0.07).

DISCUSSION

The study included a total of 42 (9 females, and 33 males) patients who had met Modified Duke Criteria. In our study we revealed that increased plasma DD (>425 ng/dL) levels predicted clinical systemic embolism with 77 % sensitivity, and 62 % specificity. Mean value of DD levels was 1001±1543 ng/dL (range.81-8818 ng/dL), while higher mean DD levels were detected in the group with clinically manifest embolism (1084 ng/dL [133-8818] *vs* 301 ng/dL [81-3758], p=0.016). Risk of general embolism is relatively higher in the IE group. While in a higher percentage (20-50 %) of patients embolic events associated with increased rates of mortality, and morbidity are seen. In a study performed to determine epidemiologic, clinical, and microbiological characteristics of IE in our country, embolic complications were reported to be 1.4 % among a total of 47 study participants.[6]

Normal DD levels in cases with deep vein thrombosis, and pulmonary embolism are important parametres in establishing diagnosis of exclusion [7,8] In addition to these medical conditions, DD

levels are known to increase in cases with arterial thromboembolism such as acute ischemic stroke [9], myocardial infarction, and peripheral arterial embolism.[10,11] Besides, higher DD levels were detected in the presence of non-occlusive thrombus located on the mechanical heart valve , and systemic embolism.[12]

Systemic embolism is a frequently (20-50 %) encountered complication in infective endocarditis, but its incidence drops down to 6-21 % with the onset of antibiotherapy.[4] Increase in the size of vegetation is considered as a relatively higher risk factor for embolism.[4,13] Increase in the size, and mobility of vegetation, infections with staphylococci, *Streptococcus Bovis* , and candida, history of embolism, involvement of more than one heart valve, and higher levels of some biological markers enhance the risk of systemic embolism.[13-17] Systemic embolism seen in bacterial infections might be secondary to the activation of coagulation cascade, and endothelial damage. Studies performed so far have demonstrated systemic bacterial infections as independent risk factors for embolic events.[14,18,19]

Higher C-reactive protein level, younger age, and increase in the size of vegetation were found to be associated with systemic embolism.[16] Still, in a separate study, a correlation was detected between increased mean platelet volume, and embolism.[17]

Increased levels of DD were found in cases with thromboembolism among patients with nonbacterial thrombotic endocarditis secondary to a solid tumour.[20] In patients with IE, a correlation between thromboembolism, and increased activation of systemic coagulation, enhanced thrombocytic activation/damage, and impaired fibrinolysis has been demonstrated.[15]

In the pathogenesis of infective endocarditis, production of tissue factor following endothelial impairment due to mechanical stress, and accumulation of fibrin, and platelets as a component of a normal healing process play important roles. [4] Several investigations have demonstrated increased DD levels in conditions where fibrin formation, and fibrinolysis occur. [1,2] Similarly, in our patients with IE, as a novel finding, a significant correlation between higher DD levels, and systemic embolism was detected. In our study additional imaging studies were not carried on so as to reveal cases with silent embolism. However, increased DD levels in IE, might be a predictive factor for silent or clinically manifest systemic embolism. Early detection of silent embolisms might be a guiding tool in arranging treatment, and deciding early surgical intervention. In such cases, determination of DD levels instead of using more expensive, and invasive methods which cause additional health problems, and affect the survival of

the patient adversely (radiation, use of nephrotoxic agents) is a simple and potentially important armamentarium contributing to the establishment of early diagnosis, and treatment. However novel, and more comprehensive studies should be planned to that end.

Conflict of interest: None declared

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Key words: Endocarditis, bacterial/etiology/therapy; embolism/blood; D-dimer; blood coagulation.

Anahtar sözcükler: Endokardit, bakteriyel/etiyoloji/tedavi; emboli/kan; D-dimer; kan koagülasyonu.