

Long-term outcome in patients with prosthetic valve endocarditis: results from a single center in Turkey

Protez kapak endokarditinde uzun dönem hayatta kalma oranları: Türkiye’de tek merkez sonuçlarımız

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ABSTRACT

Objective: Prosthetic valve endocarditis (PVE) is associated with increased mortality and morbidity. Information regarding the long-term outcome of PVE is scarce in Turkey. The aim of this study was to evaluate long-term mortality rates of PVE and identify predictors of mortality in these patients.

Methods: From January 2008 through August 2013, 44 patients (25 male, 19 female; mean age 49.3±12.1 years) who received a definitive diagnosis of PVE enrolled in the study. Median follow-up period was 23 months. Survival status was assessed for each patient by reviewing charts and making contact by phone. Cox regression analysis was used to evaluate outcome predictors.

Results: The mitral valve was the most commonly affected valve and *Staphylococcus aureus* the most prevalent microorganism. Fourteen patients (32%) underwent surgery, 7 of whom underwent early surgery. Overall mortality and in-hospital mortality rates were 39% (n=17) and 25% (n=11), respectively. In multivariate analysis, NYHA classification >2 (hazard ratio [HR] 3.7; 95% confidence interval [CI], 1.16–11.8; p=0.03), early-onset PVE (HR 4.23; 95% CI, 1.1–16.42; p=0.04), vegetation size ≥10 mm (HR 3.94; 95% CI, 1.1–14.75; p=0.04), and heart failure (HR 4.18; 95% CI, 1.36–12.8; p=0.01) were found to be independent predictors of mortality.

Conclusion: Our findings suggest that PVE is associated with increased long-term mortality rates. Poor functional status, early-onset PVE, heart failure, and vegetation size are independent predictors of survival in patients with PVE.

ÖZET

Amaç: Protez kapak endokarditi (PKE) artmış mortalite ve morbidite ile beraberdir. Ülkemizde PKE'nin uzun dönem sonuçlarına ait veriler oldukça azdır. Çalışmamızda, PKE'nin uzun dönem mortalite oranlarını ve bu hastalarda mortalite belirteçlerini saptamayı hedefledik.

Yöntemler: Ocak 2008-Ağustos 2013 tarihleri arasında PKE tanısı konan 44 hasta (25 erkek, 19 kadın; ortalama yaş 49.3±12.1 yıl) araştırmaya dahil edildi. Ortanca takip süresi 23 aydı. Hastaların hayatta kalma durumları hastane kayıtlarından ve telefonla iletişim kurularak belirlendi. Cox regresyon analizi kullanılarak mortalite belirleyicileri saptandı.

Bulgular: En fazla etkilenen kapak mitral kapak ve en çok saptanan mikroorganizma *Staphylococcus aureus* idi. On dört hasta cerrahiye verildi (%32). Bu hastaların 7 tanesi erken cerrahiye alındı. Total mortalite ve hastane içi mortalite sırası ile %39 (n=17) ve %25 (n=11) idi. Çok değişkenli Cox regresyon analizinde, NYHA fonksiyonel sınıf >2 (hazard ratio (HR) 3.7, %95 güven aralığı [GA] [1.16–11.8], p=0.03), erken PKE (HR 4.23, %95 GA [1.1–16.42], p=0.04), vejetasyon boyutu ≥10 mm (HR 3.94, %95 GA [1.1–14.75], p=0.04) ve kalp yetersizliği (HR 4.18, %95 GA [1.36–12.8], p=0.01) uzun dönemde mortalitenin bağımsız belirleyicileri olarak saptandı.

Sonuç: Çalışmamızın sonucuna göre PKE artmış uzun dönem mortalite oranları ile ilişkilidir. Kötü fonksiyonel kapasite, kalp yetersizliği, erken PKE ve vejetasyon boyutu sağ kalımın bağımsız belirleyicileri olarak saptanmıştır.

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Prosthetic valve endocarditis (PVE) constitutes 10–30% of all infective endocarditis (IE) cases and occurs in 3–6% of patients within 5 years of valve implantation, affecting mechanical and biological valves.^[1,2] Due to high prevalence of rheumatic valve disease in the Turkish population, patients are younger than those in Western countries, and PVE is more common. In a single center, PVE accounted for 44% of all IE cases, while PVE ratio was reported as 30% in a recent multicenter study.^[3,4]

Despite advanced diagnostic tools and treatment options, PVE is still associated with significant morbidity and mortality.^[1] Short-term follow-up data for PVE is available in Turkey; however, long-term outcome of this aggressive disease is unknown. The aims of this study were to determine long-term mortality rates of patients diagnosed with PVE and to identify independent predictors of mortality in these patients.

METHODS

Study population

Between January 2008 and August 2013, patients diagnosed with IE at Yüksek İhtisas Education and Research Hospital were reviewed retrospectively. PVE definition was made according to modified Duke criteria.^[5] Only patients with definite PVE were enrolled, including those with a history of antibiotic treatment prior to admission. Patients with native valve IE, lead-related IE, and suspicion of PVE, but who did not meet the requirements of definite PVE according to the modified Duke criteria, were excluded. Clinical, echocardiographic, and biochemical findings were recorded for each subject. Predisposing factors including nosocomial infection, previous history of IE, hemodialysis, and immunosuppression were evaluated. Nosocomial infection was defined according to recent guidelines.^[6] Time of the primary valvular surgery was obtained, and PVE occurring within 1 year after valve surgery was defined as early-onset PVE.^[6]

Duration of hospital stay and in-hospital mortality were noted. Complications during hospitalization such as heart failure, renal failure, abscess formation, embolic events, heart block, cerebrovascular events, and surgical treatment for IE were recorded. Cerebrovascular events consisted of one of the following presentations: intracranial hemorrhage, ischemic stroke, or transient ischemic attacks. Renal failure was defined

by serum creatinine concentration exceeding 2 mg/dL during hospital stay. Anemia was defined according to World Health Organization criteria, with hemoglobin <13 g/dL in men and <12 g/dL in women. Functional status was assessed by New York Heart Association (NYHA) classification.

All patients received prolonged antibiotic treatment, as recommended.^[6] Surgical treatment performed prior to completion of standard course of antibiotic therapy was considered early surgery. Clinical event data were collected during follow-up period by reviewing medical files and making contact by phone. Endpoint was incidence of all causes of death during follow-up after index hospitalization. Relapse and reinfection during follow-up was also assessed, as recommended.^[6] The present study was performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Laboratory

Blood samples were obtained after admission, following overnight fasting. Baseline hemoglobin, platelet count, white blood cell count, and sedimentation were measured using an automated hematology analyzer. C-reactive protein, glucose, and creatinine were measured accordingly. Troponin T was measured with an autoanalyzer running commercial assays (Eleclys 2010; Roche Diagnostics, Penzberg, Germany). These assays were reported in ng/mL, and the upper reference limit (99th percentile) was <0.01 ng/mL in studies performed with healthy volunteers. At least 3 sets of blood samples for cultures were obtained from each patient immediately after hospital admission. Any other available fluid, tissue (vegetations or intracardiac abscesses removed at surgery), and foreign body samples were used to isolate microorganisms.

Echocardiography

All patients underwent 2-dimensional transthoracic echocardiography and transesophageal echocardiography (TEE). Echocardiographic examinations were performed with the Vivid 7 system (GE Healthcare, Wauwatosa, WI, USA). Vegetation size was measured using different echocardiographic windows, and max-

Abbreviations:

CI	Confidence interval
HR	Hazard ratio
IE	Infective endocarditis
NYHA	New York Heart Association
PVE	Prosthetic valve endocarditis
<i>S. aureus</i>	<i>Staphylococcus aureus</i>
TEE	Transesophageal echocardiography

imal length was obtained. Diagnosis of dehiscence was indicated by the existence of rocking motion of the prosthetic valve, with an excursion of $>15^\circ$. Left ventricular ejection fraction was calculated by modified Simpson's rule. Severe valvular regurgitation was identified according to guideline recommendations.^[7] Pulmonary artery systolic pressure was estimated by

continuous-wave Doppler imaging of tricuspid regurgitation using Bernoulli equation.^[8]

Statistical analysis

Continuous variables were expressed as mean \pm SD or as median with interquartile range; categorical variables were expressed as numbers and percentages.

Table 1. Baseline demographic, echocardiographic, and clinical characteristics of study patients, and comparison of survivors and non-survivors

	All patients (n=44)	Mortality		p
		Alive (n=27)	Died (n=17)	
Demographics and predisposing conditions				
Female gender, n (%)	19 (43)	12 (44)	7 (41)	0.83
Age (years), Mean \pm SD	49.3 \pm 12.1	47.5 \pm 11.5	52.2 \pm 12.8	0.21
Early-onset PVE, n (%)	7 (16)	2 (7)	5 (29)	0.09
Nosocomial infection, n (%)	2 (5)	0 (0)	2 (12)	0.14
Previous infective endocarditis, n (%)	7 (16)	5 (19)	2 (12)	0.69
Hemodialysis, n (%)	1 (2)	0 (0)	1 (6)	0.38
Immunosuppression, n (%)	1 (2)	1 (4)	0 (0)	1
Prior antibiotic use, n (%)	10 (22.7)	9 (33.3)	1 (5.9)	0.06
Affected valve				
Aortic, n (%)	21 (48)	11 (41)	10 (59)	0.24
Mitral, n (%)	22 (50)	15 (56)	7 (41)	0.35
Multiple, n (%)	1 (2)	1 (4)	0 (0)	1
Echocardiography				
Cardiac abscess, n (%)	7 (16)	1 (4)	6 (35)	0.009
Severe valvular regurgitation, n (%)	14 (32)	4 (15)	10 (59)	0.002
Vegetation \geq 10 mm, n (%)	27 (61)	13 (48)	14 (82)	0.02
Dehiscence, n (%)	13 (30)	5 (19)	8 (47)	0.04
Pulmonary artery pressure (mmHg)	50 (41–65)	40 (33–45)	50 (40–62.5)	0.008
Left ventricular ejection fraction (%)	56.5 (40–60)	58 (40–60)	50 (37.5–60)	0.5
Clinical characteristics and in-hospital outcome				
NYHA >2 , n (%)	17 (39)	6 (22)	11 (65)	0.005
Heart failure, n (%)	15 (34)	5 (33)	10 (67)	0.006
Renal failure, n (%)	18 (41)	7 (26)	11 (65)	0.01
Anemia, n (%)	32 (73)	17 (63)	15 (88)	0.09
Cerebrovascular events, n (%)	8 (18)	5 (33)	3 (18)	1
Complete heart block, n (%)	4 (9)	2 (7)	2 (12)	0.63
Embolic events (excluding cerebral), n (%)	10 (23)	7 (26)	3 (18)	0.72
Surgery, n (%)	14 (32)	8 (30)	6 (35)	0.69
Spleen abscess, n (%)	4 (9)	4 (15)	0 (0)	0.15
Brain abscess, n (%)	1 (2)	1 (4)	0 (0)	1

NYHA: New York Heart Association.

Chi-square tests, Fisher's exact tests, Student's t-tests, and Mann-Whitney U tests were performed when appropriate. Kaplan-Meier survival curves were used to display survival in patient subgroups. Univariate Cox regression was used to evaluate relationship between variables and overall mortality. Variables with a p value <0.1 in univariate analysis were used in a multivariate Cox regression model via backward likelihood ratio to determine independent prognostic factors of mortality. Results of regression analysis were presented as HR and 95% confidence interval (CI). All statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). A p value of 0.05 was considered statistically significant.

RESULTS

A total of 44 patients were enrolled in the present study. The mean age was 49.3±12.1 years, with men comprising 57% (n=25) of the cohort. Median follow-up duration was 23 months. Mean duration of hospital stay was 39 days. All cases presented with a history of prosthetic valve; no cases of percutaneous or surgical repair, bioprosthetic valve, or right-sided PVE

were included. Table 1 summarizes baseline characteristics of the cohort. Mitral valve was the most commonly affected valve. The most frequent pathogen was *Staphylococcus aureus* (*S. aureus*), followed by *Brucella* species. Causative microorganism could not be isolated in 41% of the cases. Of these, 8 patients had history of antibiotic use before initial admission. Median time from primary valve surgery to PVE diagnosis was 48 months. Fourteen patients (32%) underwent surgery, 7 of whom underwent early surgery. Mean time to surgery was 28 days. All patients underwent redo surgery with implantation of prosthetic valves. Eleven patients (25%) died during index hospitalization.

Vegetation was detected in 39 patients, with mean value of 13.6±5.5 mm. Four patients had a history of recent procedure prior to symptoms of PVE: 2 underwent tooth extraction, 1 underwent thyroidectomy, and 1 underwent prostate surgery. Of these, antibiotic prophylaxis occurred in 2 patients; in the other 2, information regarding prophylactic antibiotic use could not be obtained. Complete heart block occurred in 4 patients, 3 of whom required pacemakers.

Table 2. Baseline microbiological profile, biochemical evaluation of study patients, and comparison of survivors and non-survivors

	All patients (n=44)	Mortality		p
		Alive (n=27)	Died (n=17)	
Laboratory parameters on admission				
Hemoglobin (g/dL)	10.8±2	11.5±1.8	9.7±2	0.005
Sedimentation (mm/hr)	34 (23–67.8)	38 (23v67)	34 (26–78.5)	0.81
C-reactive protein (mg/L)	33.3 (10.4–77.2)	36.7 (8.9–77)	19.5 (13–114.2)	0.9
Creatinine (mg/dL)	1.04 (0.77–1.47)	0.94 (0.7–1.1)	1.38 (1.11–2.22)	0.002
Glucose (mg/dL)	101 (89–120.8)	97 (88–120)	106 (95.5–131.5)	0.21
White blood cell count (x10 ³ /μL)	9.95 (7.25–12.6)	10.3 (7.4–14.7)	9.8 (6.7–11)	0.47
Platelet count (x10 ³ /μL)	224.5 (133.8–298)	226 (141–302)	192 (126–292.5)	0.48
Microorganism				
<i>Staphylococcus aureus</i>	11 (25%)	4 (15%)	7 (41%)	0.08
Coagulase-negative <i>Staphylococcus</i>	2 (5%)	1 (4%)	1 (6%)	1
<i>Streptococci</i>	3 (7%)	2 (7%)	1 (6%)	1
<i>Brucella spp</i>	5 (11%)	4 (15%)	1 (6%)	0.63
<i>Enterococci</i>	2 (5%)	0 (0%)	2 (12%)	0.14
Gram-negative bacilli	1 (2%)	1 (4%)	0 (0%)	1
Fungi	1 (2%)	0 (0%)	1 (6%)	0.39
Culture-negative	18 (41%)	14 (52%)	4 (24%)	0.06

During follow-up, 1 patient (2%) had reinfection, and relapse occurred in 2 (5%). Reinfection occurred 22 months after initial PVE. In that patient, initial PVE occurred with coagulase-negative *Staphylococcus*, whereas reinfection occurred with methicillin-resistant *S. aureus*. *S. aureus* infection occurred in 1 relapsing patient, *Brucella* in the other. Both patients relapsed 2 months after discharge and underwent redo surgery after PVE diagnosis.

Overall mortality rate during follow-up period was 39% (n=17). Table 1 shows differences between survivors and non-survivors regarding demographic,

clinical, and echocardiographic properties. Increased mortality rates were seen in patients with NYHA classification >2, vegetation ≥ 10 mm, dehiscence, renal failure, heart failure, cardiac abscess, and severe valvular regurgitation. Systolic pulmonary artery pressure was higher in fatal cases. There was no significant difference regarding the affected valve, surgery, age, or gender among groups.

Table 2 shows results of biochemical and microbiologic analyses, and differences between survivors and non-survivors. Creatinine levels were higher and hemoglobin levels were lower in fatal cases. There were

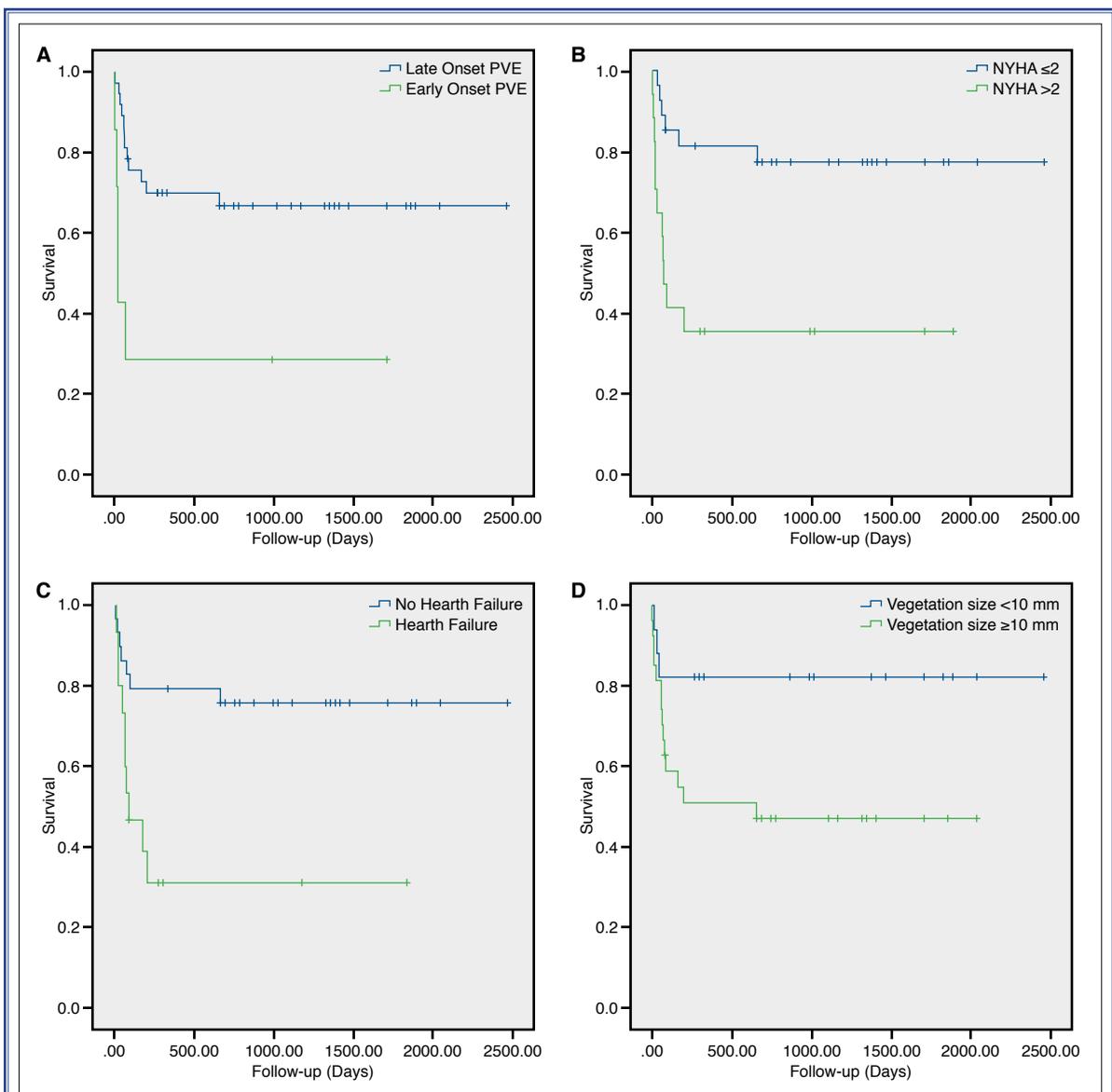


Figure 1. (A) Kaplan-Meier curves displaying outcome in patients with early- vs late-onset PVE, **(B)** NYHA ≤ 2 vs > 2 , **(C)** presence or absence of heart failure, **(D)** vegetation size < 10 mm vs ≥ 10 mm.

Table 3. Predictors of mortality in univariate and multivariate Cox regression analysis

	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	p	HR	(95% CI)	p
Nosocomial infection	4.30	(0.10–18.80)	0.06			
NYHA >2	4.44	(1.63–12.11)	0.004	3.70	(1.16–11.80)	0.03
Early onset PVE	3.98	(1.39–11.45)	0.01	4.23	(1.10–16.42)	0.04
Dehiscense	2.80	(1.10–7.30)	0.04			
Severe valvular regurgitation	4.11	(1.54–10.92)	0.004			
Vejetasyon ≥10 mm	3.46	(0.99–12.18)	0.05	3.94	(1.10–14.75)	0.04
Systolic pulmonary artery pressure	1.04	(1.01–1.07)	0.003			
Cardiac abscess	3.99	(1.45–10.96)	0.007			
Enterococcus infection	7.30	(1.50–35.50)	0.02			
Creatinine	1.40	(1.10–1.79)	0.006			
Hemoglobin	0.73	(0.57–0.94)	0.01			
Heart failure	3.96	(1.48–10.65)	0.006	4.18	(1.36–12.80)	0.01
Renal failure	3.32	(1.22–9.00)	0.02			

no significant differences between groups regarding type of microorganism. In 17 patients, baseline tropoin T measurements were available, and levels were higher in non-survivors (0.12 ng/mL [0.02–0.28] vs 0.02 ng/mL [0.01–0.03], p=0.02).

Results of the Cox regression analysis are shown in Table 3. In multivariate analysis, NYHA classification >2 (HR 3.7; 95% CI, 1.16–11.8; p=0.03), early-onset PVE (HR 4.23; 95% CI, 1.1–16.42; p=0.04), vegetation size ≥10 mm (HR 3.94; 95% CI, 1.1–14.75; p=0.04), and heart failure (HR 4.18; 95% CI, 1.36–12.8; p=0.01) were found to be independent predictors of mortality. Patients were grouped according to independent predictors of mortality. Results of Kaplan-Meier survival analysis are displayed in Figure 1.

DISCUSSION

Although in-hospital outcomes of PVE among the Turkish population are available, no study has evaluated long-term outcomes. In the present study, in-hospital mortality and total mortality rates of PVE were 25% and 39%, respectively. Our findings indicate that the course of PVE is complicated, and adverse outcome is persistent after discharge. Limited functional capacity, heart failure, early-onset PVE, and vegetation size were identified as independent predictors of PVE-related mortality.

Valvular heart disease is of mostly degenerative origin in developed countries, while rheumatic valve diseases compromise a significant proportion of patients in developing countries.^[9] Likewise, rheumatic valve disease is the single most common form of valvular disease in Turkey.^[10] IE cases demonstrate different characteristics than those in Western countries. Mean age of patient population ranges between 45 and 51.^[11,12] In a single-center study conducted in Turkey with 325 native IE and PVE patients, *S. aureus* was identified as the most common microorganism in the overall cohort, whereas different species were isolated in different subgroups: *Streptococcus* in young (<40 years) and native IE patients, *Enterococcus* in older patients (>50 years), and staphylococci species in PVE patients.^[12] In the recent multicenter study by Elbey et al., *S. aureus* was reported as the most common infectious agent in PVE.^[13] Our findings are in agreement with this microbiological profile. However, the second most prevalent microorganism was *Brucella* in our cohort. Şimşek-Yavuz et al. isolated *Brucella* species in 15 IE patients, in 60% of whom PVE was observed, indicating that prosthetic valves are prone to *Brucella* infection. Unfortunately, culture-negative rates appear to persist, according to our results. The majority of these patients had a history of antibiotic use prior to admission, which also explains the trend of lower mortality rates in culture-negative cases.

PVE is associated with significant mortality. In 61 patients with PVE, mortality rate during follow-up period of 3 years was 28%.^[1] This rate was much lower than our findings, indicating that our patients continued to experience adverse outcome during long-term follow-up. In a study by Edlin et al., long-term mortality rate was 25% after PVE surgery.^[14] Additionally, Nonaka et al. reported long-term PVE-related mortality rates of 31%.^[15] In a multicenter study conducted in Turkey, Elbey et al. found that in-hospital mortality rate of PVE was 35%.^[13] Although PVE-related mortality is still high, rates have tended to decrease in recent decades. In-hospital mortality rate at a single center was 53% between 1996 and 2002, declining to 23% between 2003 and 2009.^[1] The decline in recent years may be attributed to decreased abscess formation and heart failure, increased TEE usage, and decreased culture-negative IE rates.^[16] In the present study, in-hospital mortality rate was 25%, in line with recent data.^[1]

Clinical indicators potentially related to poor outcome in PVE have been investigated extensively in previous studies. Age, staphylococci infection, and aortic valve involvement have been associated with poor prognosis.^[17,18] Complications such as heart failure, stroke, intracardiac abscess, and renal failure were found to be strong predictors of in-hospital mortality.^[19–22] Septic shock, severe comorbidity, persistent bacteremia, and nosocomial infection were other predictors.^[19,22] Among the Turkish population, poor functional status and high C-reactive protein measured on admission were associated with increased in-hospital mortality in patients with PVE.^[13]

Studies conducted in the US and Europe show that IE is becoming more prevalent among the elderly population; intracardiac/intravascular devices and prosthetic valves are infected at an increasing rate.^[22] Those observations may also explain changing trends in epidemiological and microbiological spectrums of the disease. Recent multicenter study in Turkey showed that prosthetic valve was the most common predisposing factor in IE (30%). Compared with previous multicenter study of Leblebicioglu et al., the incidence of PVE (17%) has increased substantially (23%). Our group has recently reported the rate of PVE at our center as 45%.^[24] Similarly, in the study of Şimşek-Yavuz et al., PVE accounted for 44% of IE cases in 325 subjects.^[12]

Surgery rate was lower in our cohort than average rates in the literature, and presence of surgery was not associated with outcome.^[2] Despite a consensus that surgery is required in complicated PVE, controversy persists regarding the best treatment method. According to some studies, surgery at an early stage reduces mortality rate.^[22] Recently, in-hospital mortality rate for PVE surgeries was shown to be higher than those of surgeries for native valve IE. However, mortality rates after a long-term follow-up period were similar.^[25] Older age, prevalence of acute renal failure, and longer stay in intensive care units may increase in-hospital adverse event rates in PVE patients, compared to patients with native valve IE. In a multicenter study, out of 1,025 patients with PVE, 490 underwent surgery at an early stage; the remaining 535 received other forms of medical treatment. In this study, early valve replacement was not associated with lower mortality.^[2]

Our findings suggest that long-term prognosis of PVE is poor, though patients are younger and possess fewer comorbid factors than the average patient profile of Western nations. The impact of poor functional status and vegetation size on outcome emphasizes the importance of early diagnosis. Blood culture and TEE play important roles in diagnosis and efficient treatment. Precautions against infection must be taken during invasive procedures in patients with prosthetic valves. Close follow-up is essential in these cases to prevent complications. In all cases, prolonged antibiotic treatment should be administered according to guideline recommendations. PVE is a complex disease, the outcome of which may be affected by various factors. Therefore, complicated cases should be referred to surgery; in other cases, PVE management should be individualized.

Limitations

The main limitations of the present study were retrospective design and small sample size. Our institution is a tertiary care center, and patients are generally referred from other institutions; therefore, the study cohort may not have reflected the characteristics of the general population, and more complicated courses may have been observed. Being a referral center may have led to increased culture-negative results, due to antibiotic use prior to hospital admission. Longitudinal change in inflammatory markers during hospitalization was not evaluated. Given the higher number of

tested variables, compared with the number of events, we could not exclude the risk of chance finding in multivariate Cox regression analysis. Small sample size might have caused wide CIs. Moreover, our cohort consisted of patients with mechanic prosthetic valves; patients with surgical/percutaneous repair or bioprosthetic valves were not included. Due to these limitations, prospective studies are warranted in order to confirm our findings.

Our findings suggest that PVE was associated with significant mortality rates during a median follow-up period of 23 months. Poor functional status, heart failure, early-onset PVE, and vegetation size were independent predictors of long-term survival in these patients.

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