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Gender-Based Long-Term Surgical Outcome in Patients with Active Infective Aortic Valve Endocarditis

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Background: The aim of this observational, single-center study was to evaluate the impact of gender on surgical outcome in patients with active infective endocarditis (AIE) of the aortic valve.

Material/Methods: Between October 1994 and January 2011, 755 patients (558 men and 297 women) underwent surgery for AIE at the Leipzig Heart Center, Germany, according to the modified Duke criteria. Data were collected before surgery and as the study was ongoing. Gender influence on survival was evaluated (Kaplan-Meier curves). Cox proportional models were used to evaluate gender differences in relation to early mortality (within 30 days) and late mortality (up to 10 years).

Results: The early mortality rate was 15.0% among men and 23.0% among women, which was statistically significant different (p=0.01). In male patients, variables associated with overall mortality were age (HR 1.63, 95% CI 1.43–1.86; p<0.001), insulin-dependent diabetes mellitus (HR 2.02, 95% CI 1.48–2.75; p<0.001), preoperative low ejection fraction (OR 0.99, 95% CI 0.98–0.99; p=0.002), previous cardiac surgery (OR 1.62, 95% CI 1.22–2.13; p=0.001), preoperative ventilation (OR 1.77, 95% CI 1.14–2.75; p=0.012), preoperative dialysis (OR 1.89, 95% CI 1.20–2.98; p=0.006), NYHA Class IV (OR 1.56, 95% CI 1.12–2.15; p=0.008), and involvement of multiple valves (OR 1.65, 95% CI 1.24–2.19; p=0.001) had a statistically significant influence on the late mortality. Focus identification (OR 1.75, 95% CI 1.08–2.77; p=0.023), involvement of multiple valves (OR 1.52, 95% CI 1.02–2.26; p=0.040), preoperative dialysis (OR 3.65, 95% CI 1.96–6.77; p<0.001), and age (OR 1.53, 95% CI 1.28–1.82; p<0.004) were predictive risk factors for late mortality in women with AIE (OR 3.6, 95% CI 1.5–8.4; p<0.004).

Conclusions: This study demonstrated distinct gender-based differences in risk of mortality in patients with AIE (who were undergoing surgical treatment) with different early and long-term outcomes.

MeSH Keywords: **Aortic Valve Insufficiency • Endocarditis, Bacterial • Gender Identity**

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Background

Data from epidemiological studies have shown that gender has an important impact on the incidence of active infective endocarditis (AIE) of the aortic valve, with a greater proportion of men being affected. To date, the literature has shown this incidence as male-to-female ratios, which range from 2:1 to 9:1 [1,2]. A healthy native valve is normally protected against bacteria by an intact endothelium; however, in patients with endocarditis, this endothelium is no longer a confluent monolayer and bacteria can attach to the surface to form a biofilm [3]. This bacterial biofilm is a complex system, with inherent resistance to antimicrobial agents owing to encapsulation. This encapsulation includes bacteria arranged in organized structures that produce extracellular polymeric substances, and proteolytic enzymes that destroy the surrounding tissue and increase the infection [4]. Data from previous animal studies have suggested that oestrogen is a protector against endothelial cell damage [5], which could explain the difference in incidence of endocarditis between men and women. Song et al. demonstrated the antioxidant effect of oestrogen on bovine aortic endothelial cells [6]. Other studies have also demonstrated that estrogen deficiency and microphageal migration were more pronounced because of a reduction in junction proteins between endothelial cells [7].

In the literature, if AIE is present and surgical treatment is required, female gender seems to no longer be an independent protective factor, but becomes an independent predictor for significantly increased risk of early mortality [8–10]. Women also have a higher co-morbidity (e.g., from renal failure and diabetes), which could also influence the prognosis after AIE surgical treatment [11,12]. However, long-term follow-up in other studies did not indicate a greater risk for morbidity and mortality in women [13–15]. Many aspects of the influence of gender on AIE are still not completely understood, especially as partially contradicting data have been published. The aim of this observational, single-center study was to evaluate the impact of gender on early and late surgical outcome in patients with AIE and define independent risk factors for male and female patients.

Material and Methods

Definitions and patients

This single-center study involved adult patients (aged ≥18 years) who had undergone surgery for AIE at the Leipzig Heart Center, Germany. Patients with AIE were included according to the modified Duke criteria [16]. Data were collected prior to surgery and as the study was ongoing. Definitions for active, prosthetic, and culture-negative endocarditis were followed as published by Renzulli et al. [17]. Details have been previously described [8].

Patient variables were analysed based on previous studies [8] and their correlation with operative mortality [8].

Early mortality was defined as 30-day mortality. Postoperative complications were defined as complications occurring within the hospital stay. Late mortality included all deaths that occurred during follow-up after 30 days, up to an average duration of 3.5±3.8 years (range 0.1–16.9 years).

Surgical techniques

Surgical techniques included complete median sternotomy and partial upper sternotomy. If concomitant bypass surgery was performed in patients younger than 70 years of age, complete arterial revascularisation was performed. However, for the left descending artery, the internal thoracic artery was always used. In other cases, a saphenous vein was also used. After aortic cross-clamping, patients received either cold blood cardioplegia or crystalloid solution.

In all cases, excessive excision of all infected or necrotic tissue, while leaving a generous margin of healthy tissue, was performed. Aortic valve replacement (including tissue reconstruction, if needed) was then induced with or without concomitant procedures. All patients received intravenous antibiotic therapy for at least 6 weeks postoperatively according to the European Society of Cardiology guidelines for the treatment of endocarditis [18].

Follow-up

Follow-up was undertaken annually over 12 years and performed by using the entered patient data into the institutional database for quality control purposes. Written informed consent was obtained from all patients, but since all data entered were de-identified and this was a retrospective study, individual patient informed consent was waived by our institutional ethics committee. Information for follow-up after discharge was gained from a direct telephone interview or the referring physician. If complications were communicated from a direct telephone interview, these data were confirmed by contacting the referring physician, obtaining copies of patient medical records, or analysing post-mortem examinations (if available). These data could also be confirmed at the Ambulatory Department via an echocardiographic follow-up.

Statistical analysis

Data were entered into Microsoft® Excel worksheets (Microsoft Corp., Redmond, WA) and transferred to SPSS (version 17.0;

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SPSS, Inc., Chicago, IL) for statistical analysis. The follow-up time for survival was measured from the date of the operation to either the date of death or the date the patient was last contacted while still alive.

Quantitative data were characterized by mean and standard error of the mean, whereas qualitative data were characterized by relative frequencies and percentages. Male and female patients were compared using Student's t-test for continuous variables, and chi-square and Fischer's exact test for categorical variables. Long-term survival was analysed by the Kaplan-Meier method, and different groups were compared by log-rank tests. Research on characteristics associated with 30-day and total mortality was performed by logistic and Cox regression analyses, respectively. Common potential risk factors and covariates were tested in univariate analyses separately for women and men. Characteristics significant at 10% level (separated by sex) were assessed by forward stepwise Cox regression analysis. Final models, which were established by variables included in the stepwise procedure, were fitted to estimate hazard ratios (HRs) and 95% confidence interval (CI) limits. These results were depicted by forest plots, applying the R package Hmisc [19]. All statistical tests were performed as 2-sided tests at a 5% significance level.

Results

Patients

A total of 1394 patients (978 men, 416 women) with AIE were included between October 1994 and January 2011. A subgroup of 755 patients (558 male [73.9%] and 197 female [26.1%]) with AIE of the aortic valve were identified and included in the study analysis.

Patient characteristics are presented in Table 1. There was a highly significant difference between men and women. Furthermore, comorbidities were significantly different in both groups, with a higher incidence of ischaemic cardiomyopathy in male patients versus female patients. However, compared with male patients, female patients had a significantly higher occurrence of diabetes, and a significantly higher occurrence of preoperative stroke and higher age.

Operative results

There were 743 patients (98.4%) who had a complete median sternotomy, including 551 male (98.7%) and 192 female patients (97.5%). Eleven patients had a partial upper sternotomy (7 male [1.3%] and 4 female patients [2.0%]). One female patient (0.5%) was converted to full sternotomy. There were 215 patients (28.5%) who received cold blood cardioplegia (155 male, 60 female) and 538 patients who received crystalloid solution (401 male, 137 female). Two patients underwent surgery on a fibrillating heart.

Surgical data are provided in Table 2. The choice of implanted prosthesis was similar in both groups; however, involvement of the mitral valve (MV) was more common in female patients than in male patients. Other concomitant procedures, such as tricuspid valve surgery, were also significantly more common in women compared with men. Nevertheless, there was no significant difference among men and women in the cross-clamp time (89.5±48.1 min *vs.* 87.8±46.6 min, respectively [p=0.644]) or extracorporeal circulation time (135.1±81.6 min *vs.* 133.1±72.7 min, respectively [p=0.743]).

Postoperative morbidity

Postoperative complications are presented in Table 3. In both groups, neurological complications by preoperative embolism because of AIE were similar, and were observed as transient ischaemic attack or somnolency. Postoperative renal dialysis was significantly more common in women than in men (50/197 [25.4%] *vs.* 103/558 [18.5%], respectively; p=0.038). Preoperative chronic renal failure was 25.4% in the overall group, showing no differences between genders. Similar data were found on the preoperative chronic renal failure with dialysis: 14/198 (7.1%) in female patients and 31/558 (5.6%) in male patients.

Early mortality

The overall 30-day mortality rate was 17.2%, with 15.0% of men *vs.* 23.5% of women affected (p=0.01). All causes of death, including early mortality, are shown in Table 4. Univariate analysis showed risk factors associated with 30-day mortality for both genders, which included elderly age, high LVEF (prior operation, previous cardiac surgery, previous dialysis, ventilation prior to OP, low cardiac output, and high New York Heart Association (NYHA) class.

In male patients, 30-day mortality was significantly associated with age (HR 1.42, 95% CI 1.14–1.78; p=0.002), insulin-dependent diabetes (HR 2.25, 95% CI 1.39–3.65; p=0.001), prior cardiac surgery (OR 2.29, 95% CI 1.44–3.65; p<0.001), preoperative preserved EF (HR 0.98, 95% CI 0.97–1.00; p=0.024), NYHA Class IV (HR 2.28, 95% CI 1.40–3.71; p=0.001), and kissing MV endocarditis (HR 2.37, 95% CI 1.44–3.91; p=0.001) at multiple regression analysis. In female patients, the multiple regression analyses detected an association between 30-day mortality and age (HR 1.52, 95% CI 1.23–1.87; p<0.001), preoperative dialysis (HR 3.57, 95% CI 1.70–7.51; p=0.001), and endocarditis focus identification (HR 3.03, 95% CI 1.18–7.78; p=0.022).

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Table 1. Baseline patient characteristics specified by gender.

	Overall (n=755)	Women (n=197)	Men (n=558)	P Value
Age (years)	62.5±13.9	64.9±14.1	61.6±13.7	0.005
Native valve endocarditis	545 (72.2%)	144 (73.1%)	401 (71.9%)	0.740
Prosthetic valve endocarditis	210 (27.8%)	53 (26.9%)	157 (28.1%)	0.740
Mitral valve involvement	178 (23.6%)	54 (27.4%)	124 (22.2%)	0.140
Co-morbidity				
Heart failure (III+IV)	434 (57.5%)	116 (58.9%)	318 (57.0%)	0.644
NYHA III	342 (39.0%)	86 (41.3%)	256 (38.3%)	
NYHA IV	162 (18.5%)	34 (16.3%)	128 (19.1%)	
Peripheral vessel disease	81 (10.7%)	17 (8.6%)	64 (11.5%)	0.268
DM	231 (30.6%)	72 (36.5%)	159 (28.5%)	**0.035**
Stroke	200 (26.5%)	64 (32.5%)	136 (24.4%)	**0.026**
COPD	83 (11.0%)	15 (7.6%)	68 (12.2%)	0.078
Preoperative ventilation	64 (8.5%)	19 (9.6%)	45 (8.1%)	0.494
Chron. renal failure	147 (19.5%)	113 (28.8%)	113 (20.3%)	0.727
Dialysis	45 (6.0%)	14 (7.1%)	31 (5.6%)	
Neoplastic disease	(19.2%)	(19.2%)	(19.1%)	
Echocardiographic findings (LV EF)				
>50%	473 (62.6%)	125 (63.5%)	348 (62.4%)	0.071
30–50%	224 (29.7%)	65 (32.5%)	160 (28.7%)	
≤30%	58 (7.7%)	9 (4.3%)	50 (9.0%)	
Presence of aortic vegetation				
Size (>10mm)	430 (57.0%)	112 (56.9%)	318 (57.0%)	0.973
Aortic abscess	87 (11.5%)	23 (11.7%)	64 (11.5%)	0.938
Presence of aortic valve regurgitation	641 (84.9%)	159 (80.7%)	482 (86.4%)	0.056
Number of valves involved				
1	562 (74.4%)	137 (69.5%)	425 (76.2%)	0.067
2 or more	193 (25.6%)	60 (30.5%)	133 (23.8%)	
Complications				
Septic Emboli	334 (44.2%)	88 (44.7%)	246 (44.1%)	0.887
Localisation				
Brain	172 (22.8%)	43 (21.8%)	129 (23.1%)	0.710
Lung	17 (2.3%)	3 (1.5%)	14 (2.5%)	0.423
Spleen	209 (27.7%)	45 (22.8%)	164 (29.4%)	0.077
Kidney	80 (10.6%)	19 (9.6%)	61 (10.9%)	0.614
Limb	43 (5.7%)	11 (5.6%)	32 (5.7%)	0.937
Other	30 (4.0%)	9 (4.6%)	21 (3.8%)	0.619
Mech. Support preoperative IABP	22 (2.9%)	7 (3.6%)	15 (2.7%)	0.535

Data are expressed as mean SD or as number (percentage)

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Table 2. Operative data.

	Overall (n=755)	Women (n=197)	Men (n=558)	P Value
Valve type implanted				
Mechanical valve	236 (31.3%)	57 (28.9%)	179 (32.1%)	0.413
Stented xenogenic valve	387 (51.3%)	103 (52.3%)	284 (50.9%)	0.738
Stentless xenogenic valve	100 (13.2%)	26 (13.2%)	74 (13.3%)	0.982
Allograft	20 (2.6%)	5 (2.5%)	15 (2.7%)	0.910
Mitral valve surgery due to AIE	251 (33.2%)	75 (38.1%)	176 (31.5%)	0.094
Mitral valve replacement	116 (15.4%)	39 (19.8%)	77 (13.8%)	**0.045**
Mitral valve repair	49 (6.5%)	14 (7.1%)	35 (6.3%)	0.683
Concomitant procedures				
TK	55 (7.3%)	24 (12.2%)	31 (5.6%)	**0.002**
Aorta ascendens	233 (30.9%)	53 (26.9%)	180 (32.3%)	0.162
Ablation	22 (2.9%)	6 (3.0%)	16 (2.9%)	0.898
CABG	131 (17.4%)	32 (16.2%)	119 (17.8%)	0.633

Table 3. Postoperative complications.

	Overall (n=755)	Women (n=197)	Men (n=558)	P Value
Neurological complications (TIA, CVA)	194 (25.7%)	50 (25.4%)	144 (25.8%)	0.906
Dialysis (postoperative)	153 (20.3%)	50 (25.4%)	103 (18.5%)	**0.038**
Respiratory insufficiency	93 (12.3%)	21 (10.7%)	72 (12.9%)	0.410
Tracheotomy	78 (10.3%)	22 (11.2%)	56 (10.0%)	0.654
PM implantation	99 (13.1%)	24 (12.2%)	75 (13.4%)	0.766
acute abdominal complications	42 (5.6%)	16 (8.1%)	26 (4.7%)	0.068
Rethoracotomy	97 (12.8%)	22 (11.2%)	75 (13.4%)	0.412

Table 4. Cause of death.

	Overall (n=755)	Women (n=197)	Men (n=558)	P Value
Causes of death				
Cerebral	26 (3.4%)	9 (4.6%)	17 (3.0%)	0.314
Gastro-Intestinal	30 (4.0%)	7 (3.6%)	23 (4.1%)	0.725
Bleeding	9 (1.2%)	4 (2.0%)	5 (0.9%)	0.207
Cardiac	86 (11.4%)	22 (11.2%)	64 (11.5%)	0.909
MOF/Sepsis	91 (12.1%)	34 (17.3%)	57 (10.2%)	**0.009**
Pulmonary	30 (4.0%)	9 (4.6%)	21 (3.8%)	0.619
Renal	7 (0.9%)	4 (2.0%)	3 (0.5%)	0.060
Others	7 (0.9%)	3 (1.5%)	4 (0.7%)	0.310
Tumor	29 (3.8%)	11 (5.6%)	18 (3.2%)	0.139
Unknown	32 (4.2%)	5 (2.5%)	27 (4.8%)	0.168

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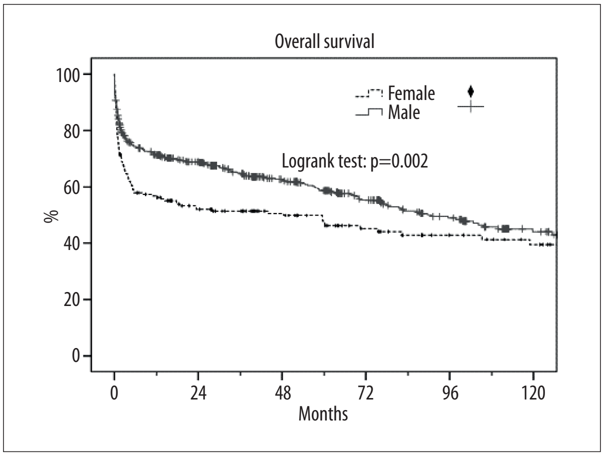

Figure 1. Kaplan-Meier survival curve (all-cause mortality).

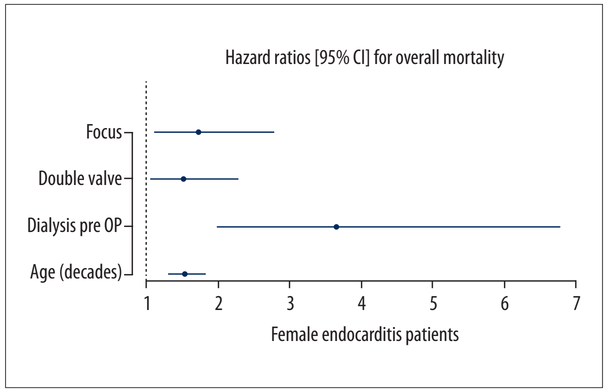

Figure 2. Independent predictors of late mortality on multivariate proportional-hazards regression analyses in women.

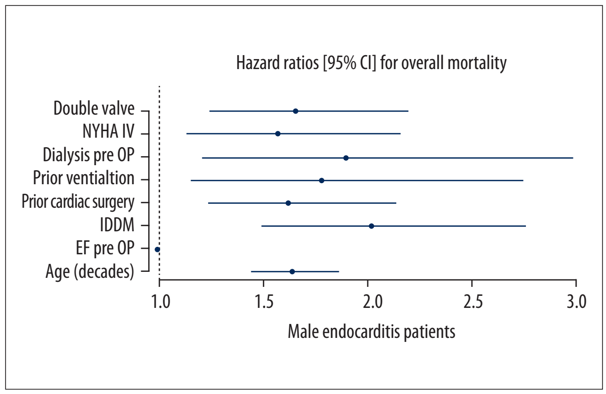

Figure 3. Independent predictors of late mortality on multivariate proportional-hazards regression analyses in men.

Long-term results

The Kaplan-Meier curve revealed that, compared with women, men who underwent surgery for AIE of the aortic valve had a statistically significant longer overall survival (p=0.002; Figure 1). However, there was no significant difference after 10 years.

For men and women, factors associated with overall survival included: increased age (men: HR 1.63, 95% CI 1.43–1.86; p<0.001 *vs.* women: HR 1.53, 95% CI 1.28–1.82, p<0.001); preoperative dialysis (men: HR 1.89, 95% CI 1.20–2.98; p=0.006 *vs.* women: HR 3.65, 95% CI 1.96–6.77, p<0.001); and double-valve involvement (men: HR 1.65, 95% CI 1.24–2.19 p=0.001 *vs.* women: HR 1.52, 95% CI 1.02–2.26, p=0.040).

The following independent risk factors were significant for male patients only: preoperative preserved EF (HR 0.99, 95% CI 0.98–0.99, p=0.002), insulin-dependent diabetes (HR 2.02, 95% CI 1.48–2.75, p<0.001), previous cardiac surgery (HR 1.62, 95% CI 1.22–2.13, p=0.001), preoperative ventilation (HR 1.77, 95% CI 1.14–2.75, p=0.012), and NYHA Class IV (HR 1.56, 95% CI 1.12–2.15, p=0.008). In contrast, endocarditis focus identification (HR 1.73, 95% CI 1.08–2.77, p=0.023) was an additional significant risk factor for female patients only. Multivariate analyses of variables influencing late mortality of women are shown in Figure 2. Variables independently associated with late mortality of men are shown in Figure 3. For both subgroups, age and dialysis were independent risk factors for late death.

Discussion

Gender itself seems to have a major role in the incidence of valvular heart disease. This study demonstrated distinct gender-based differences in patients with AIE who were undergoing surgical treatment. Women seem to have higher mortality rates because of factors such as underdiagnosed pulmonary disease, higher rates of postoperative pulmonary infection, and consecutively longer ventilation and ICU stays [20,21]. This is not the explanation we found in this study for the increased early and late mortality in female patients. The strength of this study was the accuracy of data collection and disease diagnosis owing to the direct visual intraoperative valve analysis performed by the surgeon with respect to specific valve characteristics.

Patient characteristics

In this cohort, women with AIE who underwent surgery were on average 4 years older than the men. Thus, women undergoing surgery due to AIE would have no longer been protected by estrogen. The cardiovascular risk factor of diabetes was much more prominent among women with AIE undergoing surgery (36.5%) than men (28.5%). The severity of diabetes and risk of cardiovascular events seem to have a different role in women than in men [22].

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Similar to what has been previously described in the literature [23], the incidence of stroke in this cohort was higher among women. This could be because steroid hormones only protect against cerebrovascular events premenopausal compared with men at the same age [24,25], but after menopause the incidence of stroke rapidly increases [26]. Additionally, the female patient population in this cohort had an increased number of patient with diabetes, which is also associated with an increased risk for stroke [27].

Operative results

MV involvement in AIE seems to be more prominent among women and may lead to a higher incidence of MV replacement in this gender. This higher rate could be attributable to more severe calcification based on gender-specific differences in calcium metabolism and bone resorption, especially among postmenopausal women. However, further trials are required to establish this factor [10–12].

Sambola and colleagues examined 271 patients with endocarditis [15]. These results showed increasing age and a higher incidence of MV disease were risk factors for women with AIE. These results are supported by Pfannmüller et al. [28,29]. Unlike the Sambola study, women did not refuse surgical procedures during our investigation. Gammie and colleagues investigated more than 400 000 patients and identified female gender as having no significant effect on patient outcome after MV surgery alone (OR 1.4) [30]. Tricuspid valve disease seems to be underdiagnosed in women, leading to higher mortality rates in the general population. Concomitant aortic surgery was more frequently observed in male patients [30].

Postoperative morbidities

The incidence of heart failure, independent of the underlying pathology, increases considerably in women aged 55 years and older [31]. This factor also seems to account for the stronger correlation between age and mortality observed in women with cardiovascular disease. Regitz-Zagrosek described the higher NYHA functional class as the strongest predictor for the development of heart failure and mortality in men, but the strongest predictor for women is age [31].

Early mortality

To the best of our knowledge, no study has been conducted to compare male and female patients with risk factors for early mortality; however, a previous study showed gender to be an independent risk factor for in-hospital mortality (OR 7.56; 95% CI 1.31–43.69, p=0.0147) [8]. This study also showed that renal failure had a tremendous influence on in-hospital mortality (OR 5.94; 95% CI 0.95–37.24, p=0.0524). Musci et al. was only able to show in univariate analyses that diabetes mellitus had a moderately elevated OR of 2.17 [1]; which was confirmed by the multivariate analyses of our study for male patients.

Long-term results

Based on the pathology of disease, more women received a prosthetic MV replacement compared with men. More investigations with regard to the gender-dependent differences in the demographical data of patients with AIE who are undergoing surgery are awaited.

Conclusions

This study demonstrated distinct gender-based differences in risk of mortality in patients with AIE who were undergoing surgical treatment. The data also indicate differences in disease patterns, comorbidities, intraoperative surgical treatment strategy, and long-term outcome.

Conflict of interest

No conflict of interest to declare.

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