Clinical spectrum, presentation, and risk factors for mortality in infective endocarditis: a review of 68 cases at a tertiary care center in Turkey

Üçüncü basamak bir hastanede infektif endokarditli 68 olguda klinik spektrum, başvuru şekilleri ve mortalite açısından risk faktörlerinin değerlendirilmesi

Aylin Tuğcu, M.D., Özlem Yıldırımtürk, M.D., Corç Baytaroğlu, M.D., Hilal Kurtoğlu, M.D.,[1] Özkan Köse, M.D.,[1] Murat Şener, M.D.,[1] Saide Aytekin, M.D.[1]

Department of Cardiology, Florence Nightingale Hospital, İstanbul;
[1]Department of Cardiology, İstanbul Bilim University, Florence Nightingale Hospital, İstanbul

Objectives: This study was designed to evaluate clinical, laboratory, microbiological, and echocardiographic characteristics of infective endocarditis (IE) at a tertiary care center in Turkey and to identify predictors of in-hospital mortality.

Study design: Based on a systematic retrospective review of clinical records covering 1997 to 2007, we analyzed data and outcomes of 68 patients (40 males, 28 females; mean age 51±20 years) with definite or possible IE according to the modified Duke criteria.

Results: Native valve endocarditis (NVE) was seen in 28 patients (41.2%), and prosthetic valve endocarditis (PVE) was seen in 38 patients (55.9%). Pacemaker endocarditis (PE) was observed in only two patients (2.9%). Nineteen patients (27.9%) had nosocomial IE. The most frequent predisposing factor for NVE was rheumatic heart disease (n=11; 39.3%). Echocardiography failed to show any signs of involvement in five patients (13.2%) with PVE. The most common causative microorganisms of NVE, PVE, and PE were staphylococci (n=28; 41.2%). At least one complication developed in 46 patients (67.7%), congestive heart failure being the most common (n=38; 55.9%). Forty-one patients (60.3%) underwent combined medical and surgical treatment. In-hospital mortality occurred in 17 patients (25%). Mortality rates were 37.5%, 30%, and 14.3% for early and late PVE and NVE, respectively. Mortality was significantly higher with nosocomial IE (57.9%) compared to 12.2% in the remaining patients. In multivariate analysis, septic shock (p=0.011) and nosocomial infection (p=0.032) were independently associated with in-hospital mortality.

Conclusion: Compared to the European series, IE in our cohort occurred in a relatively younger population, with rheumatic heart disease as the most common underlying heart disease. The rates of PVE, nosocomial IE, and surgical treatment were about the same.

Key words: Cross infection; endocarditis, bacterial/therapy/mortality; heart valve prosthesis; hospital mortality; prognosis.

Amaç: Çalışmada, üçüncü basamak bir hastanede infektif endokarditli (İE) olguların klinik, laboratuvar, mikrobiyolojik ve ekokardiyografik özelliklerinin incelemesi ve hastane içi mortaliteyi etkileyen etkenlerin belirlenmesi amaçlandı.

Çalışma planı: 1997 ve 2007 yılları arasında hastanemizde modifiye Duke ölçütlerine göre kesin veya olası İE tanısı konan 68 hastanın (40 erkek, 28 kadın; ort. yaş 51±20) klinik kayıtları ve tedavi sonuçları geriye dönük olarak incelendi.

Bulgular: Yirmi sekiz hastada (%41.2) nativ kapak endokarditi (NKE), 38 hastada (%55.9) protez kapak endokarditi (PKE) saptandı. Pacemaker endokarditi (PE) sadece iki olguda (%2.9) görüldü. On dokuz hastada (%27.9) hastane içi İE vardı. Romatizmal kalp hastalığı NKE açısından başta gelen risk faktörü idi (n=11; %39.3). Ekokardiyografide, PKE'li beş hastada (%13.2) tutulum bulgusuna rastlanmadı. Stafilokoklar NKE, PKE ve PE'ye neden olan en sık mikroorganizma idi (n=28; %41.2). Kırk altı hastada (%67.7) en az bir komplikasyon gelişti; bunlar içinde en sık komplikasyon konjestif kalp yetersizliği (n=38; %55.9) idi. Kırk bir hastada (%60.3) birleşik (tıbbi ve cerrahi) tedavi uygulandı. Hastane içi ölüm 17 hastada (%25) görüldü. Mortalite oranları erken ve geç PKE'de ve NKE'de sırasıyla %37.5, %30 ve %14.3 idi. Ayrıca, hastane içi İE grubundaki mortalite (%57.9), diğer olgulara göre anlamlı derecede yüksek bulundu. Çokdeğişkenli analizde, septik şok (p=0.011) ve hastane içi infeksiyon (p=0.032), hastane içi mortaliteyi etkileyen bağımsız faktörler olarak bulundu.

Sonuç: Avrupa'daki serilerle karşılaştırıldığında, hasta grubumuzda İE daha erken yaşta gözlendi ve altta yatan en sık faktör romatizmal kalp hastalığı idi. Protez kapak endokarditi, hastane içi İE ve cerrahi tedavi oranlarımız benzer bulundu.

Anahtar sözcükler: Çapraz infeksiyon; endokardit, bakteriyel/tedavi/mortalite; kalp kapağı protezi; hastane mortalitesi; prognoz.

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Correspondence: Dr. Saide Aytekin. Abide-i Hürriyet Cad., No: 290, 34381 Çağlayan, İstanbul, Turkey.
Tel: +90 212 - 224 49 50 / 4038 e-mail: saideaytekin@gmail.com

Despite recent advances in the diagnosis and medical and surgical management of patients with infective endocarditis (IE), the prognosis still remains poor, with an overall mortality as high as 20% to 25%.[1] Several series have proposed possible explanations for high mortality rates, including changes in the type and virulence of infecting organism, placement of prosthetic valves, and exposure to more invasive procedures.[2-5]

Previous studies addressed the clinical, microbiological, and echocardiographic features of IE, and predictors of mortality in the European population.[6-10] However, data on clinical presentations, the most frequent causative microorganisms, and risk factors for adverse outcome during hospital admission remain inconsistent, and data on the Turkish population is scarce. In such an attempt, Leblebicioğlu et al. [11] investigated the characteristics and risk factors for mortality in IE and reported altered mental status, mobile vegetation, and hemodialysis as independent risk factors for in-hospital mortality.

The objectives of this observational study were *(i)* to evaluate clinical, laboratory, microbiological, and echocardiographic characteristics, (ii) to compare combined medical and early surgical treatment with medical treatment alone, and *(iii)* to identify predictors of in-hospital mortality in patients with IE over a 10-year period at a tertiary care center in Turkey.

PATIENTS AND METHODS

Study design. In a systematic retrospective review of clinical records, we collected data on all patients admitted to our tertiary care center between December 1997 and April 2007. Patients with IE were identified using the hospital database as well as a systemic review of all reports from the echocardiography laboratory. Patients who met the modified Duke criteria[12] of either definite or possible IE were included in the study.

The following data were recorded for each patient:

Baseline demographics– Age, sex, origin of patients (referred or direct admission), previous antibiotic use, history of recent procedures such as dental, gastrointestinal, or genitourinary procedures, cutaneous portal of entry, history of immunosuppression, and predisposing heart disease.

Clinical findings– Duration of illness before hospital admission, fever ≥38.5 °C, chills, sweats, dyspnea of NYHA class III-IV, cough, fatigue, myalgia, back pain, splenomegaly, new heart murmur, signs of peripheral vasculitis, conduction disorders on electrocardiography, heart failure, and septic shock.

Laboratory data– C-reactive protein (CRP) concentration, white cell count (WCC), hematocrit, and serum creatinine concentration. Renal failure was defined by serum creatinine concentration exceeding 3 mg/dl.

Microbiological data– Blood culture status and type of microorganism isolated from blood cultures and from all other available fluid or tissue samples including valve tissue; number of blood cultures taken from each patient. Specific analyses including additional sets of blood on enriched media, broad-spectrum polymerase chain reaction, and serological tests for *Bartonella* spp. were also recorded.

Echocardiographic data– Location and size of visible vegetation, type of valve infected, perivalvular abscess, perforation of leaflet, and chordal rupture. The number of transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) examinations were noted.

The patients were divided into three distinctive groups: native valve endocarditis (NVE), prosthetic valve endocarditis (PVE), and pacemaker endocarditis (PE). Prosthetic valve endocarditis was classified as early or late depending on the time infection was diagnosed; hence, early PVE within 12 months after surgery and late PVE after 12 months.[13] Nosocomial IE was defined as infection occurring after 72 hours of hospital admission or acquired IE associated with a significant invasive procedure performed during a recent hospitalization ≤8 weeks before the onset of symptoms.[4,14] For each patient, the treatment modality (medical treatment alone or in conjunction with surgical treatment) and in-hospital outcome were noted.

The study was approved by the institutional ethics committee.

Statistical analysis. Descriptive statistics for each subgroup and the entire population and comparisons were performed using the SPSS 11.0 software package. Descriptive statistics were calculated, including means and standard deviations for continuous variables, and frequencies for qualitative variables. The chi-square or Fisher's tests were used to compare qualitative variables, and Student's t-test was used to compare quantitative variables. The relations between the size of vegetation and embolic events, and mortality were assessed by the Spearman correlation test. Univariate analysis included age, sex, WCC, immune

Table 1. Demographic characteristics of 68 patients with infective endocarditis

	Native valve		Prosthetic valve				Pacemaker		Total	
			Late		Early					
	n	%	n	%	n	%	n	%	n	%
Number	28	41.2	30	44.1	8	11.8	2	2.9	68	
Sex										
Male	19	67.9	17	56.7	3	37.5	1	50.0	40	58.8
Female	9	32.1	13	43.3	5	62.5	1	50.0	28	41.2
Infective endocarditis [a]										
Definite	20	71.4	27	90.0	8	100.0	2	100.0	57	83.8
Probable	8	28.6	3	10.0	–		–		11	16.2
Referred patients	15	53.6	9	30.0	1	12.5	–		25	36.8
Nosocomial infection	10	35.7	2	6.7	7	87.5	–		19	27.9
Portal of entry	9	32.1	11	36.7	7	87.5	1	50.0	28	41.2
Intravascular procedure	7	25.0	6	20.0	5	62.5	1	50.0	19	27.9
Gastrointestinal procedure	–		2	6.7	1	12.5	–		3	4.4
Genitourinary procedure	–		1	3.3	–		–		1	1.5
Dental procedure	–		2	6.7	–		–		2	2.9
Other	2	7.1	–		1	12.5	–		3	4.4
Immunodeficiency	5	17.9	6	20.0	4	50	1	50.0	16	23.5
Diabetes	3	10.7	2	6.7	2	25.0	1	50.0	8	11.8
Long-term dialysis	2	7.1	4	13.3	2	25.0	–		8	11.8
Predisposing heart disease	23	82.1	25	83.3	7	87.5	1	50.0	56	82.4
Rheumatic heart disease	11	39.3	13	43.3	3	37.5	–		27	39.7
Degenerative heart disease	6	21.4	6	20.0	3	37.5	–		15	22.1
Mitral valve prolapsus	2	7.1	2	6.7	–		–		4	5.9
Prior infective endocarditis	2	7.1	3	10.0	1	12.5	–		6	8.8
Congenital heart disease [b]	2	7.1	1	3.3	–		1	50.0	4	5.9
Mean age (years and range)	46	16-88	57	17-81	50	44-56	51	16-88	51	16-88

[a] According to the modified Duke criteria[12]; [b] Including three cases of bicuspid aorta, and one case of Tetralogy of Fallot (post repair).

deficiency, renal failure, heart failure, ejection fraction, vegetation size, chordal rupture, embolism, septic shock, nosocomial or community origin, nidus of infection (native, prosthetic or other), causative microorganism, and treatment modality (medical treatment alone or combined with surgical treatment). Multivariate logistic regression analysis was performed to identify independent prognostic factors for death. Variables included WCC, immunodeficiency, renal failure, embolic events, septic shock, nosocomial infection, and treatment modality. The standard level of significance ($p<0.05$) was chosen.

RESULTS

Patient demographics and clinical data. During the study period, 68 patients, aged 16 years or older, had definite or possible IE and were eligible for inclusion in this study. Twenty-eight patients (41.2%) had NVE, 38 patients (55.9%) had PVE, and two patients (2.9%) had PE. Of the prosthetic valves, 82% were mechanical and 18% bioprosthetic. Seven patients (10.3%) had both native and prosthetic involvement and were accepted as having PVE.

Among 19 episodes (27.9%) of nosocomial IE, 10 patients (52.6%) developed infection after 72 hours of hospital admission. A history of significant invasive procedure during a recent hospitalization ≤8 weeks before the onset of symptoms was present in nine patients (47.4%). A portal of entry was determined in 28 patients (41.2%). None of the patients had intravenous drug addiction or AIDS. The most predisposing heart disease for NVE was rheumatic heart disease in 11 patients (39.3%). Demographic data for the whole population and each subgroup are presented in Table 1.

The most frequent clinical presentations were high fever (≥38.5 °C) in 56 patients (82.4%) and a previously undetected heart murmur in 56 patients (82.4%) (Table 2). Hematuria was present in seven patients (10.3%) and peripheral vascular signs were found in 15 patients (22.1%).

Hematological findings. The mean values of CRP and WCC were 84.5±36.5 mg/dl and 16.7±7.9x10^9/l, respectively. The mean value of serum creatinine was 2.5±2.0 mg/dl (Table 2).

Table 2. Presenting symptoms and biochemical findings

	Native valve (n=28)		Prosthetic valve				Pacemaker (n=2)		Total (n=68)	
			Late (n=30)		Early (n=8)					
	n	%	n	%	n	%	n	%	n	%
Fever ≥ 38.5 °C	23	82.1	24	80.0	7	87.5	2	100.0	56	82.4
Chills	10	35.7	14	46.7	2	25.0	–		26	38.2
Sweats	7	25.0	16	53.3	4	50.0	1	50.0	28	41.2
Dyspnea	13	46.4	13	43.3	4	50.0	–		30	44.1
Cough	5	17.9	5	16.7	4	50.0	1	50.0	15	22.1
Fatigue	20	71.4	25	83.3	8	100.0	2	100.0	55	80.9
Myalgia	12	42.9	14	46.7	5	62.5	–		31	45.6
Back pain	2	7.1	5	16.7	2	25.0	–		9	13.2
Hematuria	2	7.1	5	16.7	–		–		7	10.3
Splenomegaly	6	21.4	5	16.7	–		–		11	16.2
New heart murmur	19	67.9	28	93.3	8	100.0	1	50.0	56	82.4
Osler nodes	2	7.1	–		–		–		2	2.9
Roth spots	3	10.7	–		–		–		3	4.4
Cutaneous vasculitis	6	21.4	4	13.3	–		–		10	14.7
Conduction disorders	1	3.6	7	23.3	3	37.5	–		11	16.2
Symptom duration (days; range)	31	2-90	22	2-60	7	2-20	9	7-10	24	2-90
	Mean±SD		Mean±SD		Mean±SD		Mean±SD		Mean±SD	
C-reactive protein (mg/dl)	55.1±34.9		118.9±53.2		76.7±56.2		7.0±2.0		84.5±36.5	
White blood cell count (x10^9/l)	13.9±4.1		17.7±7.3		21.9±14.1		21.8±18		16.7±7.9	
Hematocrit (%)	25.3±5.0		25.5±5.4		28.5±5.7		29.9±11.4		25.9±5.4	
Serum creatinine (mg/dl)	1.7±1.5		3.1±2.3		3.2±1.8		0.8±0.4		2.5±2.0	

Echocardiographic findings. Echocardiographic findings are summarized in Table 3. Transthoracic echocardiography was performed in 66 patients (97.1%) and TEE was performed in 51 patients (75%). Both modalities were performed in 60 patients (88.2%). Transesophageal echocardiography results were not available in eight patients with PVE because these patients underwent cardiac surgery immediately

Table 3. Echocardiographic findings

	Native valve (n=28)		Prosthetic valve				Pacemaker (n=2)		Total (n=68)	
			Late (n=30)		Early (n=8)					
	n	%	n	%	n	%	n	%	n	%
Transthoracic examination	28	100.0	28	93.3	8	100.0	2	100.0	66	97.1
Transesophageal examination	21	75.0	24	80.0	6	75.0	–		51	75.0
Infection sites										
Mitral valve	13	46.4	13	43.3	5	62.5	—		31	45.6
Aortic valve	10	35.7	13	43.3	2	25.0	—		25	36.8
Mitral and aortic valves	3	10.7	4	13.3	1	12.5	—		8	11.8
Tricuspid valve	1	3.6	–		–		—		1	1.5
Mitral and tricuspid valves	1	3.6	–		–		—		1	1.5
Pacemaker	—		—		—		2	100.0	2	2.9
Vegetation size	23	82.1	10	33.3	6	75.0	2	100.0	41	60.3
<10 mm	11	39.3	2	6.7	4	50.0	–		17	25.0
>10 mm	12	42.9	8	26.7	2	25.0	2	100.0	24	35.3
Vegetation mobility										
Mobile	15	53.6	9	30.0	2	25.0	2	100.0	28	41.2
Fixed	8	28.6	1	3.3	4	50.0	–		13	19.1
Perivalvular abscess	4	14.3	2	6.7	–		—		6	8.8
Perforation of the leaflet	8	28.6	—		—		–		8	11.8
Chordal rupture	8	28.6	—		—		—		8	11.8
Dehiscence	—		16	53.3	5	62.5	—		21	30.9

Table 4. Blood culture results

	Native valve (n=28)		Prosthetic valve				Pacemaker (n=2)		Total (n=68)	
			Late (n=30)		Early (n=8)					
	n	%	n	%	n	%	n	%	n	%
Staphylococcus aureus	9	32.1	7	23.3	2	25.0	1	50.0	19	28.0
Methicillin-sensitive *S. aureus*	7	25.0	7	23.3	1	12.5	1	50.0	16	23.5
Methicillin-resistant *S. aureus*	2	7.1	–		1	12.5	–		3	4.4
Streptococcus viridans	5	17.9	4	13.3	–		–		9	13.2
Coagulase-negative staphylococci	1	3.6	3	10.0	4	50.0	1	50.0	9	13.2
HACEK	–		4	13.3	–		–		4	5.9
Other streptococci [a]	4	14.3	3	10.0	1	12.5	–		8	11.8
Enterococci [b]	–		1	3.3	–		–		1	1.5
Other [c]	2	7.1	1	3.3	1	12.5	–		4	5.9
Negative blood culture	7	25.0	7	23.3	–		–		14	20.6
Blood cultures/patient (mean/range)	3	1-9	4	1-11	4	1-9	7	4-6	4	1-11

HACEK: *Haemophilus, Actinobacillus, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae*; [a]Including 5 *S. bovis*, 2 *S. pneumonia* and 1 *S. dysgalactiae*; [b]*E. faecalis*; [c]Including 1 *Aspergillus fumigatus*, 1 *Escherchia coli*, 1 *Bartonella spp.* and 1 *Pseudomonas aeruginosa.*

after admission due to severe, life-threatening shock. Mitral valve IE was the most common type; valves affected were mitral in 31 patients (45.6%), aortic in 25 patients (36.8%), and tricuspid in one patient (1.5%). Simultaneous involvement was seen in nine patients (13.2%), being mitral and aortic valves in eight patients and mitral and tricuspid valves in one patient.

All patients with NVE had positive echocardiographic findings. Among five patients (17.9%) with NVE and without vegetation, echocardiographic imaging revealed mitral perivalvular abscess in three patients, aortic perivalvular abscess in one patient and perforation of the mitral valve leaflet in one patient. As expected, there were fewer vegetations in PVE than in NVE (75% in early and 33.3% in late cases). In five patients (13.2%) with PVE (3 prosthetic mitral valve, 2 prosthetic aortic valve) echocardiography failed to show any signs of involvement. Diagnosis in these patients was based on positive blood cultures and three minor criteria. In two patients (2.9%) with late PVE, both TTE and TEE could not be performed due to severe, life-threatening shock, requiring immediate cardiac surgery after admission.

Vegetation size greater than 10 mm was correlated with an embolic event (Spearman: r= 0.438, p=0.004), but not with mortality (Spearman: r=0.174, p=0.275).

Microbiological findings. Blood cultures were positive in 54 cases (79.4%). The mean number of blood cultures taken from each patient was 4 (range 1 to 11). Staphylococci were the most frequent causative microorganisms isolated in both NVE (n=10, 35.7%) and PVE (n=16, 42.1%) cases, with an overall involvement of 28 cases (41.2%) (Table 4). Streptococci were

Table 5. Complications during hospitalization

	Native valve (n=28)		Prosthetic valve				Pacemaker (n=2)		Total (n=68)	
			Late (n=30)		Early (n=8)					
	n	%	n	%	n	%	n	%	n	%
Heart failure [a]	22	78.6	13	43.3	3	37.5	–		38	55.9
Renal failure [b]	8	28.6	14	46.7	4	50.0	–		26	38.2
Embolic events [c]	14	50.0	11	36.7	4	50.0	1	50.0	30	44.1
Brain	10	35.7	8	26.7	2	25.0	–		20	29.4
Lung	2	7.1	–		–		1	50.0	3	4.4
Spleen	2	7.1	2	6.7	–		–		4	5.9
Other [d]	2	7.1	1	3.3	2	25.0	–		5	7.4
Mycotic aneurysm	–		1	3.3	–		–		1	1.5
Complete heart block	–		1	3.3	–		–		1	1.5
Septic shock	5	17.9	8	26.7	2	25.0	1	50.0	16	23.5
In-hospital death	4	14.3	9	30.0	3	37.5	1	50.0	17	25.0

[a]Including patients with a regurgitation of ≥3/4 and NYHA III-IV; [b]Including patients with a serum creatinine level >3 mg/dl; [c]Two patients in NVE had both cerebral and splenic embolism; [d]Including 1 mesenteric artery embolism and 3 lower limb emboli.

Table 6. Management and primary indications and contraindications for surgical intervention

	Native valve (n=28)		Prosthetic valve				Pacemaker (n=2)		Total (n=68)	
			Late (n=30)		Early (n=8)					
	n	%	n	%	n	%	n	%	n	%
Medical treatment alone	5	17.9	16	53.3	5	62.5	1	50.0	27	39.7
Surgical treatment	23	82.1	14	46.7	3	37.5	1	50.0	41	60.3
Surgery indications										
Heart failure	20	71.4	10	33.3	3	37.5	–		33	48.5
Perivalvular abscess	4	14.3	2	6.7	–		–		6	8.8
Prosthetic valve dehiscence	—		8	26.7	3	37.5	—		11	16.2
Perforation of the leaflet	8	28.6	—		—		–		8	11.8
Large vegetation with high risk for embolization	8	28.6	2	6.7	1	12.5	1	50.0	12	17.7
Pacemaker infection	—		—		—		1	50.0	1	1.5
Failure of medical treatment	2	7.1	–		–		–		2	2.9
Septic emboli	2	7.1	2	6.7	1	12.5	–		5	7.4
Surgery contraindications	3	10.7	6	20.0	4	50.0	1	50.0	14	20.6
Major cerebrovascular events	2	7.1	2	6.7	2	25.0	–		6	8.8
High operative risk because of comorbid conditions	1	3.6	4	13.3	2	25.0	1	50.0	8	11.8
Surgical procedure										
Valve replacement	21	75.0	14	46.7	2	25.0	–		37	54.4
Plasty	2	7.1	–		1	12.5	–		3	4.4
Replacement of pacemaker	2	7.1	2	6.7	–		1	50.0	5	7.4
Removal of mycotic aneurysm	–		1	3.3	–		–		1	1.5

found in 17 cases (25%), mostly affected by *S. viridans* (n=9, 13.2%). HACEK group microorganisms were isolated in four patients (5.9%) and all were late PVE. Enterococci (E. feacalis) were isolated only in one patient. In both patients with PE, staphylococci were the causative microorganisms. Blood cultures were negative in 14 patients (20.6%). Of these, nine patients (64.3%) had received antibiotic therapy before blood cultures were taken.

Course and complications. Forty-six patients (67.7%) presented with at least one complication during the course of IE. Overall, congestive heart failure was the most common complication occurring in 38 patients (55.9%) (Table 5). Thirty patients (44.1%) presented with at least one embolic event, with a total of 32 events. Cerebral embolism accounted for 62.5% (n=20) and splenic embolism accounted for 12.5% (n=4) of embolic events. Septic shock occurred in 16 patients (23.5%), half of which was seen in late PVE.

Treatment and outcome. Antibiotic treatment was given to all patients intravenously. Two or more antibiotics were administered to 85% of the patients. The mean duration of antibiotic treatment was 45 days. Forty-one patients (60.3%) underwent combined medical and surgical treatment. Fourteen patients (20.6%) had a contraindication for surgery (Table 6). Surgical intervention was performed in 23 patients (82.1%) for NVE, in 17 patients (44.7%) for PVE, and in one patient (50%) for PE. Surgery was predominantly indicated for heart failure (48.5%), followed by large vegetation with high risk for embolization (17.7%). Surgical techniques were mechanical valve replacement in 32 (47.1%), bioprosthesis replacement in five (7.4%), annuloplasty in three (4.4%), and replacement of pacemaker electrodes in five (7.4%) cases. The median time from diagnosis to surgical intervention was 11 days.

Mortality occurred in 17 patients (25%). Mortality rate was higher in early PVE (37.5%) than late PVE (30%) and NVE (14.3%).

Eleven patients (57.9%) with nosocomial IE died, mortality being significantly higher than that of six patients (12.2%) with community-acquired IE ($p<0.001$). Eleven patients (40.7%) treated with medical therapy alone died, and this was significantly higher than six deaths (14.6%) with combined medical and surgical treatment ($p=0.022$).

In univariate analysis, WCC, treatment group, septic shock, and nosocomial infection were significantly associated with a fatal outcome (Table 7). Of these, septic shock (ß=0.253; $p=0.011$) and nosocomial infection (ß=0.132; $p=0.032$) were independently associated with death in multivariate analysis.

Table 7. Univariate analysis of prognostic variables for mortality

	Survived (n=51)		Died (n=17)			
	n	%	n	%	*r*	*p*
Male sex	31	60.8	9	52.9	0.069	0.583
Immunodeficiency	9	17.7	7	41.2	0.240	0.095
Heart failure	27	52.9	11	64.7	0.061	0.574
Renal failure	16	31.4	10	58.8	0.245	0.082
Vegetation size (n=41)					0.021	0.309
>10mm	16	31.4	8	47.1		
<10mm	14	27.5	3	17.7		
Ejection fraction (%)					0.110	0.286
>30%	43	84.3	12	70.6		
<30%	8	15.7	5	29.4		
Chordal rupture	7	13.7	1	5.9	0.105	0.669
Medical treatment alone	16	31.4	11	64.7	0.295	**0.022**
Embolic events	19	37.3	11	64.7	0.239	0.089
Septic shock	4	7.8	12	70.6	0.641	**<0.001**
Nosocomial infection	8	15.7	11	64.7	0.473	**<0.001**
Staphylococcal infection	20	39.2	8	47.1	0.075	0.583
Prosthetic valve	26	51.0	12	70.6	0.158	0.259
	Mean±SD		Mean±SD			
Age	51±19		51±23		0.008	0.947
WCC (x10^9/l)	14.6±6.7		23.7±7.5		0.497	**<0.001**

DISCUSSION

This observational retrospective study provided significant data on the epidemiology, etiology, microbiology, treatment, and outcome of IE at a tertiary care center in Turkey. In European populations, IE is commonly diagnosed in patients older than 50 years.[2,10,15] This may be mainly due to the growing proportion of the elderly population and reduction in rheumatic heart fever in Europe. In our study, the mean age of the patients was 51 years (range 16 to 88 years) and rheumatic heart disease was the most common underlying heart disease for IE. Compared to other reports from Turkey, our patient population was relatively older. In a recent study by Leblebicioğlu et al.[11] the mean age for IE was 45 years, and in a study by Çetinkaya et al.[16] the patients were under the age of 40 years. The rate of rheumatic fever is similar in our study population (11/68, 16.2%) when compared with these studies. However, the rate of PVE is higher (n=38, 55.9%) compared with rates reported in previous series.[4,7,16-18] The lower rate of right-sided IE compared to European series may be attributed to the fact that none of the patients had intravenous drug addiction or were HIV positive in the present study. According to the modified Duke criteria, definite IE was determined in 83.3% (n=57) of the patients. The rate of nosocomial infection was higher compared to older series,[4] but similar to the recent studies.[10] This may be associated with higher rates of prior hospitalization and invasive procedures.

Transthoracic echocardiography was utilized in the vast majority of patients (97.1%). The use of TEE was 75% in the whole population and this was in accordance with the guidelines.[19]

Staphylococci, in particular S. aureus, were the most frequent causative microorganisms in NVE, PVE, and PE. Recent series also found *S. aureus* as the main pathogenic agent in IE.[4,20,21] However, in some recent studies, *S. viridans* was the prevailing etiological agent.[15,17,18,22,23] The rate of enterococci was lower in the present study compared to a recent study.[10] This may be explained by the younger age of the population and the lower rate of exposure to invasive urinary and gastrointestinal tract procedures. Both cases of PE in our series were caused by staphylococci, which is in agreement with other PE series.[24]

In the present study, all patients received intravenous antibiotics for over a month and 13.2% (n=9) of the patients did not have blood cultures before antibiotics were started. This rate is lower than that observed in the Euro Heart Survey.[9] The rate of negative blood cultures was 20.6%, and in 64.3% (9/14) of these patients, previous antibiotic use was present. Recent observational series reported the

frequencies of culture-negative endocarditis between 9% to 25%.[2,4,15,25-27]

At least one complication was encountered in 67.7% of the patients due to high rates of staphylococcal IE, PVE, and nosocomial IE. Another reason may be the considerable proportion of severely ill patients transferred to our hospital owing to its tertiary status. In our study, 60.3% of the patients underwent surgery, which is higher than that reported in previous studies[2,4,9] but close to the rate of a recent study.[10] The high number of referred patients might have increased the rate of surgery. Surgery was performed in accordance with the current recommendations.[19] Five patients with heart failure were not operated on due to comorbid conditions. The type of surgery performed was mainly valve replacement, mostly using a mechanical prosthesis. Although homograft aortic valve replacement has been suggested to be the ideal method in aortic endocarditis complicated by abscess formation,[28] it was not used in our patients due to the limited availability of homografts. The valve was only repaired in 7.1% (2/28) of cases with NVE. Although several surgical series reported good results from valve repair, experience with mitral valve repair during the acute phase of IE is limited and its use is subject to debate.[29-31]

Hospital mortality was significantly higher in medically treated patients (64.7%) in univariate analysis (p=0.022). This rate is higher than the reported rates in the Euro Heart Survey and the French registry.[2,9] However, this should be carefully interpreted due to the limited number of patients. It is not known whether all patients with IE benefit from early surgery, and there are divergent opinions in this respect. It appears that potential early risks of surgery in the active phase of the infection have to be weighed against a potentially unfavorable course with medical treatment per se, i.e., early mortality caused by uncontrolled infection.

A wide variety of risk factors have been reported for mortality in IE. Those found as independent risk factors of mortality are as follows: heart failure,[32-34] neurological abnormality,[35,36] staphylococcal IE,[15,35,37,38] renal failure,[15,39] noncardiac shock,[36] septic shock,[40] cerebral emboli,[40] systemic embolism,[38] immunosuppression,[40] cardiac surgery,[40] nosocomial IE,[4] prosthetic valve,[4] comorbidity,[34] abnormal mental status,[34] medical treatment alone,[34,38] and echocardiographic evidence for paravalvular abscess.[38,41] In our study, septic shock and nosocomial infection were found to be the independent predictors of in-hospital mortality. The strong association between nosocomial IE and a fatal outcome might be explained by highly resistant bacteria in nosocomial cases. The other two factors, WCC and medical treatment alone, which were significantly associated with a fatal outcome in univariate analysis, did not show an independent association with death. However, due to the retrospective design and small sample size, it is possible that we may have failed to identify other important prognostic factors.

The main limitations of this study are its retrospective design and limited sample size. The latter restricts to draw conclusions for some specific subgroups. In addition, the fact that it reports from a referral tertiary care center might have caused a selection bias towards more severe or complicated cases.

In conclusion, the management of IE remains challenging with high morbidity and mortality rates. Although our patient population is younger compared to the European series, characteristics of IE with regard to presentation, management, and outcomes in our center reflect a changing trend towards more severe forms of disease involving more PVE and a greater staphylococcal and nosocomial contribution, as seen in the European population. Septic shock and nosocomial IE were independent risk factors for in-hospital death in our patient population.

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