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Evaluation of Systemic Embolism in Patients with Prosthetic Valve Endocarditis: Key Insights and Implications

Protez Kapak Endokarditi Olan Hastalarda Sistemik Embolinin Değerlendirilmesi: Temel Kavrayışlar ve Çıkarımlar

ABSTRACT

Objective: Prosthetic valve endocarditis (PVE) is a serious complication following heart valve surgery, presenting considerable diagnostic and therapeutic challenges. Despite advances in treatment, systemic embolism remains a major adverse event associated with poor outcomes. This study aimed to identify predictors of in-hospital systemic embolism in patients with PVE and to evaluate treatment outcomes.

Method: This retrospective, single-center study included 96 patients diagnosed with mechanical PVE between 2012 and 2024. Diagnoses were established based on the modified Duke criteria. Data on demographics, comorbidities, clinical presentation, imaging findings, and treatment strategies were collected and analyzed. Multivariate logistic regression and receiver operating characteristic (ROC) curve analysis were employed to identify risk factors.

Results: The study cohort had a median age of 52.4 years (range 22–82). Systemic embolic events occurred in 39 patients (40.6%), with stroke being the most common manifestation (26%). Multivariate analysis identified vegetation size as the only independent predictor of systemic embolism (odds ratio [OR]: 2.34, P = 0.037). ROC analysis determined a vegetation size threshold of 2 cm^2, with 66% sensitivity and 78% specificity. Elevated erythrocyte sedimentation rate (ESR) and a prior history of stroke were also associated with increased embolic risk. Among 31 patients who underwent surgery, early intervention did not significantly reduce embolism rates compared to delayed surgery. Successful treatment was associated with a lower risk of embolism (P = 0.045).

Conclusion: Larger vegetations, elevated ESR, and a prior history of stroke are key risk factors for systemic embolism in PVE. Early identification of high-risk patients and implementation of individualized management strategies are essential to improve clinical outcomes. Further multicenter studies are warranted to refine treatment protocols.

Keywords: Embolism, endocarditis, valve disease

ÖZET

Amaç: Protez kapak endokarditi (PKE), kalp kapak cerrahisinin ardından ortaya çıkan ciddi bir komplikasyondur ve önemli tanı ve tedavi zorlukları yaratır. Tedavideki ilerlemelere rağmen, sistemik embolizm, kötü sonuçlarla ilişkili kritik bir komplikasyon olarak devam etmektedir. Bu çalışma PVE hastalarında hastane içi sistemik embolizm öngörücülerini belirlemeyi ve tedavi sonuçlarını değerlendirmeyi amaçlamıştır.

Yöntem: Bu retrospektif, tek merkezli çalışma, 2012 ve 2024 yılları arasında mekanik PVE tanısı ile kabul edilen 96 hastayı içermektedir. Tanılar, modifiye Duke kriterleri kullanılarak doğrulanmıştır. Demografik veriler, eşlik eden hastalıklar, klinik özellikler, görüntüleme ve tedavi stratejilerine ilişkin veriler analiz edilmiştir. Risk faktörlerini belirlemek için multivaryant lojistik regresyon ve ROC (receiver operating characteristic) analizi kullanılmıştır.

Bulgular: Çalışma grubunun ortanca yaşı 52,4 yıl (aralık 22–82) idi. Sistemik embolik olaylar 39 hastada (%40,6) görüldü ve en yaygın olanı inme idi (%26). Multivaryant analiz, vejetasyon büyüklüğünü sistemik embolizmin tek bağımsız öngörücüsü olarak tanımladı (odds oranı [OR]: 2.34, P = 0.037). ROC analizi, vejetasyon büyüklüğü için 2 cm^2 eşik değerini %66 duyarlılık ve %78 özgüllükle gösterdi. Yüksek eritrosit sedimentasyon hızı (ESR) ve önceki inme öyküsü de daha yüksek embolizm riski ile ilişkiliydi. Cerrahi uygulanan 31 hastada, erken cerrahi ile geç cerrahi arasında embolizm oranlarında anlamlı bir fark bulunamadı. Başarılı tedavi daha düşük emboli riskiyle ilişkilendirildi (P = 0.045).

Sonuç: Büyük vejetasyonlar, yüksek ESR ve önceki inme öyküsü, PKE'de sistemik embolizmin temel risk faktörleridir. Erken tanı ve bireyselleştirilmiş yönetim stratejileri, sonuçları iyileştirmek için gereklidir. Tedavi protokollerini daha da iyileştirmek için çok merkezli araştırmalar gereklidir.

Anahtar Kelimeler: Embolizm, endokardit, kapak hastalığı

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Semih Kalkan[1]
Ahmet Güner[2]
Mustafa Ozan Gürsoy[3]
Macit Kalçık[4]
Mahmut Yesin[5]
Emrah Bayam[6]
Sabahattin Gündüz[7]
Mehmet Özkan[8]

[1]*Department of Cardiology, Başakşehir Çam & Sakura City Hospital, İstanbul, Türkiye*
[2]*Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Türkiye*
[3]*Department of Cardiology, Health Sciences University İzmir Tepecik Training and Research Hospital, İzmir, Türkiye*
[4]*Department of Cardiology, Faculty of Medicine, Hitit University, Çorum, Türkiye*
[5]*Department of Cardiology, Medical Park Hospital, Kocaeli, Türkiye*
[6]*Department of Cardiology, Koşuyolu Heart Training and Research Hospital, İstanbul, Türkiye*
[7]*Department of Cardiology, Faculty of Medicine, Bahçeşehir University, İstanbul, Türkiye*
[8]*Departmentn of Health Sciences, Ardahan University, Ardahan, Türkiye*

Corresponding author:
Semih Kalkan
✉ semihby1@gmail.com

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Prosthetic valve endocarditis (PVE) is a serious and increasingly common complication following heart valve surgery, largely due to the growing number of patients undergoing valve replacement procedures. According to a multicenter study, PVE accounts for approximately 20% of all infective endocarditis (IE) cases.[1] Effective management of PVE requires prompt diagnosis and the implementation of appropriate treatment strategies, ranging from targeted antibiotic therapy to surgical intervention, ideally coordinated by a dedicated endocarditis team. The in-hospital mortality rate among PVE patients who experience concomitant stroke can reach as high as 22.8%. Meta-analyses have identified several echocardiographic predictors of systemic embolic events, including vegetation size greater than 10 mm (relative risk [RR]: 1.87), presence of mitral valve vegetations (RR: 1.24), multiple vegetations (RR: 1.63), and mobile vegetations (RR: 2.23).[2] Additionally, double valve replacement, rheumatic heart disease, and fungal infections have been shown to be independent risk factors for stroke in patients with PVE.[3] The aim of this study was to identify additional predictors of in-hospital systemic embolism in patients with PVE.

ABBREVIATIONS

18F-FDG PET/CT	18F-fluorodeoxyglucose positron-emission tomography/computed tomography
2D	Two-dimensional
AHA/ACC	American Heart Association/American College of Cardiology
aPTT	Activated partial thromboplastin time
CRP	C-reactive protein
CTA	Computed tomography angiography
CWAs	Cell wall-active agents
ESR	Erythrocyte sedimentation rate
IE	Infective endocarditis
INR	International Normalized Ratio
LMWH	Low molecular weight heparin
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NVE	Native valve endocarditis
NYHA	New York Heart Association
OCT	Optical coherence tomography
PVE	Prosthetic valve endocarditis
ROC	Receiver operating characteristic
RR	Relative risk
RT-3D	Real-time three-dimensional
SPECT/CT	Single-photon emission computed tomography/computed tomography
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
UFH	Unfractionated heparin

Materials and Methods

This single-center retrospective study included 96 consecutive patients with mechanical PVE, enrolled between 2012 and 2024. The patients ranged in age from 22 to 82 years, with a median age of 52.4 years. Data on comorbidities, the type and anatomical location of prostheses, time elapsed since initial valve surgery, and baseline International Normalized Ratio (INR) levels were collected from patient records and the National Health Database. Inclusion criteria were: prior prosthetic heart valve surgery, diagnosis of PVE according to the modified Duke criteria, documented systemic embolism, and availability of complete clinical, imaging, and laboratory data. Exclusion criteria included end-stage malignancy, primary or acquired immunodeficiency, incomplete echocardiographic or inconclusive diagnostic imaging findings, or failure to fully meet Duke criteria with low clinical suspicion for PVE. The study was approved by the Başakşehir Çam Sakura City Hospital Ethics Committee (Approval Number: E-96317027-514.10-229614178, Date: 21.11.2023), and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants. No component of this study involved the use of artificial intelligence (AI)-assisted technologies, including but not limited to large language models (LLMs), chatbots, or image generation tools.

The definition of IE in this study was based on the modified Duke criteria, in which echocardiography and blood cultures play a central role. According to these criteria, if a diagnosis was classified as "possible" or "rejected" but a high level of clinical suspicion persisted, repeat echocardiography and blood cultures were warranted. Classic physical examination findings suggestive of PVE included fever, a new or changing heart murmur, rigors, Osler's nodes, and Janeway lesions. The identification of paravalvular lesions by transesophageal echocardiography (TEE) was considered a major criterion. Additionally, abnormal activity around the implantation site detected by 18F-fluorodeoxyglucose positron-emission tomography/computed tomography (18F-FDG PET/CT) (if the prosthesis had been implanted more than three months prior) or by radiolabeled leukocyte single-photon emission computed tomography/computed tomography (SPECT/CT) was also considered a major criterion in suspected cases of PVE. Other imaging modalities, such as cerebral magnetic resonance imaging (MRI) and whole-body CT, were used to identify systemic embolic events.[4]

Stroke was defined as a focal or global neurological deficit resulting from hemorrhagic or ischemic vascular injury to the brain, spinal cord, or retina. This definition also encompassed transient ischemic attack (TIA), which involves temporary cerebral infarction.[5] The initial imaging modality used to evaluate stroke and exclude hemorrhage was non-contrast head CT. Following this, computed tomography angiography (CTA) was performed to detect intracranial large vessel occlusions as well as cervical carotid or vertebral artery disease. If CT findings were inconclusive, MRI and magnetic resonance angiography (MRA) were utilized to obtain additional diagnostic information.[6] Vegetations can cause coronary embolism, and obstruction of the coronary arteries may result in myocardial ischemia or infarction. Diagnostic modalities such as CT, coronary angiography, intravascular ultrasound, and optical coherence tomography were employed to confirm coronary embolism.[7] The diagnosis of mesenteric, peripheral, and splenic embolism relied on a combination of clinical assessment, imaging studies, and laboratory findings. Mesenteric embolism was often suspected in patients presenting with acute abdominal pain and confirmed using contrast-enhanced computed

tomography, which provides detailed visualization of vascular occlusions and signs of bowel ischemia.[8] Peripheral embolism, affecting the limbs or other extremities, is diagnosed based on clinical signs such as sudden pain, pallor, or absent pulses, with duplex ultrasonography or CTA serving as confirmatory diagnostic tools.[9] Splenic embolism, which may present with left upper quadrant pain and splenomegaly, is typically identified via contrast-enhanced CT, which reveals perfusion deficits and splenic infarcts.[10] Early diagnosis using these imaging modalities is critical for appropriate management and to reduce the risk of complications.

Patients were managed by a multidisciplinary team comprising cardiologists, cardiac surgeons, infectious disease specialists, microbiologists, radiologists, neurologists, neurosurgeons, and congenital heart disease experts. This team ensured rapid access to essential diagnostic modalities, including transthoracic echocardiography (TTE), TEE, CT, MRI, and nuclear imaging. In accordance with current clinical guidelines, the team collaboratively determined the type, duration, and follow-up strategy for antibiotic therapy.[11]

Imaging, Clinical, and Laboratory Assessment

Echocardiographic images were independently evaluated by cardiologists with over ten years of experience. TTE was performed on all patients using either the Vivid 7 Dimension® (GE Vingmed Ultrasound AS N-3190, Horten, Norway) or the Philips iE33 (Philips Medical Systems, Andover, Massachusetts) echocardiography systems, both equipped with the S5-1 sector array transducer. However, TTE is significantly limited by prosthetic valve structures and is often inadequate for assessing the perivalvular area, where infections frequently originate. Therefore, all patients subsequently underwent two-dimensional (2D) and real-time three-dimensional (RT-3D) TEE using an X7-2t transducer on a Philips iE33 ultrasound system (Philips Medical Systems, Andover, Massachusetts).

Diagnostic criteria for identifying vegetations were based on previously published studies.[12] In most patients, both 2D and RT-3D TEE were used to differentiate vegetations from healed vegetations, marantic endocardial lesions, and non-infective thrombotic formations. CT imaging provided high-resolution cross-sectional views of the heart and surrounding anatomical structures, aiding in the detection of complications such as abscesses, pseudoaneurysms, and extension of infection beyond the cardiac valves.[13] For patients with inconclusive findings, 18F-FDG PET/CT was employed as an additional diagnostic tool to detect active lesions.[14] Upon admission, all patients underwent a complete blood count and biochemical tests, with results retrieved from the hospital database. Additional clinical data, including demographics, medical history, rhythm abnormalities, New York Heart Association (NYHA) functional class, and presenting symptoms, were collected from both hospital records and telephone interviews (Table 1).

Treatment Strategies

Treatment for IE should begin as early as possible. Before initiating antibiotic therapy, three sets of blood cultures were obtained from each patient at 30-minute intervals.[15] Our treatment regimen was consistent with recent guidelines regarding antibiotic duration and combination strategies.[4] However, we primarily utilized cell wall-active agents (CWAs) such as daptomycin and vancomycin, in combination with aminoglycosides, rather than penicillin-based antibiotics. The antibiotic regimen was adjusted based on pathogen identification, typically within 48 hours.

An additional anticoagulation strategy during hospitalization involved the use of low molecular weight heparin (LMWH) or unfractionated heparin (UFH). In the UFH group (n = 20), warfarin was discontinued, the INR was monitored daily, and UFH was initiated once the INR dropped below 2, targeting an activated partial thromboplastin time (aPTT) of 1.5–2.5 times the control value. UFH was discontinued six hours prior to planned surgery. The remaining patients (n = 76) received LMWH therapy during hospitalization, with enoxaparin dosed according to body weight and creatinine clearance, as calculated using the Cockcroft-Gault equation.

Urgent surgery was considered for patients presenting with heart failure, valve dehiscence, progressive vegetation growth, persistently elevated infectious markers. In all other cases, surgery was deferred until completion of the antibiotic course.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA, 2016). Descriptive statistics were reported based on variable type as follows:

1. Categorical variables were expressed as numbers and percentages.
2. Numerical variables were presented as means and standard deviations.
3. Variables not meeting the above criteria were reported as medians with minimum and maximum values.

Group comparisons for categorical variables were performed using the Chi-square test. For numerical variables, comparisons between two independent groups were conducted using the Student's t-test when the data followed a normal distribution; otherwise, the Mann-Whitney U test was applied. Logistic regression analysis and receiver operating characteristic (ROC) curve analysis were used to evaluate statistically significant risk factors. The alpha level for statistical significance was set at P = 0.05. The Hosmer-Lemeshow test was used to assess the goodness-of-fit and accuracy of the logistic regression model.

Results

The study population consisted of 96 patients with PVE, including 53 males and 43 females, with a mean age of 52.4 ± 12.2 years. Among these, 39 patients experienced systemic thromboembolic events, including three cases of multifocal embolism. Specifically, 26% (n = 25) suffered strokes, 15.6% (n = 15) experienced coronary embolism, and 4.2% (n = 4) had peripheral embolization. The mean vegetation size associated with each embolic event was as follows: 1.739 cm^2 for cerebral embolism, 1.793 cm^2 for coronary embolism, and 2.82 cm^2 for mesenteric and splenic embolism. However, no statistically significant difference was observed between these groups (P = 0.078). The distribution of prosthetic valve locations among patients was as follows: 42 (43.7%) aortic, 47 (48.9%) mitral, five (5.2%) both aortic and

Table 1. Previous Diagnoses, Valve Types, and Clinical Features at the Time of Patient Admission

Variables	All Patients (n = 96)	No Embolism in Hospitalization (n = 57)	Embolism in Hospitalization (n = 39)	P
Age	52.4 ± 12.2	52.1 ± 11.4	52.8 ± 13.4	0.779
Men	53 (55.2)	30 (52.6)	23 (59.0)	0.779
Hypertension	47 (49.0)	27 (47.4)	20 (51.3)	0.706
Diabetes Mellitus	30 (31.3)	15 (26.3)	15 (38.5)	0.207
Stroke History	18 (18.8)	6 (10.5)	12 (30.8)	0.013
TIA History	3 (3.4)	2 (3.5)	1 (3.3)	1.000
Atrial Fibrillation	19 (19.8)	11 (19.3)	8 (20.5)	0.883
Redo Operation	12 (14.6)	6 (11.1)	6 (21.4)	0.322
Fever	62 (64.6)	40 (70.2)	22 (56.4)	0.166
Weakness	10 (10.4)	8 (14.0)	2 (5.1)	0.193
Dyspnea	24 (25.0)	16 (28.1)	8 (20.5)	0.401
Decompansated Heart Failure	8 (8.3)	7 (12.3)	1 (2.6)	0.137
Septic Embolism On Admisssion	3 (3.1)	2 (3.5)	1 (2.6)	1.000
Wound Site Infection	3 (3.1)	2 (3.5)	1 (2.6)	1.000
Sternal Dehiscence	1 (1.0)	0 (0)	1 (2.6)	0.406
NYHA				0.438
1	44 (45.8%)	28 (49.1%)	16 (41.0%)	
2	37 (38.5%)	20 (35%)	17 (43.5%)	
3	13 (13.5%)	7 (12.2%)	6 (15.3%)	
4	2 (2%)	2 (2%)	0 (0%)	
Valve				
AVR	51 (58.6)	34 (59.6)	17 (56.7)	0.788
MVR	56 (64.4)	38 (66.7)	18 (60.0)	0.537
TVR	1 (1.1)	1 (1.8)	0 (0)	1.000
PVR	1 (1.1)	1 (1.8)	0 (0)	1.000
ETSV	30.5 (12.25-84)	36 (14-90)	25 (5-81)	0.366

TIA, Transient Ischemic Attack; NYHA, New York Heart Association (NYHA) Functional Classification; AVR, Aortic Valve Replacement; MVR, Mitral Valve Replacement; TVR, Tricuspid Valve Replacement; PVR, Pulmonary Valve Replacement; ETSV, Elapsed Time Since Valve Surgery.

mitral, one (1%) tricuspid, and one (1%) pulmonary. A history of redo valve surgery was present in 12 patients (14.6%), and 95 patients (98.9%) had bileaflet valves.

Comorbidities within the study cohort included hypertension in 47 patients (49%), diabetes mellitus in 30 (31.3%), atrial fibrillation in 19 (19.8%), and a previous history of stroke in 18 (18.8%). Patients with a previous history of stroke showed a significant association with the development of systemic embolism, including stroke, during hospitalization. Thirteen patients (15.5%) presented with NYHA class III-IV symptoms. The median time since valve surgery was 30.5 months (range: 12.25 to 84 months), and the mean INR at admission was 2.3 ± 0.68. On admission, the most common presenting symptoms were as follows: 62 patients (64.6%) had fever, 24 (25%) had dyspnea, 17 (17.7%) experienced exhaustion and general deterioration, eight (8.3%) presented with decompensated heart failure, and four (4.1%) were admitted with sternal wound infection and dehiscence. Blood cultures were positive in 45 patients (46.9%) and negative in 51 (53.1%), with no statistically significant difference between the embolism and non-embolism groups (P = 0.612). The most common pathogens identified were *Staphylococcus spp*. (31.8%) and *Candida spp*. (7.1%), with similar distributions between groups.

Among patients who did not undergo surgery (n = 65, 67.7%), 28 experienced embolism. A total of 31 patients underwent surgery: 24 had delayed surgery, and seven underwent early surgery. In the delayed surgery group (n = 24, 25%), eight patients (20.5%) developed systemic embolism, compared to 16 (28.1%) who did not. In the early surgery group (n = 7, 7.3%), three (7.7%) patients experienced systemic embolism, compared to four patients (7%) who did not. Mortality was significantly higher in the early surgery group (n = 6) compared to the delayed surgery group (n = 8) (P = 0.04). The mean vegetation area was 2.25 cm^2 in the early surgery group and 1.73 cm^2 in the delayed surgery group; however, this difference was not statistically significant (P = 0.24). Additionally, there was no significant difference in the incidence of systemic embolism between the two groups (P = 0.703). All patients were monitored using both TEE and TTE. During follow-up, 56 patients (58.3%) showed a reduction of more than 50% in vegetation burden, without death or

Table 2. Laboratory and Culture Results of the Patients

Variables	All Patients (n = 96)	No Embolism in Hospitalization (n = 57)	Embolism in Hospitalization (n = 39)	P
HGB (g/dL)	10 (9–11.1)	10 (8.95–11)	10 (9.1–11.5)	0.429
WBC (10^3/μL, min–max)	13.6 ± 5.2 (3.9–30)	14.0 ± 5.1 (4.8–28)	13.0 ± 5.5 (3.9–30)	0.391
PLT (WBC (10^3/μL)	230 (200–280)	230 (200–275.5)	225 (188.5–301.25)	0.986
ESR (min–max)	67.8 ± 28.2 (11–126)	61.6 ± 28.5 (11–116)	82.3 ± 22.1 (45126)	**0.010**
Follow-up ESR	27 (15–68)	22 (15–85.5)	29 (14.75–66.5)	0.785
CRP	6 (2–20.5)	5.5 (1.04–22.25)	8 (2–18.5)	0.606
Follow-up CRP	115 (100–134)	112 (100–130)	115 (100–147.75)	0.434
Glucose	43 (32–56)	42 (32.5–55)	44.5 (29.75–65.25)	0.535
BUN	27 (15–68)	22 (15–85.5)	29 (14.75–66.5)	0.785
Creatinine	0.93 (0.8–1.19)	0.9 (0.72–1.20)	1 (0.8–1.18)	0.488
Sodium	135 (133–138)	135 (133–138)	135 (133–137)	0.559
Potassium	4 (3.8–4.33)	4.05 (3.8–4.45)	4 (3.85–4.2)	0.329
Culture				
Positive	45 (46.9)	25 (43.9)	20 (51.2)	0.612
Negative	51 (53.1)	32 (56.1)	19 (48.7)	
Candida spp.	6 (7.1)	4 (7.0)	2 (7.1)	1.000
Staf spp.	27 (31.8)	18 (31.6)	9 (32.1)	0.958
Troponin	0.1 (0–0.39)	0.02 (0–0.13)	0.22 (0.03–0.78)	**<0.001**
Procalsitonin	2.69 (0.31–45.95)	2 (0.319–42)	4.2 (0.30–140)	0.394
Follow-up HGB	9.75 (7.45–10.68)	9.8 (6.9–11.5)	9.7 (8.1–10.65)	0.834
Follow-up PLT	191.9 ± 126.5 (0–461)	188.7 ± 132.8 (0–461)	197.2 ± 122.8 (0–403)	0.877
INR on Admission	2.12 (1.6–2.98)	2.2 (1.72–3.1)	2.05 (1.4–2.56)	0.812
Blood Type				
0	20 (25.3)	13 (25.5)	7 (25.0)	0.962
A	37 (46.8)	26 (51.0)	11 (39.3)	0.319
B	17 (21.5)	10 (19.6)	7 (25.0)	0.577
AB	5 (6.3)	2 (3.9)	3 (10.7)	0.340
RH				0.497
Negative	12 (15.4)	8 (15.7)	4 (14.8)	
Positive	66 (84.6)	43 (84.3)	23 (85.2)	

HGB, Hemoglobin; WBC, White Blood Cell; PLT, Platelet; CRP, C-Reactive Protein; ESR, Erythrocyte Sedimentation Rate; BUN, Blood Urea Nitrogen; INR, International Normalized Ratio.

with manageable complications, indicating effective medical and surgical treatment. In the non-embolism group, nine patients (19.7%) died, compared to 10 patients (25.5%) in the embolism group; this difference was not statistically significant (P = 0.081). Among the patients who died, the valve was located in the aortic position in seven cases and in the mitral position in 12 cases. Erythrocyte sedimentation rate (ESR) was significantly higher in patients with systemic embolism compared to those without (61.6 ± 28.5 [range: 11–116] vs. 82.3 ± 22.1 [range: 45–126]; P = 0.01). In patients who survived, the median ESR was 61 mm/h, and the median procalcitonin level was 3.9 μg/L. Vegetation mobility was observed in the majority of patients (n = 64, 66.6%), with 37 cases (64.9%) in the embolism group and 27 cases (69.2%) in the non-embolism group (P = 0.826). Conversely, among patients who died, the median ESR increased to 80.5 mm/h, and the median procalcitonin level was 5.6 μg/L (P = 0.206 and P = 0.075, respectively). As expected, treatment success was significantly protective against the development of systemic embolism during follow-up (P = 0.045). The vegetation area in patients with embolism was significantly larger than in those without embolism, as assessed by 2D echocardiography (1.25 [range: 0.9–2] vs. 2.4 [range: 1.5–3.2]; P < 0.001). In RT-3D TEE, the mean vegetation sizes were 1.2 cm^2 and 2.38 cm^2, respectively (P < 0.001).

Tables 1–3 summarize the demographic, clinical, laboratory, and echocardiographic characteristics of the study cohort. Univariate logistic regression analysis identified the following as significant predictors of systemic embolism: history of stroke (odds ratio [OR]: 3.778, P = 0.016), vegetation area (OR: 3.8, P ≤ 0.001), treatment success (OR: 0.429, P = 0.047), and ESR (OR: 1.031,

Table 3. Analysis of the Embolism Subgroup, Echocardiographic Findings, Treatment Strategies, and Treatment

Variables	All Patients (n = 96)	No Embolism in Hospitalization (n = 57)	Embolism in Hospitalization (n = 39)	P
Cerebral Embolism	25 (26)	0	25 (64.1)	1.000
Coronary Embolism	15 (15.6)	0	15 (38.4)	1.000
Peripheral Embolism	4 (4.1)	0	4 (10.2)	1.000
Decreased Valve Area	1.6 (1.1-1.9)	1.6 (1.125-1.98)	1.8 (1-1.9)	0.634
Leaflet				1.000
Monoleaflet	1 (1)	1 (1.8)	0 (0,0)	
Bileaflet	95 (99)	56 (98.2)	39 (100)	
Vegetation Size (cm^2)	1.5 (1-2.5)	1.25 (0.9-2)	2.4 (1.5-3.2)	**<0.001**
Mobile Vegetation	64 (66.6)	37 (64.9)	27 (69.2)	0.826
Time of Surgery				0.703
No Surgery	65 (67.7)	37 (64.9)	28 (71.8)	
Early Surgery	7 (7.3)	4 (7.0)	3 (7.7)	
Delayed Surgery	24 (25)	16 (28.1)	8 (20.5)	
Antibiotics Amount	2 (2-3)	2 (2-3)	2 (0-3)	0.119
Antiobiotherapy Length (day)	21 (14-39.75)	21 (14-35)	22 (14-42)	0.383
Use of Unfractioned Heparin	25 (27)	16 (28)	9 (23)	0.756
Use of LMWH	71 (79.1)	41 (71.9)	30 (76.9)	0.270
Death	19 (19.7)	9 (16)	10 (25.5)	0.081
Treatment Success	56 (58.3)	38 (66.7)	18 (46.2)	**0.045**

LMWH, Low Molecular Weight Heparin.

P = 0.016) (Table 4). In multivariate logistic regression analysis, only vegetation area remained a significant risk factor for systemic embolism (OR: 2.34, P = 0.037) (Table 5). ROC curve analysis for vegetation area yielded a cut-off value of 2 cm^2, with a sensitivity of 66% and a specificity of 78% (Figure 1).

Discussion

In this study, we conducted a comprehensive evaluation of systemic thromboembolism in patients with PVE, based on the largest series reported in the literature to date. The primary finding was that vegetation size is a significant predictor of systemic embolism during hospitalization in patients with PVE. Additionally, a prior history of stroke and elevated ESR were identified as factors associated with an increased risk of embolic events.

Accurately predicting embolic events in infective endocarditis is critical for optimizing therapeutic decision-making. In patients with infective endocarditis, cerebral embolism is associated with higher mortality and an increased risk of perioperative complications. Importantly, the presence of cerebral embolism, whether symptomatic or asymptomatic, does not appear to significantly affect overall clinical outcomes.[16] Although both native valve endocarditis (NVE) and PVE fall under the broader category of infective endocarditis, they differ substantially in terms of epidemiology, pathophysiology, microbiology, and clinical management.[17] However, no significant differences have been identified in the incidence of cerebral embolism between NVE and PVE.[18] Vegetation size has emerged as a significant predictor of embolic events, with larger vegetations associated with an increased risk of embolism, likely due to their greater propensity for fragmentation and detachment.[19] Understanding the relationship between vegetation size and cerebral embolism is essential for risk stratification, informed therapeutic decision-making, and the prevention of adverse neurological outcomes in patients with endocarditis. A meta-analysis demonstrated that patients with vegetations larger than 10 mm were significantly more likely to experience embolic events and had a higher risk of mortality compared to those with smaller vegetations.[20] Our study's findings suggest that vegetation size (using a cut-off value of 2 cm^2 on 2D-TEE, with 66% sensitivity and 78% specificity) may predispose patients to the development of systemic embolism. The mobility rates of vegetations observed in our cohort were consistent with findings reported in previous literature. The presence of mobility was similar in both groups, with no significant differences observed.[21] Moreover, in patient populations outside of PVE, a prior history of stroke has been identified as a risk factor for developing a subsequent stroke.[22] Therefore, clinicians should remain vigilant in managing patients with PVE who have a history of stroke, as they may be at increased risk for recurrent cerebrovascular complications upon admission. Our results indicate that a prior history of stroke may predict the development of new systemic embolic events, including recurrent stroke. These findings highlight the importance of comprehensive evaluation and close monitoring of patients with PVE who have a history of stroke, as they may require more aggressive management strategies to prevent future embolic complications. Additionally, further research is needed to investigate the underlying mechanisms of this association and to develop targeted interventions aimed at reducing the incidence of recurrent systemic embolism in this high-risk population.

Table 4. Univariate Logistic Regression Analysis shows the Factors that Increase Systemic Embolism Risk During

Variables	P	Oddss Ratio	95% CI min-maks
Age	0.776	1.005	0.972-1.039
Men	0.540	1.294	0.568-2.946
Hypertension	0.706	1.170	0.518-2.643
Diabetes Mellitus	0.209	1.750	0.730-4.193
Atrial Fibrillation	0.883	1.079	0.390-2.988
Stroke History	**0.016**	3.778	1.276-11.184
TIA History	0.966	0.948	0.082-10.904
INR on Admission	0.071	0.682	0.450-1.033
AB Length (Day)	0.237	1.020	0.987-1.053
Use of UFH	0.956	1.030	0.361-2.938
Decompensated HF	0.125	0.188	0.022-1.593
Infected Valve (AVR)	0.788	0.885	0.361-2.165
Infected Valve (MVR)	0.538	0.750	0.300-1.872
Decreased Valve Area	0.255	0.550	0.197-1.539
Vegetation Size	**<0.001**	3.800	2.068-6.981
Dsypnea	0.403	0.661	0.251-1.742
Fever	0.168	0.550	0.235-1.287
Weakness	0.178	0.331	0.066-1.652
ETSVS (months)	0.521	0.998	0.992-1.004
Early Surgery	0.991	0.991	0.205-4.709
Late Surgery	0.407	0.661	0.248-1.761
Treatment Success	**0.047**	0.429	0.186-0.989
Staf spp.	0.958	1.026	0.389-2.707
Candida spp.	0.983	1.019	0.175-5.93
HG	0.337	1.154	0.862-1.545
WBC	0.388	0.962	0.881-1.051
PLT	0.816	1.001	0.995-1.006
ESR	**0.016**	1.031	1.006-1.056
Follow-up ESR	0.147	1.014	0.995-1.034
CRP	0.824	0.999	0.992-1.006
Follow up CRP	0.705	1.002	0.992-1.012
Troponin	0.989	0.999	0.870-1.147

CI, Confidence interval; TIA, Transient Ischemic Attack; NYHA, New York Heart Association (NYHA) Functional Classification; AVR, Aortic Valve Replacement; MVR, Mitral Valve Replacement; TVR, Tricuspid Valve Replacement; PVR, Pulmonary Valve Replacement; ETSV, Elapsed Time Since Valve Surgery; HF, Heart Failure; AB, Antibiotherapy; UFH, Unfractioned Heparin.

Table 5. Multivariate Logistic Regression Analysis Finds Vegetation Size is Only Significant Factor for Systemic Embolism During Hospitalization (Hosmer and Lemeshow P = 0.968)

Variables	P	Oddss Ratio	95% CI min-maks
Vegetation Size (cm^2)	**0.037**	2.340	1.052-5.204
Treatment Failure	0.730	1.323	0.270-6.478
ESR	0.126	1.024	0.993-1.055
Stroke History	0.722	1.427	0.202-10.10

CI, Confidence interval; ESR, Erythrocyte Sedimentation Rate.

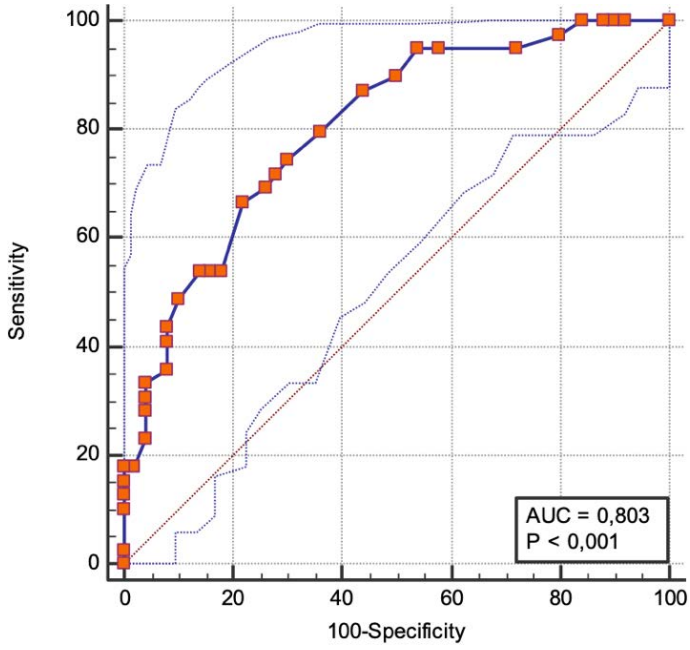

Figure 1. Receiver operating characteristic (ROC) curve analysis for vegetation area, demonstrating a cut-off value of 2 cm^2 with a sensitivity of 66% and specificity of 78%.

Despite advancements in antibiotic regimens and surgical techniques, PVE remains associated with high morbidity and mortality. In our study, the overall mortality rate was 19.7%, which is consistent with findings reported in the literature.[2] Combination therapy and pathogen-specific treatment are critical components of effective antibiotic management. At our center, the heart valve team frequently employs combination therapy using CWAs such as daptomycin and vancomycin, in conjunction with aminoglycosides. This regimen is particularly effective in treating PVE caused by *viridans* group *Streptococci* and *Staphylococcus aureus*, often requiring the addition of rifampin with a prolonged antibiotic course lasting more than six weeks. Double beta-lactam therapy may also be effective when the causative microorganism is *Enterococcus spp*.[15] Approximately half of patients with IE may require surgical intervention during their hospitalization.[23] In our series, 31 patients (32.3%) required surgery. All cases of complex IE, such as endocarditis involving heart failure, abscess formation, or embolic and neurological complications, necessitate early consultation with the surgical team and access to appropriate facilities to ensure optimal management. In patients with PVE, warfarin therapy should be carefully discontinued in anticipation of potential surgical intervention. The general approach in such cases is to transition to LMWH. However, determining the optimal LMWH dose can be challenging, as it depends on factors such as body weight and renal function. To ensure appropriate dosing, monitoring of anti-Factor Xa levels in the blood is recommended.[24] In some patients, to avoid the complexities associated with LMWH dosing, UFH was used as an alternative.

These patients were closely monitored to maintain an activated aPTT within the therapeutic range, targeting 60 to 70 seconds, with assessments performed every six hours. This approach aimed to achieve effective anticoagulation while minimizing the risk of bleeding or thromboembolic events. In our series, no significant difference in the incidence of systemic embolism was observed between patients treated with UFH and those receiving LMWH. The effectiveness of each anticoagulation strategy may require further investigation through large-scale, comprehensive studies.

The timing of surgery in patients undergoing valve operations remains a subject of ongoing debate.[25] According to the European Society of Cardiology guidelines, surgical indications are categorized as emergent (within 24 hours), urgent (within a few days), and elective (after one-two weeks of antibiotic therapy). In contrast, the American Heart Association/American College of Cardiology guidelines define early surgery as any surgical intervention performed during the initial hospitalization, prior to the completion of a full course of antibiotics.[26] Valve surgery may be postponed in favor of conservative treatment unless the patient presents with heart failure, uncontrolled infection, abscess formation, or a high risk of embolism. Surgery is generally indicated when these complications are present, except in cases where contraindications such as intracranial hemorrhage, coma, severe comorbidities, or acute stroke with extensive damage necessitate delaying surgical intervention under conservative treatment.[27] Early surgery can prevent systemic embolism, further vegetation growth, and serious complications that may lead to heart failure. In contrast, delayed surgery (defined as surgery performed seven days after hospitalization in our study) allows for complete resolution of vegetation and reduces the risk of postoperative IE by allowing antibiotic therapy to control the active infection.[26] However, early surgical intervention may sometimes lead to unnecessary procedures in patients who might respond adequately to antibiotic therapy alone and may also reveal increased tissue fragility. In patients with intracranial hemorrhage, surgery should generally be postponed for at least one month.[28] The timing of cardiac surgery in patients with valvular IE and acute stroke is especially critical, as it involves balancing the neurological risks of systemic heparinization for cardiopulmonary bypass against the ongoing threat of embolization and heart failure. While earlier studies suggested delaying surgery to reduce the risk of hemorrhagic transformation, more recent evidence challenges this view, showing no significant benefit in postponing surgery beyond 48 hours after stroke onset.[27] In our study, no significant difference was observed between early and delayed surgery with respect to the incidence of systemic embolism. However, we found that the risk of stroke decreased when treatment, whether surgical or conservative, was successful during hospitalization.

ESR is a nonspecific marker of inflammation and is frequently elevated in cases of endocarditis. Inflammatory markers such as C-reactive protein and procalcitonin reflect active inflammatory response and serve as valuable diagnostic and prognostic tools in IE.[29] Although ESR and procalcitonin levels were elevated in the mortality group, the differences were not statistically significant when compared to the survival group. However, our findings indicate that elevated ESR levels may correlate with the severity of infection and could be associated with more extensive disease, including complications such as systemic embolism. Additionally, monitoring ESR levels can aid in evaluating treatment effectiveness, as a declining ESR may indicate a positive response to therapy.

Study Limitations

Although this study is retrospective and conducted at a single center, the sample size is relatively adequate given the rarity of PVE. Nevertheless, multicenter studies with larger populations are needed to provide more robust data on early versus late surgical intervention and to help clarify the controversial aspects of this topic. Including details about surgical techniques and the experience of the operating surgeons may offer further insights into surgical outcomes. While vegetation size emerged as a significant parameter in our study, characterizing vegetations based on mobility and shape may also prove useful in assessing the risk of embolism.

Conclusion

Despite advancements in diagnostic tools and therapeutic strategies, PVE remains associated with high morbidity and mortality. One of the most serious complications contributing to these outcomes is systemic thromboembolism. This study identified several significant risk factors for development of systemic thromboembolism, including a prior history of stroke, vegetation size exceeding 2 cm^2, elevated ESR, and treatment failure. These factors should be carefully considered by the endocarditis team when determining treatment strategies.

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