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Early clinical results of surgical treatment of active infective endocarditis

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ABSTRACT

Objectives: In this study, we present early results of surgery in patients who were surgically treated for active infective endocarditis (IE).

Patients and methods: Between October 2015 and June 2020, a total of 28 patients (21 males, 7 females; mean age: 62±9 years; range: 46 to 78 years) with an active IE who were not previously operated were retrospectively analyzed. The diagnosis of IE was made on the basis of clinical and transthoracic echocardiographic findings, and microbiological growth in the blood culture. The patients were divided into two groups according to the type of surgery [Group 1 (valve replacement group; n=21) and Group 2 (valve repair; n=7)]. Baseline and operative data of the patients were compared.

Results: The median follow-up was 3.4 (range: 2-5 yeras) years. Blood cultures were positive in 19 (67.8%) patients. Coagulase-negative *Staphylococci*, *Staphylococcus epidermidis*, and methicillin-resistant *Staphylococcus aureus* were the most common microorganisms. The main symptoms were fever, fatigue, shortening of breath, and dyspnea. We performed an urgent surgery in six patients who had congestive heart failure resistant to medical treatment (n=2) and pulmonary embolic events (n=4). If there were perivalvular abscess formation, and multiloculated mobile and large vegetations in patients with sepsis or hemodynamic instability despite intense medical treatment including inotropic administration, we preferred early surgery. The postoperative mortality rate was 10.7%.

Conclusion: Our study results suggest that active IE is associated with high mortality rates. Valve repair may be chosen in eligible patients after the extensive resection of infected leaflets with acceptable results.

Keywords: Complications, heart failure, infective endocarditis, medical treatment, surgery.

Active infective endocarditis (IE) is a rare, but severe clinical condition.[1-3] Despite advancements in early diagnosis, new medical treatments, comprehensive antibiotics regimens, and accumulated experiences with surgical approaches, it is still associated with a high mortality rate. The main risk factors are congenital heart diseases, previous cardiac surgery, degenerative valvular disease, central venous catheter insertion, and placement of a pacemaker or implantable cardioverter defibrillator (ICD), and intravenous drug use (IVDU).[4-10]

The treatment of IE and the optimal timing of surgery have been described by the European Association for Cardiothoracic Surgery (EACTS),[7] American College of Cardiology (ACC)/American Heart Association (AHA),[8] and the Turkish Society of Cardiovascular Surgery and Turkish Society of Thoracic Surgery (TSCVS).[9,10] To prevent high morbidity and mortality in patients with heart failure, or mobile and large vegetations, as well as in patients with recurrent embolic events, early surgery has been proposed.[9,10] Early surgery has also been suggested in patients with periannular abscess formation, serious valvular stenosis or valvular regurgitation related to multiple vegetations, and septic embolic events.[9,10] In addition, the guidelines of the EACTS[7] AHA,[8] and TSCVS[9,10] suggest an early surgery as evidence of Class IIb in patients with a vegetation size of >15 mm.

About a quarter of the patients can be treated using antibiotics without requiring a surgical intervention.[11] In a multi-center study, Oylumlu et al.[11] reported the clinical results of 116 patients with IE who underwent medical treatment and surgery. They recommended surgery in 53% of patients who had severe valvular destruction. In this series, the mortality rate was 19.5%. The predictors of mortality were higher New York Heart Association (NYHA)

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functional class, elevated C-reactive protein, and renal dysfunction.

In the present study, we report early clinical results of surgical treatment of IE after valvular replacement and repair.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Elazığ Fethi Sekin Eğitim ve Araştırma hastanesi, Department of Cardiovascular Surgery between October 2015 and June 2020. A total of 28 patients (21 males, 7 females; mean age: 62±9 years; range: 46 to 78 years) with an active IE for the first time. The diagnosis of IE was made on the basis of clinical and echocardiographic findings, and microbiological growth in the blood culture.[12] The patients were divided into two groups according to the surgical approach as Group 1 (n=21; valve replacement group) and Group 2 (n=7; valve repair group). Written informed consent was obtained from each patient. The study protocol was approved by the Elazığ Fethi Sekin Research and Training Hospital Ethics Committee (No: 903.05.99-399). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical pproach

After the induction of anesthesia, the transesophageal echocardiography (TEE) probe was inserted in the appropriate position. After a median sternotomy, aorto-bicaval cannulation was performed, and an extracorporeal circulation (ECC) was instituted. We used moderate hypothermia in all operations. Cardiac arrest was achieved by the antegrade aortic route with cold blood cardioplegia.

The aim of our surgical strategy was based on *(i)* intensive debridement of the infected area followed by vegetectomy, *(ii)* whenever possible, we performed valve repair with the use of bioprosthetic materials, *(iii)* if the patients had severe destruction of the valves, we performed cardiac valve replacement using a biological substitute without the use of any artificial materials. Since the majority of patients were older than 60 years, we preferred bioprosthetic valve implantation. If the patient had no severe destruction of valves' leaflets with small size vegetation and if there was no evidence of periannular abscess formation, we used the valve repair technique. The chordal transfer was performed following the leaflet repair after the excision of the infected tissue. Leaflet excision was performed using a triangular or a quadrangular-shaped resection in an isolated mitral valve IE. We repaired the hole in the right coronary sinus of the aortic valve using fresh pericardium. If there was a periannular abscess formation, we removed the periannular tissue with the valve(s) and we repaired it using a bovine or fresh pericardium. Furthermore, we also implanted an artificial valve. In patients with a history of cardiac valve replacement, we removed all the infected materials and prosthetic valve, and we debrided the periannular tissue. We performed Kay annuloplasty or bicuspidization in patients with tricuspid valve IE. An annular ring was inserted following valvuloplasty. We replaced the pulmonary valve using a decellularized pulmonary homograft in one patient who had severe destruction of the valve accompanied by a pulmonary embolic event, followed by the extensive removal of vegetation including the pulmonary valve. Thrombectomy from the left pulmonary artery was performed. In one older patient with mitral valve IE combination, we performed coronary artery bypass grafting using the left internal thoracic artery and an artificial mitral valve was implanted.

To confirm the valve regurgitation in the repair group, TEE was performed after weaning from ECC for each patient routinely. We only observed a mild mitral valve regurgitation in two patients after repair. Broad-spectrum antibiotics were given to all patients for four to six weeks after surgery. Our postoperative antibiotic regimen included vancomycin, meropenem, and rifampicin. We discontinued rifampicin at the end of Day 10.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed in mean ± standard deviation (SD), while categorical variables were expressed in number and frequency. Two-sample Student's t-test and chi-square test were used to compare the demographics of valve replacement and repair groups. All continuous variables were analyzed using the t-test. The Fisher exact test was used for categorical data. A p value of <0.05 was considered statistically significant.

RESULTS

Preoperative patients' demographics are summarized in Table 1. The mean NYHA class was 2.9±1.1. Congestive heart failure was observed in

two patients (7.1%). Pulmonary embolic events were detected using thoracic computed tomography (CT) in four patients. Two patients had an isolated right-sided IE. Left-sided IE accompanied with a right-side involvement was detected in the remaining two patients.

Fever, shortening of breath, and fatigue were the main symptoms. Severe left anterior descending artery stenosis was detected in one patient. We performed an urgent surgery on six patients due to intractable heart failure or pulmonary embolic events. We performed valve replacement or valve repair. The

Table 1
Data of patients

	Valve replacement group			Valve repair group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
No of patients*	21	75		7	25		0.0001
Mean age (year)			66.1±4.7			58.6±7.4	0.66
Sex							-
Male	16			5			
Female	5			2			
Biochemical data							
Anemia	8	38		2	28.5		0.46
Leukocytosis	9	42.8		4	57.1		0.68
Thrombocytopenia*	7	33.3		2	28.2		0.010
Reasons for infective endocarditis							
Rheumatic valvular disease	11			-			
History of valve surgery	6			-			
Intravenous drug use	3			-			
Hemodialysis catheter insertion	4						
Pace-maker lead implantation	3						
ICD lead	1						
Total	28						
Preoperative TTE							
LVEF (%)			54±5			50±4	0.864
Mean PAP (mmHg)			44±21			39±17	0.720
Mean vegetation size (mm)*			44±0.9			22±0.4	0.0034
Complications of AIE							
Perivalvular abscess	2						
Intracardiac thrombus	2						
Pulmonary embolic event	4						
Congestive heart failure	2						
Duration of hospitalization (days)			53±38			49±28	0.79
NYHA functional class							
Class I	11	39.2		3	42.8		0.445
Class II	6	21.4		2	28.5		0.554
Class III	3	14.2		1	14.2		0.667
Class IV	1	4.7		1	14.2		0.023

SD: Standard deviation; ICD: Implantable cardioverter defibrillator; TTE: Transthoracic echocardiography; LVEF: Left ventricular ejection fraction; PAP: Pulmonary artery pressure; AIE: Active infective endocarditis; NYHA: New York Heart Association; * Statistical significance.

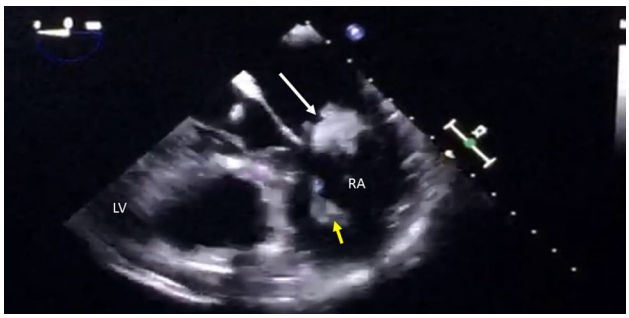

Figure 1. Transthoracic echocardiograms showing large intracardiac vegetation of tricuspid valve in a young intravenous drug abuse patient (white arrow). The vegetation is the cause of valvular stenosis. The yellow arrow shows interatrial thrombus formation.

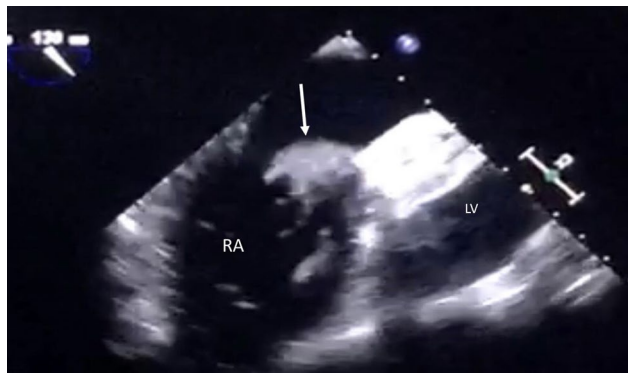

Figure 2. Transthoracic echocardiogram showing vegetation of tricuspid valve. The diameter of vegetation is 33 mm (white arrow). This patient has severe tricuspid valve regurgitation.

mean age in the replacement and repair group was similar (p=0.66).

Rheumatic valvular disease and previous cardiac valve replacement were common reasons of IE. Blood cultures were positive in 19 (67.8%) patients. Coagulase-negative *staphylococci*, *S. epidermidis*, and methicillin-resistant *Staphylococcus aureus* were the predominant agents (n=14; 50%). We used TTE as a diagnostic tool for definition of IE in all patients (Figures 1, 2, and 3).

The mean time from the diagnosis of IE to surgery was 33±12 (range, 15 to 46) days. The aortic and mitral valve were the most commonly affected valves (81%). Isolated right-sided IE was observed in four patients.

Three patients died after surgery (10.7%). Acute renal failure developed in one patient. The median length of hospitalization in the replacement and repair group were similar (p=0.76). The mean left ventricular ejection fraction (LVEF) was similar in the replacement and repair group (p=0.644). The mean duration of ECC and an aortic cross-clamp time are summarized in replacement and repair group in Table 2. The median duration of ECC and an aortic cross-clamp time in patients who underwent double valve replacement were significantly longer compared to the repair and single valve replacement group (p=0.0022 and p=0.0001, respectively). Cardiopulmonary bypass time, and ACC time in

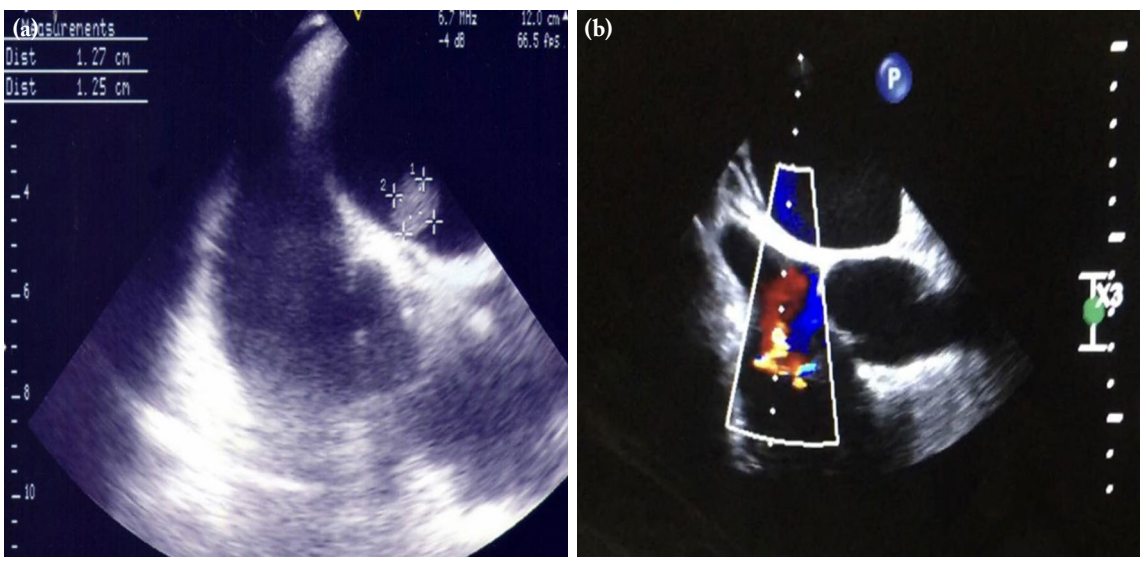

Figure 3. **(a)** Transthoracic echocardiogram showing vegetation in the subaortic region in a male patient who has a rheumatic valvular disease. **(b)** There is an aortic valvular insufficiency.

Table 2
Surgical approaches in replacement and repair groups

	Single valve replacement				Valve repair				Double valve replacement				
	n	%	Mean±SD	%	n	%	Mean±SD	%	n	%	Mean±SD	%	*p*
No of patients	11	39.2			7	25			10	47.6			0.0001
ECC time (min)			111±53				121±44				176±63		0.0026
Ao-x-clamp time (min)			76±33				83±37				124±29		0.0001
Bleeding from the mediastinum (mL)			406±55				366±80				720±160		0.0020
Vasoactive inotropic score				4.9				5.6				9.7	
Kind of surgery													
AVR	3	10.7			1*	3.5*							
MVR	4	14.2			3†	10.7†							
TVR	3	10.7			3‡	107‡							
PVR	1	3.5											
AVR+MVR									8	28.5			
MVR+TVR									3	10.7			
TEE after surgery													
Mild regurgitation					2	28.5							
Mean LVEF			52±1				49±6				53±1		0.644

SD: Standard deviation; ECC: Extracorporeal circulation; Ao-x-Clamp: aortic cross-clamp; AVR: Aortic valve replacement; MVR: Mitral valve replacement; TVR: Tricuspid valve replacement; PVR: Pulmonary valve replacement; TEE: Transesophageal echocardiography; LVEF: Left ventricular ejection fraction; * Aortic valve repair; † Mitral valve repair; ‡ Tricuspid valve repair.

the repair and single valve replacement group were similar. The mean amount of bleeding from the mediastinum was significantly higher in the double valve replacement group compared to the repair group (720±180 mL *vs.* 366±80 mL, respectively; p=0.002). Double valve replacement group received a mean of 3.1±0.9 packed red blood cells and 450±80 mL fresh frozen plasma after surgery. In the double valve replacement group, the vasoactive inotropic score was significantly higher compared to the repair and single replacement group (VIS: 9.7) (p=0.001). Transesophageal echocardiography showed that there was a mild valvular regurgitation in two patients after their valve repair.

Intubation time was longer than 24 h in two patients with congestive heart failure who underwent urgent surgery. Duration of ICU was longer in patients who underwent a double valve replacement. The duration of inotropic support was long and recovery in pulmonary function tests took time in two elderly patients. We performed hemodialysis, since two patients developed transient kidney failure. Kidney functions recovered on Day 5.

Follow-up period

The mean follow-up was 980±651 (range, 456 to 1,234) days. The survival rate after the operation was 85.8% at six months. Survival rate at the end of the first year and third year were 82.2% and 75%, respectively. The reasons for mortality were myocardial infarction, cerebrovascular accident, cancer, and congestive heart failure. We performed periodic TTE to investigate the recurrence of IE, valvular, and myocardial functions. We performed mitral valve replacement in one patient from the repair group, as there was a serious mitral valve regurgitation during follow-up. At the end of the fourth year, we detected a mild degree of tricuspid valve impairment in two patients. The mean pulmonary artery pressure decreased significantly, and the patients' NYHA class improved to Class I-II. There was no recurrence of endocarditis in any of the patients at the end of the follow-up.

DISCUSSION

More than 50 to 70% of patients with IE are referred to a hospital with cardiovascular or systemic symptoms such as fever, heart failure, sepsis, anorexia within two to four weeks after the initiation of IE.[5-7] In the present study, we used modified Duke criteria for the definitive diagnosis of IE.[12] In patients with IE symptoms, positive blood culture from two separate blood samples, TTE with an oscillating intracardiac mass on valves, new onset of valvular regurgitation, or periannular abscess, as well as the partial dehiscence of prosthetic valve were the main diagnostic criteria. Rheumatic cardiac disorder, congenital heart defects, and previous valve surgery are the main risk factors of IE.[8-10] In the initiation of the treatment of IE, it is essential that the microorganism should be eradicated using broad-spectrum antibiotics to reduce mortality, morbidity, and the recurrence of IE. Cardiac surgery in confirmed patients is the primary treatment method following antimicrobial therapy in elective patients.[7-10]

In the current study, we presented our surgical experiences of 28 patients who had an IE in the urgent or elective setting. We also demonstrated the causative microorganisms in our series with IE, pre- and postoperative echocardiographic results, surgical approaches, and mortality rates. Microorganisms and TTE results were similar to previous reports.[11,12] In our cohort, dyspnea with low oxygen saturation related to a pulmonary embolic event in patients with an isolated right-sided or left-sided accompanied with left-sided IE, who required early surgery, was observed. Based on these findings, we suggest thoracic computed tomography (CT) in these particular cases, even if their hemodynamic status is stable with dyspnea to confirm pulmonary embolic events prior to surgery. According to our clinical experience, in the NYHA Class III and IV patients who underwent emergency surgery, the use of inotropic agents was higher, while the duration of intubation and length of hospital stay were longer. However, further randomized clinical studies are needed to draw more reliable conclusions on this subject. In our study, no statistically significant difference was observed when ECC and aortic cross-clamp times were compared with repair and single-valve replacement procedures. However, ECC and aortic cross-clamp times were significantly longer in double-valve replacement.

Baddour et al.[6] reported that IE was a complex disease requiring management by a team of physicians and health providers. Previous reports and guidelines[5-7,10] and previous meta-analyses describe the management of patients with IE. According to the clinical variations and complex situations of IE, the experienced surgeons may dictate some recommendations to the clinicians in the management

of AI for individual patients. Management of IE may be performed according to the clinical status of patients with IE by an experienced team including a cardiologist, an infectious disease specialist, and a cardiac surgeon.

Before the development of early diagnostic techniques and a broad range of antibiotics, uncontrolled septic shock and embolic events were mainly responsible for the mortality and morbidity in patients with IE.[2,8] Thanks to specific and a broad range of antimicrobial agents administrated immediately after the diagnosis and also owing to a multidisciplinary approach, the survival rates of patients have increased up to 80 to 90%.[7-10]

Multidisciplinary approach is important topic to decrease the mortality and morbidity of patients with AI. Despite advances in early diagnosis and treatment, AI still has a high mortality, and for a favorable outcome, it is very important to determine the optimal surgical timing.[7-9] The use of mechanical or bioprosthetic heart valves,[13] and the various kinds of surgical approaches, such as replacement or repair,[14,15] were compared in large-case series. No significant difference was found between patients who underwent mechanical or bioprosthetic valve implantation. Therefore, age of the patient, the presence of comorbid disorders, and surgeons' preferences may be considered while deciding the type of valve selection. The surgeons preferred valve replacement following an extensive excision of perivalvular and valvular tissues in these patients, particularly in complicated patients.

In a retrospective study, Berdajs et al.[15] investigated postoperative atrioventricular block following mitral valve replacement and mitral valve annuloplasty. They suggested valve repair in eligible patients, since the atrioventricular block and reoperation rates were significantly lower in patients who underwent valve repair in various case series in experienced centers. Gottardi et al.[16] also showed that IE was not seen again and there was no valve leakage in the follow-up of patients with isolated tricuspid valve endocarditis who underwent valve repair surgery. They suggested tricuspid valve replacement in patients with severe valvular destruction. We, therefore, performed tricuspid or mitral valve repair in six patients in our study. Preoperative TTE showed no evidence of complications related to an infection such as congestive heart failure, embolic event, or perivalvular abscess formation in these patients. We only observed severe valvular regurgitation in one patient who needed mitral valve replacement during follow-up. Since the majority of patients in our cohort were older than 60 years, we preferred bioprosthetic valve replacement. Rostagno et al.[17] suggested mitral valve repair, which was associated with a favorable clinical long-term outcome, when technically possible. Podesser et al.[18] also proposed mitral valve reconstruction in IE with a low incidence of valve-related complications with postoperative good results and survival.

Antibiotherapy alone or surgery following antibiotics has been previously compared in the treatment of IE. Alvarado-Alvarado et al.[19] reported that the patients who underwent surgery had lower mortality than the patients who only received medical treatment. They found the mortality rate in the medical and surgical treatment group to be 34.3% and 65.7%, respectively (p=0.049). According to the experiences of clinics, surgical treatment is accepted as the gold standard strategy for IE. In the study of Oylumlu et al.,[11] 110 patients with IE required surgery with a 28% mortality rate, as they had severe valvular destruction. Kocabas et al.[20] also reported their 15-year experiences in 210 patients with active IE and similar to previous studies,[13,14] the main causes of IE were previous prosthetic valve replacement and rheumatic valvular disorders. The mortality factors in the study were embolic events and congestive heart failure. In a small number of patients with IE, Tiryakioğlu et al.[13] proposed early surgery, if there was a valvular involvement by IE. They suggested that the indication of surgical treatment should be planned accordingly with the patients' condition and TTE results.

Indications for urgent or elective surgery and mortality factors in patients with an isolated left-sided or right-sided IE are well described.[10-13,18,20] Remadi et al.[21] showed that the clinical results of IE due to *S. aureus* were poor, particularly in patients with comorbid disorders, or with the presence of congestive heart failure, sepsis, as well as major neurological events. Early surgery is independently associated with reduced overall mortality and should be considered in selected cases to improve the outcome.[8,13,21-23] Inadequate control of sepsis or heart failure, intracardiac abscess, serious and paravalvular regurgitation, and prevention of embolic events in

patients with a large and mobile vegetations require early surgery.[8-10,17-19,21,22] Some authors have proposed tricuspid valve repair instead of valve replacement in patients with an isolated right-sided IE.[21,23] No significant difference was found when compared with the clinical outcomes after implantation bioprosthetic and mechanical valve in previous study.[24] However, Toyoda et al.[24] suggested that the surgeons could be used cardiac valve according to patients' characteristics in a large series. Dereli et al.[25] reported a 74-year-old female patient with prosthetic valve endocarditis who previously underwent mitral valve replacement. They performed redo-mitral valve replacement using a bioprosthetic valve in surgery.

Previous reports of IE include non-homogenous groups and different mortality rates.[21,23] Some authors have demonstrated that if surgery is performed with optimal timing, it may be possible to reduce the risk of mortality in the treatment of IE.[9-11,13] Thus, it should be kept in mind that the common consensus issued by the international and national scientific committees in the diagnosis, treatment, and reduction of mortality in patients with IE significantly contributes to the prevention of patient mortality and morbidity.

According to our experiences, pulmonary embolic events were more common in a limited but important case series in patients who had a right-side involvement of IE. We, therefore, suggest a thoracic CT for the confirmation of a pulmonary embolic event in patients with respiratory symptoms. To prevent morbidity and mortality, similar to previous authors, we propose early surgery in the presence of perivalvular abscess formation, congestive heart failure, or embolic events to reduce the mortality and morbidity rates.

In our study, we observed positive blood culture in 67.8% of patients. Staphylococci were the most commonly seen microorganisms in our cohort. Cardiac or pulmonary complications were common complications in our case series. Pulmonary infarction and localized abscess along with pleural effusions were detected in our two patients with an isolated right heart involvement in IVDU. As a result, pulmonary embolism should be ruled out with thoracic CT in case of respiratory distress. Although we had a limited number of cases, according to our clinical experience, we recommend early surgical intervention in patients whose liver enzymes and kidney function tests are impaired during medical treatment, even if hemodynamic values are stable. However, we believe that further randomized clinical studies are needed to establish its effectiveness in the clinical setting.

In conclusion, the surgical principles of IE should be determined according to the patients' conditions and characteristics to provide satisfactory clinical results. Our main principle in surgical practice is to carefully re-inspect the infected heart valve during surgery, perform vegetectomy and the cleaning of infected tissues, then repair the valve in suitable patients. However, in the light of the current guidelines in the literature, wide resection is performed in complicated patients, as all infected tissue and the entire valve are removed, and then valve replacement is performed. In eligible patients, valve repair can be performed. Broad-spectrum antibiotics should be administered after surgery for four to six weeks until negative blood culture results are obtained at least two times postoperatively. If patients are older and have comorbidities, then a bioprosthetic valve may be preferred.

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