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Management of infective endocarditis and long-term outcomes of patients who underwent surgery: The fifteen-year experience of a tertiary care center

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Abstract

Infective endocarditis (IE) is still associated with severe complications and poor prognosis. The surgery of IE has various technical difficulties due to severe infection, inflammation of heart tissue, and systemic effects, so controversies continue about the optimal timing of operation. This study presents the treatment approaches, early and late-term outcomes of IE patients, who underwent surgery.This retrospective descriptive study is conducted with 46 patients (31males) operated between 2002-2018. The demographics and preoperative, intraoperative and postoperative data of patients were analyzed from the clinical database and patient records. Emergency surgery was performed to 15 (32.26%) patients.Numbers of patients with mitral valve, aortic valve, and prosthetic valve endocarditis were 14, 25, 7 respectively. Aortic valve replacement (AVR), mitral valve replacement (MVR), MVR + AVR and mitral valve repair were performed in 24, 12, 8 and 2 patients, respectively. Additionally, pericardial patch repair (periannular abscess or damage (n=12), aorta-right atrial fistulae (n=3)), debulking of associated tricuspid valve vegetation (n=2), tricuspid De Vega annuloplasty (n=3), Bentall operation (n=1) and aortic root enlargement (n=5) were performed. The mean follow-up period and mortality rates were 24.86 ± 38.98 months, 13.04% respectively. The mean survival and reoperation-free time were 179.02 ± 13.78 and 203 ± 10.09 months, respectively. Patients can be managed appropriately with early diagnosis, aggressive medical and surgical treatment via a multidisciplinary approach with customized management according to guidelines in terms of individual characteristics. In cases of worsening hemodynamic status, uncontrolled infection, large and mobile vegetations surgery should be performed as soon as possible

Keywords: Infective endocarditis, cardiac surgical procedures, disease management, heart valve diseases

Introduction

Infective endocarditis (IE), which is a multisystemic disease, describes the infection of the endocardial surface of the heart which may also include the heart valves, and which is caused by microorganisms such as bacteria, viruses or fungi [1]. Although this rare disease has an annual incidence of 3-10:100,000 and recent epidemiological studies suggest increasing incidence [2]. The increasing number of older patients, along with iv drug abuse especially in developed countries and healthcare-associated IE can be counted among the factors that cause an increase in incidence [3-5].

The diagnosis of IE has remained a challenge due to its various etiology and changing epidemiological factors related to the disease [6].

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It is customary to establish a diagnosis of IE by using the modified Duke criteria [6]. However, in some clinical conditions such as the subclinical course of infection; diagnosis may be missed, and a delayed diagnosis made with the development of severe complications significantly reduces the success of surgical treatment. Surgery has been the choice of treatment for active IE in the last decades and has been progressively performed with a current ratio that almost reached up to half of the IE patients [4,5].

Despite the improvement in multidisciplinary management of IE with advanced diagnosis and treatment modalities using efficient systemic antibiotherapy and surgical intervention, IE is still associated with severe complications, poor prognosis, and high mortality rates.

The surgical approach to IE patients has various technical difficulties due to severe infection, inflammation of the heart tissue, and systemic effects, so there are ongoing controversies about the optimal timing of the operation. This study presented the treatment approaches and the early and late-term outcomes of IE patients, who had undergone surgery in a tertiary care center.

Materials and Methods

Clinical data, study population and definitions

This retrospective study, which complies with the ethical rules declared by the Helsinki Declaration and Good Clinical Practice, was conducted after the approval of the Ethics Committee. The demographics preoperative, intraoperative, and postoperative data of patients were analyzed from the clinical database and patient records retrospectively. A total of 46 patients with complete data were enrolled in the study (31 males, 15 females; mean age 35.89 ± 14.64 years; range 11-68 years). All patients fulfilled the modified Duke criteria, were precisely diagnosed with IE and underwent open-heart surgery between January 2002 and December 2018. A multidisciplinary team involving cardiologists, infectious disease specialists, and cardiac surgeons decided on the indications and timing of surgery.

The criteria of exclusion from the study consisted of patients whose files showed a lack of data, who were older than 80 years, who had a comorbid diagnosis such as major embolic stroke with hemorrhagic transformation risk or different serious conditions like a malignant disease.

Data of demographic variables, clinical findings, New York Heart Association (NYHA) functional classification, medications used, etiology, results of blood culture analysis and echocardiographic valve diagnostics, complications, surgical techniques and type of valve prosthesis used, and the outcome after surgery were recorded.

All patients had at least one transthoracic echocardiogram at the time of diagnosis. Transesophageal echocardiography (TEE) was used in cases that required further information. If an urgent or an elective surgery was scheduled, a preoperative transthoracic echocardiogram was performed just before the surgery to figure out the latest findings. A total of eight patients had TEE (17.39%). The presence of NYHA class 3 or 4 symptoms and the need for inotropic drugs were defined as congestive heart failure. The persistence of fever despite intravenous antibiotherapy for at least a week was described as an uncontrolled infection. The presence of clinical stroke without supportive results from imaging studies was defined as embolic stroke while computed tomography verified cerebral lesions or clinical stroke was handled as cerebral embolism. If the size of vegetation was observed to be larger than 10 mm on echocardiogram, it was described as large vegetation. A classification of insignificant, mild, moderate and severe regurgitation was used according to semiquantitative or quantitative methods for assessing the degree of valve regurgitation. A region with heterogeneous echogenic or echolucent appearance raised the suspicion for a diagnosis of perivalvular extension and abscess. The length of maximal vegetation was also estimated.

The time-lapse between the scheduling and the operation was defined as the timing of the surgery. In this study, the timing of the surgery was described by using a simple classification; “Emergency surgery” (operation was performed in the first 24 hours), “Urgent surgery” (operation was performed in less than a week), and “elective surgery” (the operation was performed after at least 2 weeks of appropriate antibiotics treatment in cases, whose cardiac function was stable). The main indications for early surgical intervention, comprising of both “emergency” and “urgent” surgery in this study are heart failure (HF), uncontrolled infection, irreversible structural damage like paravalvular extension, abscess, fistulae, severe valvular regurgitation, size of the vegetation, microorganisms, and prevention of embolic events as previously reported [6,7]. Although the presence of cerebral emboli did not affect the timing of surgery, the patients with hemorrhagic cerebral infarction or with the risk of hemorrhagic transformation had conservative management procedures for 4-6 weeks before further evaluation for surgery.

Surgical technique

Surgery was performed during the antibiotic treatment. The definition of the surgery during the initial hospitalization stage for IE was regarded as the replacement or repair of the affected valve. Concomitant procedures during surgery included the repair of periannular abscess or destructions, the repair of fistula and dehiscence.

The surgical operations of all patients were performed under general anesthesia conditions and via a median sternotomy approach. For ascending aorta, aortic cannulation was performed in cardiopulmonary bypass with mild hypothermia, while the venous drainage was provided either by atrial or separate cannulation of both the superior and inferior vena cava. In order to achieve cardiac arrest, the combination of antegrade and/or retrograde cold blood cardioplegia was administered.

The valve repair technique or replacement with a mechanical valve was used when the infection was intraoperatively observed as limited to the valve leaflets. After the surgeon explored the extent of the infected tissue and considered it resectable with a high possibility of sufficient leaflet tissue that would be retained for a satisfactory outcome, the attempt for repair technique was performed. If the infection was observed to extend to the surrounding structures or there was an annular abscess and disruption or fistula, the technique of surgery consisted of annular reconstruction by using a pericardial patch, or the replacement of aortic root using valve graft.

Radical resection of the affected tissue, followed by a topical antibiotic agent (Cefazolin Na) application, was performed in all of the patients as a routine procedure. The debridement of paravalvular infected structures was performed despite potential damage to the conduction system or myocardial/fibrous tissue. A careful examination of the valvular annulus and surrounding structures was carried out for potential extensive abscess resection. The use of artificial material was kept as low as possible. The type of valve implemented was generally determined by the preference of each surgeon and according to the patient characteristics.

Postoperative care

Apart from patient stabilization, in terms of hemodynamics and weaning from respiratory support, strict monitoring of the local and systemic infective process was the primary target of early therapy in the intensive care unit (ICU). The appropriate regimen for postoperative antibiotic therapy, which was recommended and initiated by infectious disease specialists was continued in ICU. Patients without any postsurgical complications were transferred to the infectious disease ward for finishing the rest of the 6-8 weeks of antibiotherapy.

Statistical Analysis

For statistical purposes, descriptive analysis was performed. Continuous and categorical variables were expressed in terms of median and mean, absolute values and percentage ratios, respectively. Data related to survival were indicated as mean standard deviation with a 95% confidence interval. Survival analysis was performed by Meier method, and related curves were drawn.

Results

In this study, two patients were iv drug abusers while two patients had a history of embolism event, and three patients were dependent on hemodialysis due to chronic renal failure. The clinical, laboratory and echocardiography findings of the cases were listed in Table1.

Table 1. Demographic and Echocardiographic data of patients

Variables	Mean ± SD / n	(%)
Age (years)	35.89 ± 14.64	
Male	31	67.39
Female	15	32.60
Obesity	3	6.52
Diabetes	5	10.86
HTA	4	8.69
Smoking	20	43.7
NYHA III- IV	39	84.78
Blood culture negative	14	30.43
CKD with hemodialysis	2	4.34
Cerebral Embolism	2	4.34
Blood culture positive	9	19.56
Euroscore	5.72 ± 3.18	
Ejection fraction %	57.03 ± 7.96	
SPAP (mmHg)	52.68 ± 18.06	
LVESD (mm)	47.13 ± 8.08	
LVEDD (mm)	60.15 ± 9.96	
NVE	39	84.78
PVE	7	15.21

BMI: Body Mass Index, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, NVE: Native valve endocarditis, PVE: Prosthetic valve endocarditis.

The number of patients who were diagnosed with native valve endocarditis (NVE) and prosthetic valve endocarditis (PVE) was 39 (84.78%) and 7 (15.21%), respectively. Among the patients with NVE, 14 patients had mitral valve endocarditis while 25 of them had aortic valve endocarditis. The bicuspid aortic valve was present in 3 of the patients (6.52%). During initial hospitalization, 39 (84.78%) of the patients were recorded as NYHA functional class III or IV.

The diameter of the vegetation was measured to be over 10 mm. in 12 patients out of 24 (52.17%), who were found to have had vegetation on echocardiography. Additionally, three patients had concomitant right atrial vegetation. Among the cases with native valve endocarditis, aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation, and tricuspid regurgitation were observed as the dominant valve pathology in 5, 22, 2, 16, and 4 cases, respectively. Two of the patients were found to have mitral valve leaflet perforation that caused regurgitation (one with anterior, one with posterior leaflet).

The blood and tissue culture results that were obtained for 23 of the cases showed that responsible microorganism was not detected in culture samples of the 14 (30.43%) and detected in 9 (19.56%) of the patients. The microorganisms isolated by culture analysis are listed in Table 2.

Table 2. Identified Microorganisms from blood culture

Microorganism	n	(%)
Streptococcus viridans	1	11.1
Streptococcus pneumonia	1	11.1
Staphylococcus aureus	3	33.3
Brucella spp	1	11.1
Enterococcus faecalis	2	22.2
Staphylococcus Lugdunensis	1	11.1

For all the cases in the study, the mean duration of ventilation, ICU, and hospital (surgery clinics) stay were 7.97 ± 4.78 hours,3.5 ± 1.96, and 11.59 ± 7.08 days, respectively. During the postoperative intensive care period, 18 patients received inotropic therapy.

In this study, out of 9 (19.56%) patients who had a history of open-heart surgery, 2 had a coronary bypass, 5 had mitral valve replacement (MVR) (1 bioprosthesis), 1 had aortic valve replacement (AVR), and 1 had MVR + AVR operations. Emergency surgery was performed to 15 (32.26%) patients who were etiologically classified as congestive heart failure (13 patients) and recurrent embolism attacks (2 patients). Among the patients, who were operated in an emergency state, 4 of them were intubated before the onset of the surgery.

Among all patients, isolated AVR, isolated MVR, MVR + AVR and isolated mitral valve repair were performed in 24, 12, 8, and 2 patients, respectively. Additionally, pericardial repair due to either periannular abscess or damage in 12 patients and aorta-right atrial fistulae in 3 patients, debulking of associated tricuspid valve vegetation in 2 patients, tricuspid De Vega annuloplasty in 3 patients, Bentall operation in 1 patient, and aortic root enlargement in 5 patients were performed. Apart from redo operations, disseminated epicardial adhesions were present in 10 patients.

The mortality rate was 13.04% (n= 6). Out of the deceased patients, three had prosthetic valve endocarditis (one of them with double valve replacement), one had coronary bypass surgery a year ago, and four patients had emergency surgery while intubated. Multiorgan failure, uncontrolled infection related to severe sepsis and low cardiac output were the etiology of in-hospital mortality

in 2, 2, and 2 patients, respectively. The mean follow-up period of this study was 24.86 ± 38.98 months (2-214). There was no patient admission due to recurrent endocarditis during the follow-up period. A patient was re-operated for pseudoaneurysm due to aortic root separation after six months from endocarditis surgery. During the follow-up period, the mean survival and reoperation-free time were found to be 179.02 ± 13.78 (CI: 152.01-206.039) and 203 ± 10.09 (CI: 182.047-223.95) months, respectively as shown in Figure1-2.

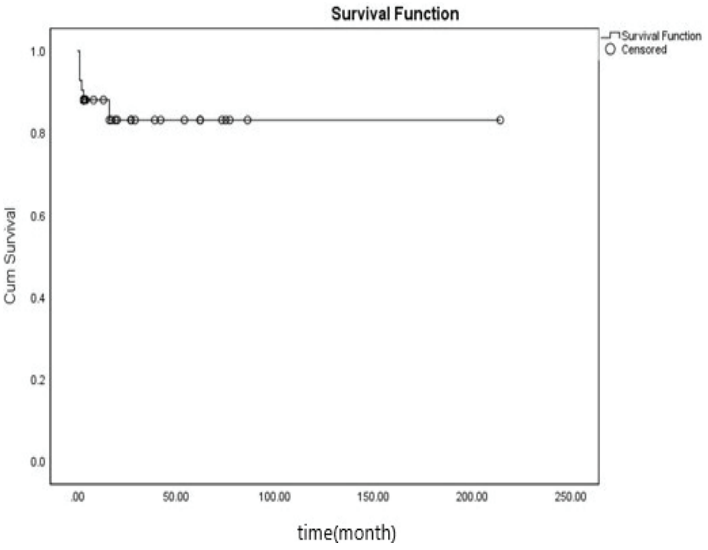

Figure 1. The mean survival of patients during the follow-up period

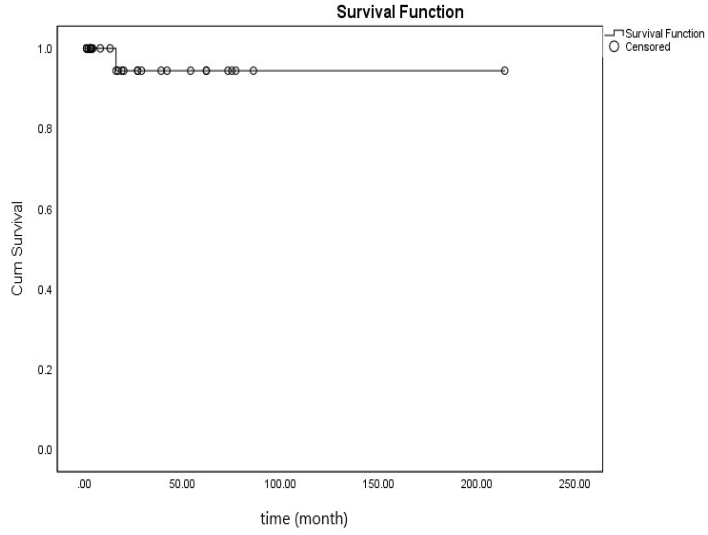

Figure 2. The mean reoperation free time of patients during the follow-up period

Discussion

Currently, the incidence of IE, especially in developed countries, has been on the rise as a result of either highly virulent microorganisms or health-related issues such as people with a history of medical intervention, or who have comorbid diseases, prosthetic valves, or intracardiac devices [4,5,8,9]. Therefore, rapid diagnosis and potent treatment of IE is essential for survival. Complications and poor prognosis would be a result of delayed diagnosis or the onset of treatment [10,11]. In this study, the mean age of patients is not compatible with the IE patient profile that has been recently getting older. However, the number of patients, who were admitted due to IE as a result of highly virulent microorganisms or due to complications and IE of prosthetic valves, was similar to the literature.

Although there is marked advances in the diagnosis and management of IE, it is still among the most fatal diseases with an in-hospital mortality rate of 10-30% that is mostly due to the lack of surgery in 25% and 50% of the patients with clear indications for cardiac surgery in the acute phase [12]. The mortality rate (13.04%) of this study was consistent with recent reports. The parameters of hemodynamic instability, stroke, expected poor prognosis independent from treatment, death before surgery, sepsis and surgeon denied operating were the reasons for avoiding surgery and maintaining nonsurgical treatment and also a lack of surgery reported in patients with Staphylococcus Aureus IE and poor prognosis factors [2,12]. Therefore, European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) guidelines both emphasize that patients should be referred to centers that have a specific team that would approach endocarditis from the most proper medical and surgical aspect with a special focus on the optimal timing for the surgical intervention [6,8].

The optimal timing of surgery is the main issue of IE and still unclear, actually, ESC guideline reported a proper staging according to the hemodynamic status of the patient [6]. According to this guideline, the surgery performed during the first 24 hours is graded as "emergency", if it is performed within a week and in at least 1-2 weeks after the antibiotherapy, its stage is classified as "urgent" and "elective" respectively. While the patient receiving antibiotherapy in the active phase of IE, early surgery option should be considered in order to avoid the development of progressive HF, infection-related irreversible structural damage and to refrain from systemic embolism [6,13,14].

In this study, the management and surgery decisions of patients with IE were made by a multidisciplinary team and early surgery (starting from first 4-6 hours and lasting up to a week) preferred in high-risk patients with heart failure symptoms or severe valve regurgitation and/or stenosis, large vegetations (above 10 mm) and IE caused by Staphylococcus aureus.

There are some occasions when the duration of the antibiotherapy is inconsiderable for deciding on an emergency (in the first 24 hours) or urgency (within a few days and in less than a week) based surgical intervention. At other times, however, the clinical course allows ample delay of surgery to complete one or two weeks of antibiotherapy under clinical and echocardiographic surveillance prior to scheduling elective surgery [6,14].

The primary indications for early surgical intervention for IE involve HF, uncontrolled infection, and the aim of avoiding embolic events [6,15,16]. However, the prognosis becomes dreadful whenever a heart failure accompanied by progressive symptoms, cerebral emboli, and reduced cognitive skills develop [17,18]. The decision to perform surgery in IE remains a challenge because of the potential for acute and life-threatening complications of this disease, uncertain response to antibiotic therapy, and comorbid host conditions [4,5]. Compared to delayed surgery, surgery in the

early term is customarily accepted as riskier due to inflammation of tissues and technical difficulties related to surgery.

In approximately half of the patients with IE are treated by both medical and surgical approaches via cardiac surgery and antibiotherapy [4,5]. It appeared that preoperative antibiotherapy duration did not either affect mortality in the perioperative period or the rate of recurrent IE [19,20]. In this study, all patients had surgery while receiving antibiotherapy; on the other hand, the reason for the relatively low ratio of patients with negative blood cultures for microorganisms was considered to be due to intensive antibiotherapy in the preoperative period.

The essential purpose of surgical intervention like debridement of the infected tissue in IE is the limitation of infectious foci to prevent or treat heart failure and dissemination of the infection, and it also decreases the risk of embolism related morbidity and even mortality in the optimum clinical conditions [15,12,21-23]. The main principle of the surgical approach in this study depends on the repair of paravalvular complications by completely removing all the infected and necrotic tissue with a minimal residual foreign body. By using this approach, after initial evaluation of the affected valve intraoperatively, debulking and debridement of the vegetation and abscess foci was performed, and in case of a fistulae presence, preferred management included repair by pericardial graft and re-evaluation of the valves for valve preservation/repair when there is no rheumatic changes or there is an isolated leaflet perforation [24].

When medical therapy is not sufficient for treating IE, especially in complicated cases with abscess, fistulae, valve perforation, and alike, surgical intervention can be life-saving, however, the reciprocity among indications for surgery, acute clinical status, surgical considerations, and outcome prediction is very intricated, and has not been fully delineated yet. Surgery performed very early may improve survival with an increased surgery risk at seriously complicated IE patients. When the surgery is performed too soon, a high risk of relapses and dysfunction of the valves in the postoperative period is not surprising [14].

In this study, no admissions for recurrent IE in the postoperative follow-up period were found. We concluded that this outcome was the result of a multidisciplinary approach to the patients that included not only intraoperative source evaluation and proper removal of the infectious foci but also ensuring to complete a full course of antibiotherapy in the infectious disease ward, which the patients were transferred after the surgical surveillance in the postoperation period. However, a single patient had been re-operated for pseudoaneurysm due to aortic root separation in the sixth postoperative month. The surveillance is crucial in all the patients, especially the ones who have emergency surgery, and full attention should be paid for the complications that do not cause acute deterioration of the clinical course, i.e., valve dehiscence, pseudoaneurysm. It is possible to detect severe complications and intervene accordingly by rigorous patient follow-up before the development of any complaints or progression to the life-threatening clinical status.

The presence of a neurological complication is specifically a problem when considering the proper time for surgery [19,20]. When the patient has associated ischemic stroke, the risk of the surgical operation increases and complicated neurological findings by the addition of hemorrhagic infarct can be caused by early surgical intervention. On the contrary, the substantial risk of disease progression and cerebral embolism recurrence based on delayed surgery were pronounced by the advocates of early surgery [25].

In a meta-analysis of comparing results of studies regarding the timing of the surgery within one versus two weeks of diagnosis, Christos et al. found that the outcome of an early surgery for valvular IE which was complicated by embolic ischemic stroke was not favorable with an increased risk of mortality. The researchers stated that early surgery did not result in lowering the incidence of perioperative stroke or the 1-year survival and proposed that especially in high-risk patients, surgery might better be delayed if there are no absolute emergency indications for valve surgery [26]. However, when a patient develops heart failure associated with progressive symptoms or cerebral emboli associated with declined cognitive skills, the prognosis is dreadful [18].

In a recent update report of the 2014 ACC/AHA guideline, Nishimura et al. reported that when a neurological event did not cause widespread neurological injury or intracranial hemorrhage, recent data favored early surgery with a low risk of postoperative neurological deterioration for better overall outcomes. They also stated that when there was widespread neurological damage or intracranial hemorrhage, cardiac surgery posed a high mortality risk when performed in the first 4 weeks after a hemorrhagic stroke [27]. In this study, postponing the surgery based on the hemodynamic status, the size of the vegetation, and the clinical presentation of the patients with a cerebral complication during the acute phase in initial hospitalization was preferred. Early surgery is preferred especially in patients with Staphylococcus aureus related IE if the patients do not have any significant comorbid prohibitive conditions such as ischemic cerebral infarction which affects a broad region risky for hemorrhagic transformation, factors for poor prognosis (advanced age, cancer, chronic obstructive pulmonary disease, morbid obesity, cachexia), and hemodynamic instability.

In a review by Delahaye, it was reported that no firm conclusions for performing early surgery in all IE patients could be drawn despite the results of observational studies that suggested the benefits of current surgical practices concerning the long-term survival [28]. A favorable outcome of the surgery was related to the surgeon who based the operation decision on the IE presentation and characteristics of the patient. Furthermore, the patients who fulfilled the criteria put forward in management guideline were the ones, who most benefited from the surgery [21,22,26].

The clinical course before the surgery is an independent predictor of survival in patients who had an operation for native mitral valve IE. The presence of preoperative embolic stroke, congestive heart failure or disseminated infection significantly decreased the five-year survival rate in patients with IE, accordingly, postponed surgery may raise the possibility and severity of preoperative complications and thereupon postoperative mortality [17]. In a recent meta-analysis by Liang et al., the association of early surgery with lower rates of in-hospital and long-term mortality was reported in IE, especially in NVE patients; however, there are still controversies concerning the optimal surgery time for both NVE and PVE [29].

The most severe type of IE is PVE, which has an incidence of 0.3-1.2% per patient-year and develops in 1-6% of patients who have valve prostheses [6]. PVE affects mechanical and bioprosthetic valves in equal rates and accounts for one-tenth to one-third of all IE cases [6,8]. It is still challenging to diagnose and determine the best treatment option for PVE, which consequently leads to poor prognosis. The diagnosis of NVE is more straightforward. If no surgical intervention is performed for complicated and staphylococcal PVE, the prognosis becomes dismal. Therefore, aggressive management approaches should be used for these advanced forms of PVE while uncomplicated and late PVE due to microorganisms other than staphylococcus can be treated conservatively by appropriate antibiotherapy and close follow-up [6]. The rates of morbidity and mortality can remain high due to ongoing infection, which might not even be controlled with aggressive surgical therapy [6]. In this study, half of the patients that had a fatal course were PVE patients, and their prognosis was worse than others. There is no consensus over the favorable type of aortic prosthesis for PVE patients, and the surgical techniques, as well as prosthetic valve types, show a wide range of variation among these patients [30]. There are no well-defined data on the proper valve substitute in IE, and in this study, it was found that all patients who required replacement had mechanical valve prosthesis. This was concluded to be the result of a relatively younger patient population. On the other hand, patients with complicated IE in this study had 26 additional procedures.

One of the limitations of the present study was a single-center experience of the same surgical team with two senior surgeons. Also, retrospective design of the study and the relatively low number of patients were other limitations. Multicenter prospective studies with high number of patients can reveal significant results. This study includes both NVE and PVE so that the mortality rate may be biased, and predictors of mortality could be assessed with a larger sample size in both isolated groups of NVE and PVE. The relationship between causative microorganism and mortality could not be evaluated because of the high ratio of negative blood culture.

Conclusion

Despite high mortality and morbidity rates, patients can be managed appropriately with early diagnosis, aggressive medical and surgical treatment (early or elective) via a multidisciplinary approach with customized management according to guidelines in terms of individual characteristics. In cases of worsening hemodynamic status, uncontrolled infection, large and mobile vegetations surgical intervention should be performed as soon as possible.

Competing interests
The authors declare that they have no competing interest.

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Ethical approval
This study was approved by local ethics committee (No: 2019/298).

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