Original Research

Surgical Management of Infective Endocarditis: Early and Long-Term Mortality Analysis. Single-Center Experience and Brief Literature Review

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Introduction: In this study we evaluated factors that affect the early and long-term postoperative outcomes of patients with infective endocarditis.

Methods: We retrospectively reviewed 94 patients (68 male, 26 female, mean age 58.3 ± 13.1 years, range 20-85 years) with proven infective native (n=85) or prosthetic valve (n=9) endocarditis who underwent heart valve surgery between September 1997 and December 2007. Fifty-four patients (57.4%) underwent aortic, 28 (29.8%) mitral, 3 (3.2%) tricuspid, 8 (8.5%) double, and one patient (1%) triple valve surgery. In 75.5% of the procedures we implanted mechanical valves, in 13.8% biological prostheses, and 10.7% were reconstructive or other procedures. Midterm follow up was 100% complete with a cumulative duration of 545 patient-years (maximum 12 years).

Results: Overall hospital mortality (30 days) was 8.5% (n=8). Causes of early mortality were low cardiac output syndrome in 2 cases, sepsis with multiple organ failure in 5 cases, and intracerebral bleeding in one patient. Development of postoperative low cardiac output syndrome (p=0.01) was identified as an independent predictor of early mortality. Overall late mortality was 25.6% (n=22) with a cumulative rate of 4.03% per patient-year. Causes of late death were predominantly of extracardiac origin. Kaplan–Meier survival analysis revealed a cumulative survival rate at 12 years of 57.2%. Cox regression analysis identified diabetes mellitus (p=0.016) and postoperative low cardiac output syndrome (p=0.03) as independent late mortality factors.

Conclusions: Heart valve surgery in patients with infective endocarditis is associated with increased but acceptable early and long-term mortality. The mid-term prognosis is similar to that of patients undergoing elective valve replacement surgery.

Infective endocarditis (IE) is associated with a high risk of morbidity and mortality.[1] Prolonged appropriate antibiotic therapy remains the most important component in the treatment for native valve endocarditis once the causative organism has been identified. Rapid diagnosis, effective treatment, and prompt recognition of complications are essential to improve patient outcome. Nevertheless, depending on the virulence of the microorganism, the extent of involvement of surrounding tissues, and whether the infected valve is native or prosthetic, surgery may become indispensable to eradicate the infection.[2]

In recent years, the introduction of newer antibiotics and the more aggressive surgical treatment of the disease have resulted in a significant decrease in mortality from 100% to around 30% and have paved the way for more sophisticated therapies, as proposed today.[3]

In this paper we provide a retrospective review of a single-center experience of surgical treatment for active infective endocarditis and an evaluation of the factors affecting early and long-term outcomes.

Methods

From September 1997 through December 2007, 94 consecutive patients with infective endocarditis underwent surgical treatment at the Heart Center Munich Bogenhausen. All patients with prosthetic valve endocarditis (PVE) underwent primary valve replacement at the same institution.

Data regarding demographics, preoperative clinical status, intra- and early postoperative course were collected prospectively and are part of a data registry of all cardiac surgical patients at the institution. Operative mortality risk was assessed for every patient according to the European System for Cardiac Operative Risk Evaluation (EuroSCORE, ES) (additive and logistic), which is routinely used at our institution. Additional pertinent information about the disease, such as causative microorganism, intraoperative findings, and technical details of the surgical procedures performed, were obtained from a review of the hospital medical records. Follow-up data were gathered predominantly by mail and telephone contact with the patients or relatives and/or their referring physicians, according to a detailed questionnaire.

Patient group

Our study group included 94 patients who were surgically treated for infective endocarditis. The majority of them (69.1%, n=65) were referred from peripheral hospitals with the indication for surgery, while the rest were primarily admitted and treated in other departments at our institution. Follow up was complete in 100% of the cases. There were 68 men and 26 women, aged 20 to 85 years (mean 58.3 years). Eighty-five patients presented with native valve endocarditis (NVE) and 9 with PVE. In 54 cases the infection affected the aortic and in 28 patients the mitral valve. Eight patients with double-valve disease presented lesions on the aortic and mitral valves (n=7) or on the aortic and tricuspid valves (n=1), while in 3 cases the infection involved only the tricuspid valve. One patient underwent triple valve surgery. In 5 cases the infection affected mechanical prostheses and in 4 cases biological implants. Six of those were classified as early (within 1 year after implantation) and 3 as late infections. The mean follow-up period was 5.8 years, with a maximum of 12 years. The cumulative observation duration consisted of 545 patient-years; for aortic valve (AVR/r), mitral valve (MVR/r) and double-valve replacement/repair (DVR/r) the duration was 335, 139 and 58 patient-years, respectively. Table 1 summarizes the main demographic and clinical characteristics of the study population.

The indications for surgery were the presence of abscess associated with valvular deformation and/or dysfunction, cardiogenic and/or septic shock, congestive heart failure, persistent sepsis despite antibiotic therapy, persistent size of vegetation larger than 1 cm despite medical treatment, and central or peripheral arterial embolization. Surgery was predominantly performed at least one week after starting maximal antibiotic therapy (95% of cases; n=89), unless deterioration of clinical status forced an earlier intervention (5 patients). The setting of the operation was defined as urgent (22 patients) if it was undertaken on the next day after admission and as emergent (23 cases) if it was performed because of unstable hemodynamic conditions on the admission day.

According to the risk predictions delivered by the additive ES and using arbitrary threshold values, the patients were divided into 3 groups, characterized as low ($ES \leq 8$), moderate (ES 9-12), and high risk ($ES > 12$). The populations of the three groups were comparable. The cutoff point above which a patient is considered to be of "high risk" is variously defined in the literature.[4] However, a calculated additive $ES > 12$ seemed reasonable for the stratification of patients with increased operative mortality risk.

In 71 cases the offending microorganism was identified by preoperative blood cultures. In the remaining 23 patients, although they had clinical and pathological evidence of endocarditis, no microorganism could be cultured and they were treated as culture-negative endocarditis. Figure 1 presents the cultured microorganisms responsible for the infection. The most commonly detected bacterium was *Staphylococcus aureus*, accounting for 17% of the cases, followed by *S. epidermidis* (14%).

Operative technique

All patients were operated in a standard fashion with cardiopulmonary bypass under moderate hypothermia (32-34°C). Myocardial protection was achieved

Table 1. Demographic characteristics of the study population.

Variable	AV n=54	MV n=28	DV n=8	TV n=3	Total n=93*
Sex (%)					
Male	43 (79.6)	16 (57.1)	5 (62.5)	2 (66.7)	66 (70.2)
Female	11 (20.4)	12 (42.9)	3 (37.5)	1 (33.3)	27 (29.8)
Age @ OR (y)					
Range	25-85	20-77	36-73	54-72	20-85
mean ± SD	56.7±13.6	61.0±14.1	58.1±14.1	62.3±9.0	58.3±13.1
Valve endocarditis (%)					
Native	46 (85.2)	27 (96.4)	8 (100)	3 (100)	84 (90.3)
Prosthetic	8 (14.8)	1 (3.6)	0 (0)	0 (0)	9 (9.7)
NYHA preop. (%)					
I	8 (14.8)	4 (14.3)	1 (12.5)	0 (0)	13 (14)
II	14 (25.9)	8 (28.6)	2 (25)	1 (33.3)	25 (26.9)
III	20 (37)	11 (39.3)	4 (50)	2 (66.7)	37 (39.8)
IV	12 (22.2)	5 (17.8)	1 (12.5)	0 (0)	18 (19.3)
Cardiac rhythm (%)					
SR	43 (79.7)	22 (77.8)	6 (75)	2 (66.7)	73 (78.5)
AF	4 (7.4)	5 (18.5)	1 (12.5)	1 (33.3)	11 (11.8)
Other	7 (12.9)	1 (3.7)	1 (12.5)	0 (0)	9 (9.7)
Renal function (%)					
Normal	35 (64.8)	21 (75)	6 (75)	3 (100)	65 (69.9)
Compensated	17 (31.5)	4 (14.3)	2 (25)	0 (0)	23 (24.7)
Dialysis/ filtration	2 (3.7)	3 (10.7)	0 (0)	0 (0)	5 (5.4)
LV Ejection fraction (%)					
>50%	28 (51.8)	17 (60.7)	4 (50)	3 (100)	52 (55.9)
30-50%	21 (38.9)	7 (25)	1 (12.5)	0 (0)	29 (31.2)
<30%	5 (9.3)	4 (14.3)	3 (37.5)	0 (0)	12 (12.9)
Arterial hypertension (%)	22 (40.7)	11 (39.3)	1 (12.5)	2 (66.7)	35 (37.6)
Diabetes mellitus (%)	12 (22.2)	8 (28.6)	0 (0)	2 (66.7)	22 (23.7)
Peripheral embolization (%)	11 (20.4	8 (28.6)	1 (12.5)	0 (0)	20 (21.5)
Arterial disease (%)	8 (14.8)	2 (7.15)	1 (12.5)	0 (0)	11 (11.85)
Setting (%)					
Elective	25 (46.3)	15 (53.6)	5 (62.5)	3 (100)	48 (51.6)
Urgent	12 (22.2)	8 (28.6)	2 (25)	0	22 (23.7)
Emergent	17 (31.4)	5 (17.8)	1 (12.5)	0	23 (24.7)
EuroSCORE					
Additive (range; mean±SD)	5-18; 10.5±3.3	5-16; 10.8±3.1	6-14; 9.7±2.75	5-11; 7.3±3.2	5-18; 10.4±3.2
Logistic (range; mean±SD)	4.4-79.3; 27.3±0.2	4.4-59.6; 28.1±0.2	6-50.9; 22.2±0.15	4.4-24.7; 11.3±0.1	4.4-79.3; 26.4±0.2
Paravalvular abscess (%)	6 (21.4)	2 (28.6)	0 (0)	27 (29)	19 (35.2)
Staphylococcal infection (%)	10 (35.7)	1 (12.5)	0 (0)	33 (35.1)	22 (40.7)
Times (min)					
Bypass [range;mean]	41-401; 99.5	54-205; 95.6	68-138; 108.4	31-86; 61.3	31-401; 97
X-clamp [range;mean]	31-200; 74.8	41-171; 75.2	56-160; 99.5	0-73; 31	0-200; 75
OR [range;mean]	90-555; 186	105-285; 175.5	135-230; 182.1	75-170; 125	75-555; 180.2
Status @ OR-end (%)					
Stable without inotropes	4 (25.9)	7 (25)	1 (12.5)	2 (66.7)	24 (25.8)
Low inotropes	26 (48.2)	17 (60.7)	6 (75)	1 (33.3)	50 (53.8)
High inotropes/ IABP	14 (25.9)	4 (14.3)	1 (12.5)	0 (0)	19 (20.4)
ICU stay (d) [range; mean]	0-5; 3.2	2-6; 3.96	2-5; 3.7	2-5; 4	0-6; 3.5
Procedure (%)					
Mechanical VR	42 (77.7)	23 (82.15)	5 (62.5)	1 (33.3)	71 (76.4)
Biological VR	10 (18.6)	2 (7.15)	2 (25)	0 (0)	14 (15)
Reconstructive / other	2 (3.7)	3 (10.7)	1 (12.5)	2 (66.6)	8 (8.6)

*excluding one case of triple valve endocarditis.

AV – aortic valve; MV – mitral valve; DV – double valve; TV – tricuspid valve; OR – operation; NYHA – New York Heart Association; preop. – preoperative, SR – sinus rhythm; AF – atrial fibrillation; X-clamp – cross clamp; IABP – intra-aortic balloon pump; VR – valve replacement; n – number; y – years; SD – standard deviation.

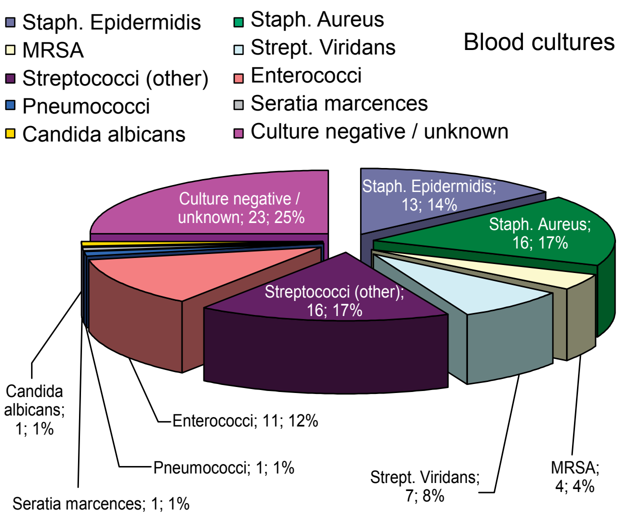

Figure 1. Causative microorganisms in blood cultures.

using a cold hyperkalemic crystalloid solution (Brettschneider). Surgical procedures consisted of valve replacement with mechanical or bioprosthetic devices, or valve repair/reconstruction, when feasible. One PVE case with an infected aortic mechanical prosthesis was reoperated twice, receiving firstly a biological prosthesis and after re-recurrence of the infection a homograft, which completed the aortic root replacement. Operation was complicated in 27 cases by the infection extending into the valvar annulus and surrounding structures, or by the formation of paravalvular abscess. The major surgical principle consisted of the radical excision of all affected tissue, regardless of the infection's extent. Abscess cavities were closed after disinfection, either directly by suture or by the prostheses' sutures if the cavity was localized in the valvular annulus. In case of an extraordinary extension of the infection into the periannular tissue, the annulus was reconstructed with pericardial patches. The surgical techniques applied in these radical procedures have been described extensively in a previous publication.[5] All surgical instruments, equipment and surgical gloves used for resecting the infected tissues were discarded afterwards and replaced by new ones for the ongoing surgical procedure. Valve prostheses were implanted using single, Teflon-coated sutures irrigated and disinfected with a 2.5% povidone–iodine solution. All patients were admitted to the intensive care unit and were treated postoperatively with appropriate intravenous antibiotics for at least 6 weeks. All operative procedures, including concomitant surgical interventions, are listed in Table 2.

Table 2. Surgical procedures.

Variable	n	(%)
Surgical procedures performed:		
Mechanical VR	67	(71.3)
Biological VR	10	(10.6)
Reoperation with mechanical VR	5	(5.3)
Reoperation with biological VR	3	(3.2)
Reoperation with homograft	1	(1.05)
Valve repair with annuloplasty ring	2	(2.1)
Valve repair without ring	2	(2.1)
Other	5	(5.3)
Concomitant procedures:		
Coronary artery bypass grafting	4	(4.3)
Ascending aorta replacement	2	(2.1)
Paravalvular abscess debridement	27	(28.7)
Valvular annulus reconstruction	2	(2.1)
Congenital atrial septal defect closure	1	(1.05)
Devices:		
Mechanical		
Sorin Bicarbon™	52	
ATS Medical Inc.	19	
Biological		
Mosaic® Medtronic	5	
Carpentier Edwards Perimount	6	
Sorin Pericarbon More	1	
Mitroflow® Carbomedics	1	
Annuloplasty rings		
Carpentier Edwards physio	2	

VR – valve replacement

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are reported as frequencies unless otherwise stated. Clinical, laboratory, and pathological variables were tested by the chi-square and Fisher's exact test to determine their statistical value as predictors of operative mortality. A multivariable early mortality analysis was performed by log linear estimation through a statistical model including all those variables that presented a significant association in the univariate analysis ($p<0.05$) and those that were considered potentially clinically relevant, but did not achieve statistical significance in the univariate evaluation ($0.05<p<0.07$).

Long-term survival estimates were calculated using the method of Kaplan– Meier, whereas univariate comparisons of survival data were tested using the log-rank and the χ^2-test. Linearized rates, expressed as percentage per patient-year, were calculated by dividing the number of events by the total follow-up time in years and multiplied by 100. Survival was analyzed with regard to variables that were related to the patient, infection, preoperative clinical status, and operation. For the multivariate analysis of long-term survival, the proportional hazard model of Cox was assembled and predictions were derived.

A p-value <0.05 was considered statistically significant.

Results

Eight patients died within 30 days after operation or prior to hospital discharge, which resulted in an early mortality rate of 8.5%. For patients who had undergone AVR/r, MVR/r, and DVR/r, the early mortality rates were 9.2%, 7.1%, and 0%, respectively (p=0.036). One case out of 8 eight early deaths suffered from early PVE. This patient was addicted to heroin and developed valve endocarditis after AVR with a mechanical prosthesis, was scheduled for reoperation, but died before surgery from left ventricular heart failure. Three of the 8 non-survivors presented an extended infection affecting the surrounding tissues with formation of paravalvular abscess.

The causes of early mortality were sepsis with multiple organ failure in 5 cases, cardiac output syndrome in 2 low, while 1 patient died on the 18th postoperative day because of intracerebral bleeding attributed to anticoagulation treatment and was therefore classified as valve-related early death.

The univariate analysis demonstrated that early mortality was significantly higher in patients who underwent AVR (p=0.003) and in those who developed low cardiac output syndrome (LCOS) postoperatively (p=0.048). Non-survivors of the operation had a significantly higher preoperative serum creatinine level (p=0.025), and their operations lasted significantly longer (p=0.001). Early mortality was also higher in diabetic patients, although the difference did not reach statistical significance (p=0.06). None of the other variables tested (Table 3) appeared to have an influence on the early outcome.

Further early mortality analysis included log-linear testing, by constructing a statistical model including the aforementioned significant variables and additionally those considered potentially clinically relevant, such as renal failure, sex, preoperative clinical status according to the New York Heart Association (NYHA) classification, and emergent setting of the operation. Of the risk factors tested, only the postoperative development of LCOS (p=0.01) was identified as an independent predictor of early mortality. Patients who suffered from postoperative LCOS had an approximately 5.5-fold higher risk of not surviving the operation (Table 5).

In terms of late mortality, 22 patients (25.6%) died during the follow up. With regard to the site of infection and consecutive operative procedure, the late mortality rates for AVR/r, MVR/r, and DVR/r were 22.45% (n=11), 42.31% (n=11), and 0% (n=0), respectively. The causes of death were cardiac failure in 6 cases, malignant diseases in 3 patients, central neurological events in 2 (one of them due to intracerebral bleeding), multiple organ failure in 2, while 3 patients died from either suicide, pulmonary embolism, or sepsis. In the remaining 6 cases, the causes of death were not determined and they were therefore classified as death from an unknown cause.

The overall late mortality rate was 4.03% /patient-year: with regard to the implant site, for AVR/r and MVR it was 3.3% /patient-year and 7.9% /patient-year, respectively. The actuarial cumulative survival rate at 12 years was 57.2% (Figure 2), with the 25th percentile (lower quartile) having a survival time of approximately 61 months. Table 4 depicts the impact of various variables on the actuarial survival at 12 years. The survival analysis, including log-rank testing, demonstrated that age at operation >60 years (p=0.0013), a history of arterial hypertension (p=0.0012) or peripheral arterial disease (PAD) (p=0.0046), comorbidity of diabetes mellitus (p=0.002), operative procedures in the mitral valve position (p=0.047), postoperative development of LCOS (p=0.006), and higher additive ES (>8) (p=0.015) were associated with significantly lower survival rates.

A proportional Cox hazard model was assembled for the late mortality multivariate analysis, including all those variables that approached significance in the univariate evaluation. In addition the impact of renal failure was evaluated, which almost achieved statistical significance in the univariate analysis (p=0.057) and was therefore considered as potentially clinically relevant.

Of the variables tested, only diabetes mellitus (p=0.016) and the development of LCOS postoperatively (p=0.03) were independent statistically significant factors associated with lower long-term survival (Table 5). Diabetic and LCOS patients showed a 3.6- and 4.2-fold, respectively, higher long-term mortality risk compared to the normal population. Other variables evaluated, such as advanced age (>60 years) and PAD, presented a 2.5- and 2-fold higher risk, respectively, for long-term mortality, but neither factor approached statistical significance in the model.

Table 3. Univariate analysis evaluating the impact of various variables on early mortality and differences between survivors and non survivors.

Variable	Early mortality % (n)	χ^2	p
Patient related			
Sex (male / female)	5.9 (4) / 14.8 (4)	1.93	0.164
Age at OR (≤60y / >60y)	6.4 (3) / 10.6 (5)	0.55	0.459
Infection related			
Valve endocarditis (native / prosthetic)	8.2 (7) / 11.1 (1)	0.08	0.768
Paravalvular abscess (yes / no)	11.1 (3) / 7.5 (5)	0.33	0.566
Staphylococcal infection (yes / no)	8.8 (3) / 8.3 (5)	0.01	0.934
Systemic embolization (yes / no)	14.3 (3) / 6.9 (5)	1.16	0.281
Preoperative clinical status related			
Mechanical ventilation (yes / no)	9.1 (1) / 13 (7)	0.13	0.721
NYHA class (I / II / III / IV)	7.7 (1) / 7.7 (2) / 5.4 (2) / 16.7 (3)	2.02	0.566
LVEF (>50%, 30-50%, <30%)	9.3 (4) / 9.4 (3) / 5.3 (1)	0.32	0.851
Renal Failure (yes / no)	13.8 (4) / 6.1 (4)	1.5	0.220
Heart rhythm (SR / AF / other)	0 (0) / 7 (9.8) / 1 (8.3)	1.19	0.755
Pacemaker, ICD (yes / no)	0 (0) / 9 (8)	0.49	0.483
Hypercholesterolemia (yes / no)	13.3 (2) / 7.6 (6)	0.53	0.465
Art. hypertension (yes / no)	9.1 (3) / 8.3 (5)	0.02	0.58
Pulm. hypertension (yes / no)	0 (0) / 9.9 (8)	1.4	0.236
Diabetes mellitus (yes / no)	18.2 (4) / 5.6 (4)	3.45	0.063
Nicotine abuse (yes / no)	3 (1) / 11.5 (7)	1.96	0.161
PAD (yes / no)	14.3 (1) / 8.1 (7)	0.32	0.569
EuroSCORE (≤8 / 8<x≤12 / 12<)	0 (0) / 10.8 (4) / 15.4 (4)	4.7	0.094
Operation related			
Emergency (yes / no)	16.7 (4) / 5.7 (4)	2.75	0.097
Device (mechanical / biological / other)	8.1 (6) / 8.3 (1) / 12.5 (1)	0.18	0.914
Type of OR (AVR, MVR, DVR, TVR, tVR)	9.2 (5) / 7.1 (2) / 0 (0) / 100 (1) / 0 (0)	11.9	0.036
LCOS postop. (yes / no)	28.6 (2) / 6.9 (6)	3.9	0.048
ICU stay (<4d / ≥4d)	6.5 (3) / 8.3 (4)	0.13	0.716

Variable	mean	p
Age at OR (y) (survivors / non survivors)	57.86 / 65	0.154
BMI (survivors / non survivors)	24.75 / 24.86	0.953
Crea preop. (mg/dL) (survivors / non survivors)	1.27 / 1.86	0.025
OR time (min.) (survivors / non survivors)	172.26 / 265.62	0.001
EuroSCORE (ad.) (survivors / non survivors)	10.2 / 12.4	0.067
EuroSCORE (log.) (survivors / non survivors)	26.65 / 34.5	0.198

AVR – aortic valve replacement; MVR – mitral valve replacement; DVR – double valve replacement; TVR – tricuspid valve replacement; tVR – triple valve replacement; ICD – implantable cardioverter – defibrillator; Art. – arterial; Pulm. – pulmonary; PAD – peripheral arterial disease; n – number of non survivors; BMI – body mass index; Crea – creatinine. Other abbreviations as in Table 1.

Discussion

Although surgery is potentially lifesaving[6] and has become the treatment of choice in 25-50% of cases in the acute phase of complicated IE and in 20-40% of cases during convalescence,[7-9] the decision to operate is often complex and difficult. Surgery is technically demanding and is often associated with high mortality and morbidity rates, due to the fact that IE patients are often severely ill, with involvement of various organ systems and hemodynamic instability. In addition, the lack of high-quality clinical evidence supporting the recommendations arising from international guidelines[10,11] makes the identification of patients who are at high risk for surgical treatment even more challenging. This series represents an institutional non-randomized retrospective review, providing an early and long-term mortality analysis. It consists of patients who were referred for surgery after having been treated medically elsewhere. It has to be mentioned that, firstly, we had no input concerning the pre-surgical medical management and, secondly, being a referral surgical department no patient was refused for operation, even though their clinical status was unstable accompanied by high morbidity.

A comparison with other published data, as well

Time Interval (months)	N Patients entering	N Patients @ risk	N Patients died	Cumulative proportion survival
0-12	86	82	10	1.00
12-24	68	63.5	1	0.878
24-36	58	55	5	0.864
36-48	47	44.5	0	0.785
48-60	42	39	1	0.776
60-72	35	30.5	1	0.756
72-84	24	22.5	2	0.707
84-96	19	16.5	0	0.644
96-108	14	12	1	0.624
108-120	9	5	1	0.572
120-132	1	1	0	0.572
132-144	1	0.5	0	0.572

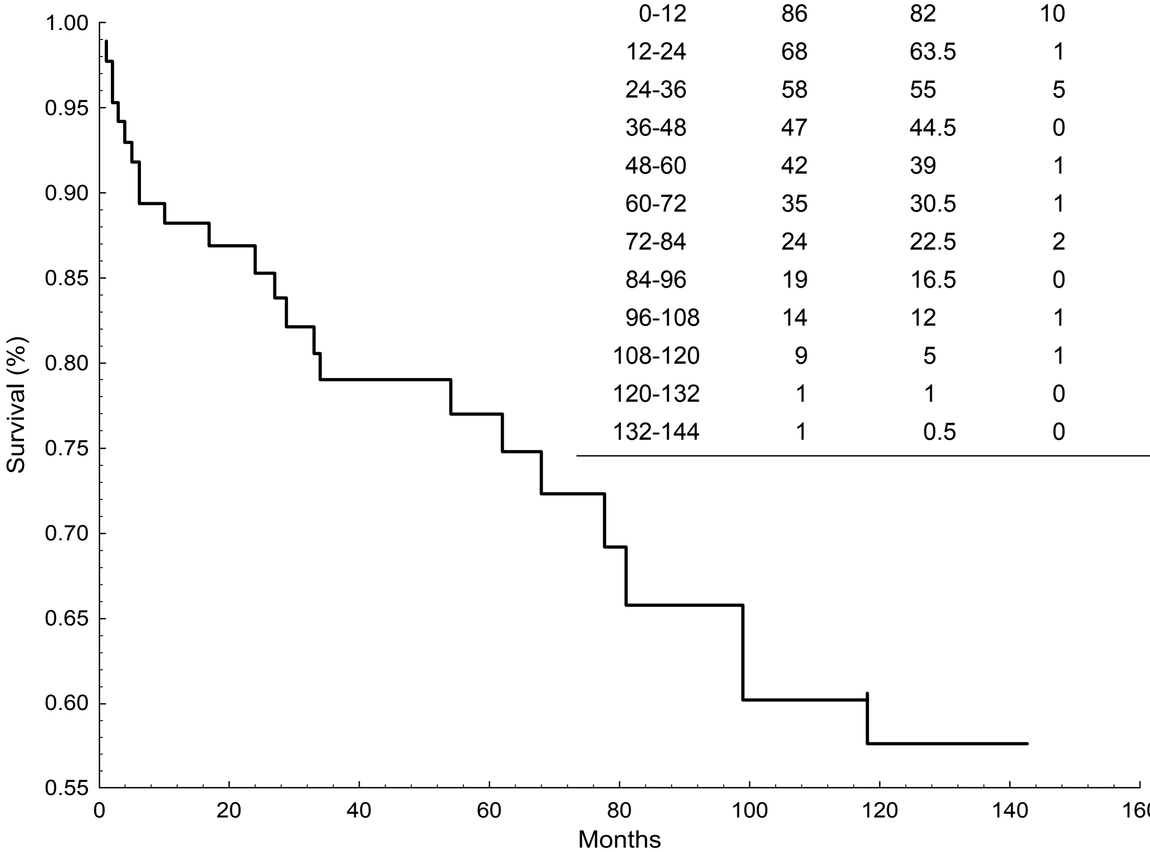

Figure 2. Overall actuarial cumulative survival at 12 years (Kaplan–Meier).

as a brief literature review, can contribute to the debate addressing the risk stratification in surgically treated IE patients.

The rate of culture-negative endocarditis in this series was approximately 25%, a percentage which is similar to other surgical studies.[2,12-14] Our patients were predominantly referred for surgery from peripheral hospitals, after receiving there a wide spectrum of empirical antibiotic therapy before the definite diagnosis was established. Since in all these cases the diagnosis of IE was established by echocardiographic, and subsequently confirmed by intraoperative findings, the negative results of blood cultures may be attributed to the antibiotic therapy administered.[15,16]

The most common offending microorganisms were *Staphylococci*, accounting for 35% of the cases—comparable to data in the literature.[3,8,9] Although some investigators[16-20] identified staphylococcal infection as an independent predictor of poor outcome, we did not observe any statistical relationship between the etiological agent and the prognosis in our series, probably because of the relative small sample size. However, 3 out of the 8 early non-survivors had positive blood cultures for *Staphylococcus*. In particular, in two of them the cultured agent was MRSA, which caused extensive tissue defects requiring more complex surgical procedures.

The overall operative mortality of 8.5% is comparable to results reported by other authors, ranging from 6-26% for native and 8-67% for prosthetic valve endocarditis.[3,7,8,12-14] Nevertheless, this observed operative mortality is significantly lower than that predicted by the logistic EuroSCORE (mean 26.4%); this finding confirms the widely reported observation that the model overestimates operative mortality, especially in high-risk patients.[4,21,22] Although there are scant reports evaluating the performance of the recently introduced new ES-version (ES II), further multicenter prospective studies including large patient cohorts are needed to draw safe conclusions about the expected higher predictive power of the new model.[4]

Table 4. Univariate analysis evaluating the impact of various variables on survival at 12 years.

Variable	Survival at 12 years (%)	Log-rank test p
Patient related		
Age at OR (≤60y / >60y)	80.4 / 39.9	0.0013
Gender (male / female)	65.2 / 47.0	0.214
Infection related		
Type of endocarditis (prosthetic / native)	63.6 / 59.6	0.807
Systemic embolization (yes / no)	51.6 / 61.5	0.714
Paravalvular abscess (yes / no)	62.4 / 58.5	0.634
Staphylococcal infection (yes / no)	55.8 / 62.9	0.405
Preoperative clinical status related		
Mechanical ventilation (yes / no)	70 / 75.6	0.429
NYHA class (I / II / III / IV)	83.3 / 63.6 / 51.7 / 47.5	0.687
LVEF (>50%, 30-50%, <30%)	51.1 / 55.4 / 75.1	0.304
Renal failure (yes / no)	44.5 / 69.7	0.057
Heart rhythm (SR / AF / other)	59 / 40.5 / 74.7	0.991
Pacer / ICD (yes / no)	75 / 57.1	0.545
Hypercholesterolaemia (yes / no)	17.8 / 65.3	0.207
Arterial hypertension (yes / no)	29.6 / 74.0	0.0012
Pulmonary hypertension (yes / no)	90 / 54.9	0.081
Diabetes mellitus (yes / no)	39.5 / 66.0	0.002
Nicotine abuse (yes / no)	59.1 / 58.1	0.865
PAD (yes / no)	16.7 / 66.1	0.0046
EuroSCORE (≤8 / 8<x≤12 / 12<)	66.2 / 57.2 / 53.1	0.015
Operation related		
Emergency (yes / no)	64 / 59.65	0.249
Type of OR (AVR/r / MVR/r)	60.1 / 49.5	0.047
Prosthetic device (mechanical / biological)	55.5 / 72.7	0.740
Low cardiac output syndrome (yes / no)	20 / 62.7	0.667
ICU stay (<4d / ≥4d)	60.2 / 58.4	0.487

AVR/r – aortic valve replacement/repair; MVR/r – mitral valve replacement/repair.
Other abbreviations as in previous tables.

The fact that the operative mortality was clearly higher than that of normal patients undergoing valve operations at our institution[23,24] underscores the higher risk of IE patients. The abovementioned wide ranges reported in operative mortality rates result from the variety of the conditions under which patients were operated, as well from the surgical procedures performed and the prosthetic devices used. Some series presented better operative outcomes when homografts were implanted in the aortic position.[25,26] Our data revealed no significant differences in the early or long-term operative outcomes with regard to the implanted prosthetic device (mechanical, biological or reconstruction) (Table 5). In the present series only one patient received a homograft, after being operated twice because of recurrent prosthetic valve endocarditis. The patient survived the reoperation and the early and long-term postoperative course was unremarkable. Homograft valves have theoretical advantages over prosthetic valves, such as higher resistance to recurrent infection, flexibility, and additional periannular tissue. On the other hand, their major drawbacks are limited availability and a higher degeneration rate, leading to reoperation. Even in the group of IE patients with paravalvular abscesses, a population considered to require more complex, challenging operations accompanied by high morbidity and mortality, the implanted device type was not significantly influential on the operative mortality and long-term survival, as our group has previously reported.[5] The presence of a paravalvular abscess was in our series not a predictor of adverse early or long-term outcome (Table 3 and 4). These findings correlate with the suggestion of David and co-authors,

Table 5. Multivariate analysis for early mortality and long-term survival (12 years).

Log-linear analysis (early mortality) Variable	χ^2		p
Sex	1.76		0.184
Age @ OR	0.55		0.457
Preop. NYHA class	1.78		0.617
Type of OR	0.11		0.741
Diabetes mellitus	2.96		0.085
PAD	0.28		0.598
Renal failure	0.57		0.451
Emergency	2.43		0.119
LCOS	6.50		0.01
EuroSCORE (additive)	4.07		0.13
Cox Regression survival analysis (at 12y) Variable	**HR**	**95% CI**	**p**
Age @ OR (≤60y. / >60y.)	2.5388	0.8140–7.9185	0.1084
Arterial hypertension	1.8499	0.6863–4.9861	0.2240
Diabetes mellitus	3.5826	1.2649–10.1469	0.0163
PAD	2.0191	0.5825–6.9988	0.2679
Renal failure	0.8212	0.2993–2.2530	0.7020
Type of OR (AVR/r, MVR/r, DVR/r)	0.7891	0.4270–1.4583	0.4498
LCOS	4.2161	1.1261–15.7858	0.0327
EuroSCORE (≤8 / 8<x≤12 / 12<)	1.1246	0.7834–5.4837	0.7547

Multivariate analysis for early mortality, applying log-linear analysis of a test model with df:24 at p:0.3 including the following variables: sex, age at operation, preoperative NYHA class, art of operation, diabetes mellitus, peripheral arterial disease (PAD), emergency setting of the operation.
Cox regression survival analysis (at 11.25 years) of a test model with df:8 at p:0.0007 and chi-square=27.769 including the following variables: age at operation, type of operation, diabetes mellitus, arterial hypertension, peripheral artery disease, renal failure, postoperative low cardiac output syndrome (LCOS), and risk stratification with the EuroSCORE.

that freedom from persistent or early recurrent endocarditis and operative outcomes depend more on the ability of the surgeon to recognize and remove all infected tissues than on the type of the prosthesis used.[27] Our surgical strategy followed this principle, and the choice of the prosthesis type was met according to the international guidelines by having the "cutoff" selection-point for a mechanical or biological prosthesis in general at the age of 65 years. The relatively low mean age of our study population, 58.3 years, as well as the urgent and emergent operation setting in approximately half of the sample (45 cases), justified the predominant (75%) use of mechanical bileaflet prostheses.

Multivariate analysis evaluating various potential clinically relevant variables demonstrated that only the postoperative development of LCOS was an independent predictor for operative mortality. It is noteworthy that variables such as preoperative cardiac and/or renal failure, or emergent setting of the operation, which have been identified in several studies[3,9,12,13,17] as independent hospital mortality predictors, were in our study not associated with significant adverse outcomes. An explanation for this observation may be the relative small sample size arising from a single-center experience.

The actuarial survival of 57.2% at 12 years concurs with data reported in the literature (Table 6)[3,7,15,17,28] and is quite similar to that of "normal" patient populations after cardiac valve operations.[23,24] The highest mortality rate, namely 10 out of 22 "long-term non-survivors" was within the first year after operation (Figure 2), when the risk of recurrent valve infection is highest. After this early "high-risk" phase, the survival reaches a level of constant hazard, where the mortality risk is similar to that of normal cardiac surgical patients. In fact, the univariate analysis predominantly revealed factors unrelated to the infection as predictors for long-term survival, such as age at operation, arterial hypertension, diabetes mellitus, postoperative LCOS, and ES≤8. The substantial role of diabetes and postoperative LCOS in predicting early as well long-term survival has been described by Aksoy and colleagues,[29] whereas the impact of arterial hypertension on cardiac surgery outcomes, especially in coronary artery bypass grafting operations

Table 6. Literature overview including main series of the last decade.

Author Year	Study design	Cases (n)	Mean age (y)	Patient characteristics	Mean follow-up, (y)	Early mortality / late survival (%)	Predictors of mortality
Manne 2011[17]	Retrospective single-center	428	56.1 ± 14.7	NVE 58%, PVE 42%; surgery 100%	max.5	10 / 29-35	Outcomes within the 30 days were better for NVE than for PVE. Long-term outcomes were similar. Finally, *S. aureus* was associated with significantly higher mortality compared with other pathogens.
Funakoshi 2011[8]	Retrospective single-center	212	55 ± 18 53 ± 17	NVE 100%; surgery 81%	5.5	5-13 / 82-94	Early surgery in the active phase was associated with better long-term outcomes in patients with left-sided NVE.
Ota 2011[31]	Retrospective single-center	152	47 ± 17 51 ± 16	NVE 100%; surgery 100%	max. 5	7.9 / 56.4	Multivariate analysis of the multivalve group identified postoperative RF as a predictor of late mortality with no predictors identified for early mortality, reoperation, and recurrence. Multivalve endocarditis was not an independent predictor of early and late mortality.
Fayad 2011[14]	Retrospective single-center	141	56.3 ± 14.9	NVE 87%, PVE 13%; surgery 100%	6 mo	16 (6mo)	In univariate analysis, factors linked to operative mortality were age, PVE and inadequate antimicrobial therapy. In multivariate analysis, only PVE was an independent adverse predictor.
Gaca 2011[7]	Analysis of database (STS)	19543	55.11	Surgery 100%	6 mo	8.2 (6mo)	Significant preoperative risk factors for mortality: emergency, salvage status, or cardiogenic shock, preoperative hemodialysis, RF, or creatinine level less than 2.0, preoperative inotropic or balloon pump support, active (vs. treated) endocarditis, multiple valve involvement, insulin dependent diabetes.
Musci 2010[32]	Retrospective single-center	349	59.2 ± 14.2	PVE 100%; surgery 100%	max. 19.4	28.4 / 71.4 (10y)	Predictors of early mortality were mechanical support, emergency operation, preoperative high doses of catecholamines, mitral valve replacement and age at operation.
Thuny 2009[12]	Retrospective single-center	291	53 ± 16 58 ± 15	NVE 82%, PVE 18%; surgery 100%	6 mo	13 (6mo)	Very early surgery (<7 days) associated with improved survival (especially in highest risk patients) but greater likelihood of relapse or post-operative valve dysfunction.
Tleyjeh 2008[28]	Retrospective single-center	546	62.3 ± 16.3	NVE 100%; surgery 24%	0.5	27.1 / 73-76	No survival benefits associated with surgery despite correction for timing and early operative deaths. Prospective study recommended.
Aksoy 2007[29]	Prospective single-center	426	58.3 ± 26.2	NVE 69%, PVE 19%, “other”12%; surgery 29%	5	17 / 28-48	Factors associated with surgical treatment: age, interhospital transfer, staphylococcal infection, CHF, intracardiac abscess, hemodialysis with IV catheter. Surgery associated with long-term benefit. Factors associated with mortality: DM, paravalvular infection, indwelling IV catheter.

Wang 2007[33]	Prospective multicenter	556	65	PVE alone; surgery 49%	-	23 / -	Predictors of in-hospital mortality: age, healthcare-associated infection, *S. aureus* infection, CHF, stroke, intracardiac abscess, persistent bacteremia.
Remadi 2007[34]	Prospective multicenter	116	55.8 ± 16.8	NVE 83%, PVE 17%; surgery 47%, *S. aureus* IE alone	3	26 / 57	Predictors of mortality: Comorbidity, CHF, severe sepsis, PVE, major neurological events. Early surgery associated with improved outcome
Hill 2007[19]	Prospective single-center	193	63 ± 1.1	NVE 66%, PVE 34%; surgery 63%	0.5	16 / 78	Predictors of mortality: age, *S. aureus*, CI to surgery (present in 50% of deaths).
Revilla 2007[15]	Prospective multicenter	508	56 ± 14	NVE 66%, PVE 34%; surgery 100%	-	36 / -	Poor clinical outcome after urgent surgery. Persistent infection and RF associated with higher mortality.
San Román 2007[18]	Prospective multicenter	317	57 ± 16	NVE 64%, PVE 36%; surgery 28%	-	21 / -	Predictors of high risk: interhospital transfer, AV block, acute onset, CHF, periannular complications, *S. aureus* infection
Delahaye 2007[13]	Prospective multicenter	559	59 ± 16.8	NVE 85%, PVE 15%; surgery 47%	-	17 / -	Predictors of mortality: CHF, immunosuppression, insulin dependent DM, left-sided IE, septic shock, coma, cerebral hemorrhage, high C- reactive protein.
Habib 2005[20]	Retrospective multicenter	104	60 ± 16	PVE; surgery 49%	2.7	21 / 62	Predictors of in-hospital mortality: CHF, *S aureus*. Predictors of long-term mortality: early PVE, comorbidity, CHF, staphylococcal infection, new prosthetic dehiscence. Mortality reduced by surgery in high-risk subgroups with staphylococcal infection and complicated PVE
Vikram 2003[35]	Retrospective multicenter	513	53 ± 16.3 56.6 ± 18.6	NVE; surgery 45%	0.5	- / 74	Valve surgery associated with reduced mortality after adjustment for baseline variables and propensity scores. Benefits of surgery greatest in patients with CHF.
Hasbun 2003[36]	Retrospective multicenter	513	55.5 ± 17.6	NVE; surgery 45%	0.5	- / 74	Mortality associated with comorbidity, abnormal mental status, CHF, non-streptococcal IE, or medical therapy. Prognostic classification proposed.
Wallace 2002[37]	Retrospective single center	208	52 ± 1.2	NVE 68%, PVE 32%; surgery 52%	0.5	18 / 73	Duration of illness, age, gender, site of infection, organism, and LV function did not predict outcome. Abnormal white cell count, raised creatinine ≥2, Duke criteria, or visible vegetation conferred poor prognosis.

NVE – native valve endocarditis; PVE – prosthetic valve endocarditis; CHF – congestive heart failure; IV – intravenous; LV – left ventricular; AV – atrioventricular; DM – diabetes mellitus; IE – infective endocarditis; max – maximum; CI – contraindication.

has also been recently reported.[30] In our study, neither worse preoperative functional NYHA status, nor a lower preoperative left ventricular ejection fraction were predictive of adverse outcomes. This indicates that the surgical elimination of the severe acute hemodynamic overload in IE patients may preclude the development of irreversible left ventricular dysfunction, resulting in higher survival rates. Nevertheless, postoperative LCOS, due to septic shock or surgical trauma, represents the stage of irreversible cardiac failure associated with decreased early and long-term outcomes.[3,7,13,15,29,31]

The role of the ES scoring system as a predictor for mid- or long-term outcome in cardiac surgical patients has been investigated in several studies, despite its primary goal being to estimate only the operative mortality. Most of these series evaluated the model's accuracy in patients after either coronary artery bypass grafting, or valve surgery, showing that ES is a potential predictor of midterm or late postoperative survival.[4]

Analyzing the subgroup of PVE cases, their proportion of 9.7% in the entire collective seems to be low, but two aspects have to be taken into consideration. First this percentage correlates with reported data in the literature,[3,32-34] and secondly the total PVE number after also including the population of PVE cases treated either conservatively or even surgically elsewhere, in relation to the total number of valve procedures performed at our department in the same time period, accounts for our institutional estimated PVE-incidence of 0.15-0.75% /patient-year,[23,24] which also concurs with that reported by other groups.[3,32,33]

Table 6 summarizes the main findings of recently published series evaluating the impact of various factors on early and late mortality in surgically treated IE patients. They consist mainly of retrospective institutional reports, including patients with heterogeneous expressions of IE, evaluated through different statistical methods.[35-37] In addition, the study populations usually included cases that were referred to surgery after the failure of conservative treatment, quite often in an unstable clinical condition. Although there is no clinical evidence supporting the superiority of surgical treatment in specific subpopulations of IE patients (i.e. persistent sepsis, neurological-embolic complications), surgery is usually recommended and performed.

The fact that the statistical analysis with sophisticated propensity scoring models in recent publications yielded conflicting results about the efficacy of surgery[28,29,38] underlines the necessity for an adequate high-quality prospective assessment.

Limitations of the study

This retrospective non-randomized series refers to a single-center regional experience; thus, the results may not be generalizable to the entire population, since there are significant differences between institutions and countries. The study population included patients with IE affecting all the valves, as well as cases with NVE and PVE. Although the proportion of PVE cases is rather low at 9.7%, nonetheless the sample size was inhomogeneous. Additionally, its relative small size of 94 cases may be another source of bias in the statistical analysis of the results.

Conclusions

Despite the aforementioned limitations, early and long-term mortality analysis in surgically treated patients with IE revealed some trends, which compared to other series' results allow us to draw the following conclusions.

Considering the complexity of the disease, radical surgical treatment delivers high but acceptable operative and long-term mortality. The choice of the prosthetic device seems not to be influential as regards either the early or the long-term outcomes.

As long as no evidence-based data are available, decision making regarding the appropriate treatment of IE patients remains often difficult, and overall highly dependent on the expertise of the surgical team, requiring a close cooperation with cardiologists and microbiologists. The lack of robust data confirming the efficacy of surgery in those patients underlines the necessity for an adequate high-quality prospective assessment supported by sophisticated propensity scoring models.

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