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Sex Differences and Pathogen Patterns in Surgically Treated Aortic Valve Endocarditis over 15 Years

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Abstract: Background: Infective endocarditis (IE) is a serious public health concern due to its high morbidity and lethality. This study investigates epidemiological trends in aortic valve endocarditis, focusing on sex-related differences in microbial etiology and surgical outcomes over a 15-year period. Methods: From January 2010 to January 2024, 608 patients underwent cardiac surgery for IE at our center. Of these, 274 patients received isolated aortic valve replacement. This retrospective, single-center study analyzes these cases. Results: Despite a decline in overall aortic valve replacement surgeries, a significant increase in surgeries due to aortic valve endocarditis was observed ($p < 0.001$). Both sexes showed a rising incidence of aortic valve endocarditis, with females undergoing surgery at an older age, particularly in native valve cases ($p = 0.008$). In prosthetic valve cases, this age difference was less pronounced ($p = 0.050$). While sex did not influence microbial etiology in native valve endocarditis, females with prosthetic valves were more frequently infected by *Streptococcus* ($p = 0.033$). *Staphylococcus aureus* infections increased in native valves ($p = 0.016$). Conclusions: Over 15 years, surgical aortic valve endocarditis has risen in both sexes. Males are more often affected by native valve cases, while females develop it later. Neither gender nor microbial etiology independently predicts death.

Keywords: sex; bacterial endocarditis; native aortic valve; prosthetic aortic valve

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1. Introduction

Infective endocarditis (IE) remains a severe and ongoing public health concern due to its high morbidity and lethality rates globally [1–3]. Annually, the incidence of IE is estimated at 3–10 cases per 100,000 individuals, resulting in approximately 66,300 deaths worldwide as of 2019 [4]. While IE can affect any cardiac valve, it most frequently involves the left-sided valves, with the aortic and mitral valves presenting distinct clinical characteristics and pathogen associations [5]. Over the past 50 years, and particularly in the last decade, the epidemiology of IE has transformed significantly. Notably, *Staphylococci* and *Enterococci* have become more common causative agents, while *viridans streptococci* and *coagulase-negative Staphylococci* have declined in prevalence. Consequently, the mean age at IE diagnosis has increased, accompanied by a growing male-to-female incidence ratio, highlighting the evolving demographic landscape of the disease [6]. Sex-based differences in IE epidemiology are increasingly documented, with recent studies indicating that male patients are more likely to undergo cardiac surgery for IE, while female patients are generally older and present a higher surgical risk profile and exhibit increased early postoperative complications [7]. Moreover, in the female population the mitral valve looks to be more frequently affected than in males [8]. *Staphylococcus* spp. seems the most frequent causative agent and is associated with a significantly higher death rate [9]. Consequently, female patients display a higher 30-day mortality and lower estimated mid-term survival rates [10], even if female sex does not always represent an independent predictor of in-hospital death [11]. In fact, it appears that the severity of presentation and the underlying clinical conditions are responsible for the increased surgical risk for females with infective endocarditis, and not female sex itself [12].

Importantly, the majority of existing studies focus on IE affecting all cardiac valves across multiple centers, often combining a wide range of valve types and patient populations into a single analysis [10]. In contrast, our study narrows its focus to isolate cases of aortic valve endocarditis affecting both native and prosthetic aortic valves. By concentrating on aortic valve IE specifically, this study aims to address a significant gap in the literature. To our knowledge, no comprehensive study to date has analyzed the trends in aortic valve endocarditis over a 15-year period, particularly with attention to sex-related differences and changes in microbial etiology. This study's primary objectives are to investigate sex-specific disparities, identify shifts in microbial spectra over time, and assess how these factors influence clinical and surgical outcomes, particularly in relation to aortic valve replacement procedures. By providing a focused, detailed retrospective analysis of aortic valve IE, we aim to elucidate an underexplored dimension of IE epidemiology. The insights gained from this research may contribute to more personalized therapeutic approaches and ultimately support more effective clinical decision-making for patients with aortic valve endocarditis.

2. Materials and Methods

All patients over 18 years of age who had an indication for surgical treatment of isolated aortic valve endocarditis were included. The demographic and key baseline characteristics of the patients were gathered and documented. These included factors such as age, sex, body mass index, creatinine clearance, preoperative condition, cardiovascular risk factors, functional status, and left ventricular ejection fraction. Additionally, the additive and logistic EuroSCORE was used to assess the risk of mortality associated with cardiac surgery. Alongside these baseline characteristics, intraoperative data and short-term outcomes were also recorded.

To assess cardiac function and the efficacy of the surgical procedures, echocardiograms were conducted both before and after surgery. This imaging method provided essential information on the structure and function of the heart valves, as well as overall heart performance, in the pre- and postoperative phases.

Blood samples were collected using strict aseptic techniques to minimize contamination. Blood was drawn from a venipuncture site and divided into separate blood culture bottles, one for aerobic microorganisms and the other for anaerobic ones. In cases of suspected catheter-related infections, blood was drawn simultaneously from both peripheral veins and the catheter to compare the time to positivity between the two samples and identify catheter-associated infections. Blood cultures were processed using the BACT/ALERT® 3D system (bioMérieux, Craponne, France), an automated blood culture system designed to detect microbial growth. The system allows early detection of bacterial growth. If a positive result was obtained, the contents of the culture bottle were transferred to different agar plates for further examination and microbial isolation. Following this, the microbial isolates were analyzed using the VITEK® 2 Compact System (bioMérieux, France), an automated identification and antibiotic susceptibility testing platform. The VITEK® 2 system provides rapid and accurate antibiotic susceptibility testing. Rejection criteria for blood samples included signs of contamination, such as the presence of skin flora or insufficient sample volume. Samples that were improperly collected, stored, or transported, or those that showed signs of contamination or inappropriate handling, were discarded and not processed. The identification of microorganisms was conducted according to standardized laboratory protocols. All procedures were conducted following strict infection control guidelines to minimize contamination and improve diagnostic reliability.

2.1. Study Design and Outcomes

Between January 2010 and January 2024, a total of 608 patients underwent cardiac surgery for endocarditis at our center. Of these, 274 patients received isolated aortic valve replacement. This single-center, retrospective study focuses exclusively on these 274 cases. Specifically, among the 608 patients, 406 had endocarditis involving the aortic valve; of these, 220 had native valves, while 186 had aortic prosthetic valves. Among the 220 patients with aortic valve endocarditis, 152 underwent isolated aortic valve replacement since the other valves were not involved. Of these 152 patients, 15 did not have an identifiable pathogen; thus, they were excluded from the study, resulting in an initial population of 137 patients. Regarding the 186 patients with endocarditis on prosthetic valves, 150 were treated with isolated aortic valve replacement. Among these, 13 patients also did not have an identifiable pathogen, leading to a second population of 137 patients (Figure 1). No formal sample size calculation was conducted; instead, all eligible patients within the defined timeframe were included in the study.

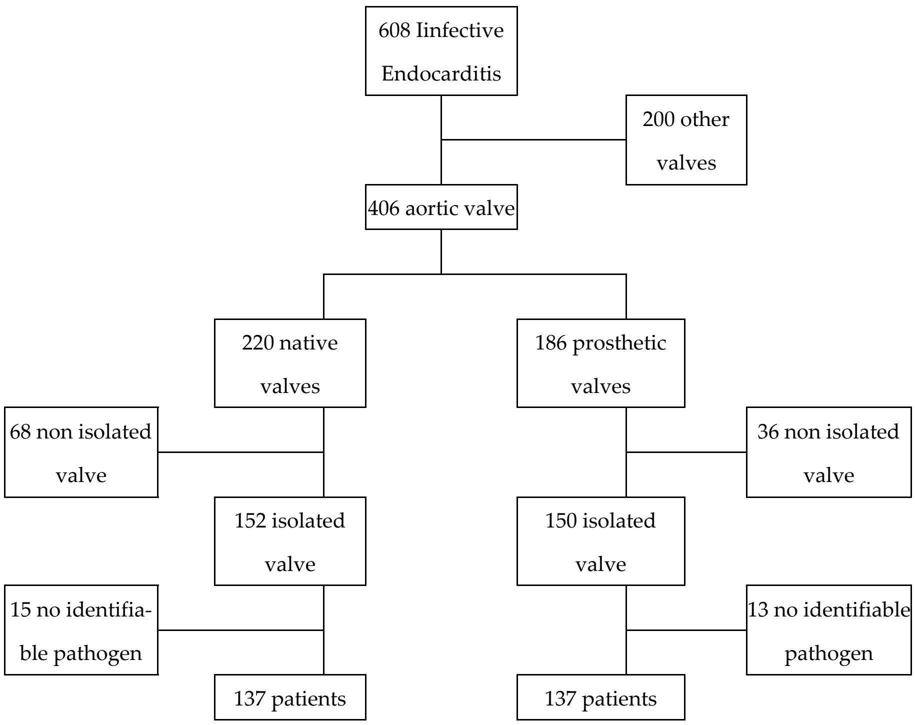

Figure 1. Flow-chart for included patients.

The study protocol was approved by the Romagna Ethics Committee on 30 June 2023 (protocol number 4497/2023 I.5/95). Patients enrolled provided written consent for data collection as part of clinical routine practice, quality assessment, and for scientific research purposes. Data collection was performed using clinical charts and systematically organized into a dedicated registry. Significant efforts were made to minimize the presence of missing data. When data were missing, it was attributed to gaps in clinical documentation and assumed to be missing completely at random. To preserve data quality, only complete cases were included in the analysis.

2.2. Statistical Analysis

Continuous variables were presented as medians with interquartile ranges (IQR) and compared using the Mann–Whitney test. Categorical variables were expressed as absolute numbers and frequencies, and comparisons were made using the chi-squared test or Fisher's exact test, as appropriate. No imputation was performed for missing data. The overall study period was also stratified in three 5-year intervals (2010–2014, 2015–2019, 2020–2024); this time span was selected in order to have an adequate number of patients in each sub-period; a chi-squared test for trend was applied to evaluate trends across 5-year intervals.

Multivariable logistic regression was conducted to assess in-hospital death, using baseline and intraoperative characteristics as covariates. For variable selection, the Least Absolute Shrinkage and Selection Operator (LASSO) method with 50-fold cross-validation was employed; in order to avoid possible overfitting, we selected the lambda with 1 Standard Error rule to select the most parsimonious model. The model's discrimination was evaluated by reporting the Area Under the Receiver Operating Characteristic (ROC) Curve.

All analyses were performed using R version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria), with p-values < 0.05 considered as statistically significant.

3. Results

The baseline characteristics of the entire patient cohort, stratified into two groups based on the type of surgical treatment, are summarized in Table 1. It is observed that females undergo surgery at a more advanced age, particularly in cases of endocarditis affecting native aortic valves ($p = 0.008$). This age difference is not as pronounced in cases of endocarditis involving aortic valve prostheses, where the p-value is borderline at 0.050. Additionally, females present for surgery with a higher EuroSCORE, with the increase being particularly significant for endocarditis on native aortic valves ($p = 0.006$) compared to prosthetic valve endocarditis ($p = 0.041$).

The interval between the initiation of antibiotic therapy and surgery is also longer in females, although this difference does not reach statistical significance ($p = 0.1$). However, a statistically significant trend over time (p for trend = 0.022) indicates a notable shortening of this interval in recent years. In detail, for men, the median interval was 35 days [IQR 16–60] during the 2010–2014 period, decreasing to 22 days [13–34] between 2015 and 2019, and further reduced to 19 days [10–25] in the 2020–2024 period ($p = 0.010$). For females, the median interval was 35 days [IQR 29–55] during the 2010–2014 period, decreasing to 23 days [18–34] between 2015 and 2019, and further reduced to 21 days [11–46] in the 2020–2024 period, but did not reach statistical significance ($p = 0.665$).

Over the past 15 years, despite a reduction in the absolute number of aortic valve replacement surgeries (as shown in Figure 2A), a statistically significant upward trend has been observed in cases of endocarditis associated with aortic valve pathology requiring surgical intervention as the primary etiology ($p < 0.001$). When stratifying the population by sex, it is observed that both males and females exhibit a statistically significant increase in the incidence of aortic valve endocarditis (as shown in Figure 2A). During the same time period, the percentage of endocarditis on either native or prosthetic aortic valves did not display any significant trend in either direction, with a p for trend of 0.271. The percentage fluctuated over time, as illustrated in Figure 2B.

Table 1. Preoperative characteristics comparing female and male sex in the context of native aortic valve endocarditis and prosthetic aortic valve endocarditis.

	Native Aortic Valve			Prosthetic Aortic Valve		
	Male	**Female**	***p***	**Male**	**Female**	***p***
n	106	31		108	29	
Age, median (IQR)	61 (50–71)	72 (61–75.50)	0.008	73 (66–78)	75 (71–80)	0.050
Hypertension, n (%)	62 (58.5)	16 (51.6)	0.635	89 (82.4)	20 (69.0)	0.182
Diabetes, n (%)	20 (18.9)	4 (12.9)	0.617	22 (20.4)	8 (27.6)	0.561
Obesity, n (%)	29 (27.4)	6 (19.4)	0.506	17 (15.7)	5 (17.2)	>0.999
Chronic obstructive pulmonary disease, n (%)	9 (8.5)	4 (12.9)	0.697	8 (7.4)	1 (3.4)	0.732
Ejection Fraction %, median (IQR)	60 (50–65)	60 (55–65)	0.165	55 (51.75–60)	58 (51–60)	0.517
Drug addict, n (%)	8 (7.5)	3 (9.7)	0.993	1 (0.9)	0 (0.0)	>0.999
Peripheral arterial disease, n (%)	10 (9.4)	2 (6.5)	0.876	17 (15.7)	4 (13.8)	>0.999
Neoplasm, n (%)	9 (8.5)	4 (12.9)	0.697	14 (13.0)	4 (13.8)	>0.999
Previous neurological disease, n (%)	23 (21.7)	11 (35.5)	0.185	19 (17.6)	5 (17.2)	>0.999
Cirrhosis, n (%)	1 (0.9)	1 (3.2)	0.936	0 (0.0)	0 (0.0)	/
Chronic kidney disease (creatinine > 2.0 mg/dL), n (%)	11 (10.4)	3 (9.7)	>0.999	7 (6.5)	4 (13.8)	0.367
Dialysis, n (%)	6 (5.7)	0 (0.0)	0.392	2 (1.9)	1 (3.4)	>0.999
Permanent pacemaker, n (%)	4 (3.8)	1 (3.2)	>0.999	15 (13.9)	8 (27.6)	0.141
Shock, n (%)	6 (5.7)	1 (3.2)	0.938	4 (3.7)	0 (0.0)	0.667
Heart failure, n (%)	28 (26.4)	9 (29.0)	0.953	27 (25.0)	7 (24.1)	>0.999
Myocardial infraction 90 days, n (%)	5 (4.7)	0 (0.0)	0.492	0 (0.0)	0 (0.0)	/
Previous intubation, n (%)	12 (11.3)	2 (6.5)	0.653	3 (2.8)	1 (3.4)	>0.999
Additive EuroSCORE, median (IQR)	7.0 (5.0–9.0)	10.0 (6.5–11.5)	0.006	12.0 (11.0–14.3)	14.0 (12.0–15.0)	0.041
Logistics EuroSCORE, median (IQR)	8.5 (4.7–15.7)	16.8 (8.0–30.4)	0.006	33.9 (20.9–55.0)	47.3 (26.4–56.9)	0.143
Active endocarditis (%)	96 (90.6)	27 (87.1)	0.823	100 (92.6)	23 (79.3)	0.080
Negative blood cultures	12 (11.3)	1 (3.2)	0.315	13 (12.0)	2 (6.9)	0.651
Staphylococcus aureus, n (%)	21 (19.8)	7 (22.6)	0.801	8 (7.4)	1 (3.4)	0.684
Staphylococcus non aureus, n (%)	8 (7.5)	4 (12.9)	0.468	34 (31.5)	9 (31.0)	>0.999
Streptococcus, n (%)	33 (31.1)	9 (29.0)	>0.999	23 (21.3)	12 (41.4)	0.033
Pseudomonas, n (%)	0 (0.0)	0 (0.0)	/	0 (0.0)	0 (0.0)	/
Enteroccoccus faecalis, n (%)	17 (16.0)	5 (16.1)	>0.999	15 (13.9)	3 (10.3)	0.764
Fungus, n (%)	1 (0.9)	1 (3.2)	0.403	2 (1.9)	1 (3.4)	0.513
Other pathogen, n (%)	12 (11.3)	6 (19.4)	0.241	18 (16.7)	2 (6.9)	0.245
Abscess, n (%)	24 (22.6)	4 (12.9)	0.353	65 (60.2)	20 (69.0)	0.516
Vegetation, n (%)	100 (94.3)	27 (87.1)	0.331	74 (68.5)	23 (79.3)	0.366
Leaflet perforation, n (%)	17 (16.0)	4 (12.9)	0.887	8 (7.4)	1 (3.4)	0.732
Endocarditis-intervention days, median (IQR)	21 (12–34)	28 (18–40)	0.107	21 (13–35)	25 (18–39)	0.114

IQR, interquartile range.

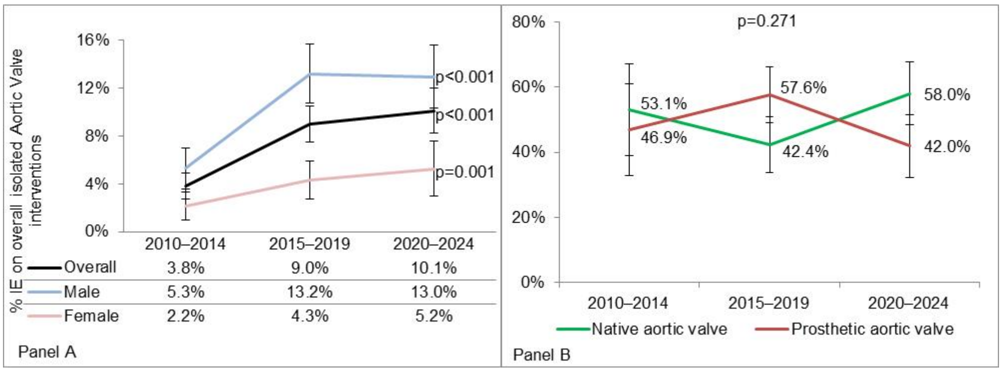

Figure 2. Panel (**A**) shows the increasing percentage of patients undergoing isolated aortic valve replacement for endocarditis over time, with a significant trend observed over each 5-year period. Panel (**B**) illustrates that, in cases of isolated aortic valve endocarditis, there is no linear trend in the ratio of patients with prosthetic valve endocarditis compared to those with native valve endocarditis.

3.1. Microbial Etiology

Regarding microbial etiology, *Staphylococcus non-aureus* was the primary pathogen responsible for IE in patients with prosthetic aortic valve endocarditis, while *Streptococcus* was the main causative agent in patients with native aortic valve endocarditis. The data presented in Table 1 suggest that sex does not impact the microbiological agent in cases of endocarditis on native aortic valves. However, a difference appears to exist in infections of aortic prostheses, as females are significantly more frequently affected by Streptococcal infections ($p = 0.033$).

Over the past 15 years, divided into 5-year periods, a statistically significant increase in *Staphylococcus aureus* infections in patients with native valves ($p = 0.016$) and an apparent statistically significant decrease in fungal infections ($p = 0.019$) was observed; however, such significance requires cautious interpretation of these findings due to the small sample size and the limited number of patients affected by fungal infections.

In patients with prosthetic aortic valves, no statistically significant increase was noted, although there was a trend toward a higher incidence of *Streptococcus* infections ($p = 0.074$) (Table 2).

Table 2. Trends of microbial etiological agents over time divided into 5-year periods.

Native Aortic Valve	2010–2014	2015–2019	2020–2024	*p* for trend
n	26	53	58	
Staphylococcus aureus, n (%)	1 (3.8)	11 (20.8)	16 (27.6)	0.016
Staphylococcus non aureus, n (%)	4 (15.4)	4 (7.5)	4 (6.9)	0.257
Streptococcus, n (%)	9 (34.6)	13 (24.5)	20 (34.5)	0.768
Enteroccoccus faecalis, n (%)	6 (23.1)	7 (13.2)	9 (15.5)	0.506
Fungus, n (%)	2 (7.7)	0 (0.0)	0 (0.0)	0.019
Other pathogen, n (%)	4 (15.4)	8 (15.1)	6 (10.3)	0.456
Prosthetic Aortic Valve	**2010–2014**	**2015–2019**	**2020–2024**	***p* for trend**
n	23	72	42	
Staphylococcus aureus, n (%)	2 (8.7)	6 (8.3)	1 (2.4)	0.250
Staphylococcus non aureus, n (%)	11 (47.8)	19 (26.4)	13 (31.0)	0.180
Streptococcus, n (%)	3 (13.0)	18 (25.0)	14 (33.3)	0.074
Enteroccoccus faecalis, n (%)	3 (13.0)	6 (8.3)	9 (21.4)	0.189
Fungus, n (%)	0 (0.0)	2 (2.8)	1 (2.4)	0.613
Other pathogen, n (%)	2 (8.7)	14 (19.4)	4 (9.5)	0.781

Among the patients with prosthetic valve endocarditis (PVIE), 57 (41.6%) were classified as early cases (≤12 months). When comparing the microbiological agents, we observed a significantly higher incidence of coagulase-negative staphylococci (CoNS) in early prosthetic valve endocarditis, with a statistically significant difference (47.4% vs. 20.5%, $p = 0.001$), confirming the data from the literature. Conversely, in late (>12 months) prosthetic valve endocarditis, a statistically significant difference was noted in the higher incidence of Streptococcus species (32.1% vs. 15.8%, $p = 0.044$) (Table S1).

3.2. Trends by Sex and Pathogens

In order to address sex differences, we observed a statistically significant increase in the incidence of male patients with native aortic valve endocarditis over time ($p = 0.024$). This rise in males occurred alongside a corresponding decrease in incidence among female patients. In contrast, within the group of patients with prosthetic aortic valves, no significant sex-related differences in the incidence of endocarditis were observed. These findings suggest that while the incidence of endocarditis in native aortic valves has shifted toward a higher male prevalence, the occurrence in prosthetic valve patients remains stable across sexes (Figure 3).

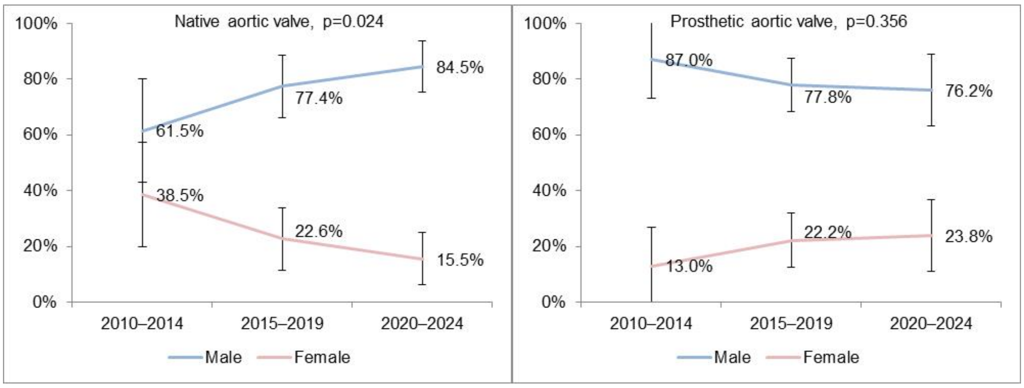

Figure 3. Trends by sex over time divided into 5-year periods.

The distribution of etiological microbial agents according to sex, in order to identify any potential sex-related differences, was also analyzed. As shown in Table 1, no statistically significant differences were found, indicating that the incidence of microbial pathogens in native aortic valve endocarditis is similar between males and females. However, it is noteworthy that there was a higher incidence of *Streptococcus* infections in females with prosthetic aortic valves (p = 0.033).

3.3. Postoperative Outcomes

The surgical technique adopted for aortic valve replacement included both traditional median sternotomy (n = 207, 75.5%) and minimally invasive ministernotomy/minithoracotomy (n = 67, 24.5%).

Surgical data and postoperative outcomes are reported in Table 3.

Table 3. Surgical data and postoperative outcomes comparing female and male sex in the context of native aortic valve endocarditis and prosthetic aortic valve endocarditis.

	Native Aortic Valve			Prosthetic Aortic Valve		
	Male	**Female**	***p***	**Male**	**Female**	***p***
n	106	31		108	29	
CPB time, median (IQR)	76 (59–101)	58 (49–75)	0.015	115 (95–169)	93 (75–164)	0.102
Cross clamp time, median (IQR)	63 (48–85)	48 (39–62)	0.011	96 (77–136)	81 (60–131)	0.083
Ventilation time (hours), median (IQR)	10 (6–19)	9 (6–15)	0.881	12 (8–24)	15 (9–72)	0.079
ICU (days), median (IQR)	2 (2–5)	3 (2–5)	0.413	3 (2–6)	6 (3–11)	0.024
Sepsis, n (%)	9 (8.5)	3 (9.7)	1.000	6 (5.6)	3 (10.3)	0.616
Permanent pacemaker, n (%)	4 (3.8)	1 (3.2)	1.000	19 (17.6)	6 (20.7)	0.910
Atrial fibrillation (%)	24 (22.6)	10 (32.3)	0.393	31 (28.7)	7 (24.1)	0.799
Acute kidney injury (%)	7 (6.6)	4 (12.9)	0.447	25 (23.1)	9 (31.0)	0.528
Dialysis, n (%)	7 (6.6)	2 (6.5)	1.000	6 (5.6)	6 (20.7)	0.029
Hospital stay (days), median (IQR)	7 (6–9)	7 (6–9)	0.650	8 (6–14)	10 (8–15)	0.145
30 days death (%)	9 (8.5)	3 (9.7)	1.000	8 (7.4)	4 (13.8)	0.478

Regarding the general population, it is observed, as expected, that patients undergoing reoperation for prosthetic valve endocarditis experienced longer operative times for cardiopulmonary bypass and aortic cross-clamping, as well as an extended stay in the intensive care unit and hospital. They also showed a higher incidence of acute kidney injury and a greater need for permanent pacemaker implantation. However, the 30-day death rate was the same in both groups (8.8%), with females showing a higher, but not statistically significant, death rate (11.7% vs. 7.9%), p = 0.520. This lack of statistical significance should be interpreted with caution due to the small number of events. When examining differences in outcomes between males and females, it is noted that for females undergoing surgery on the native valve, cardiopulmonary bypass and aortic cross-clamp times were significantly shorter than for males (p = 0.01). This difference was not present in cases of surgery on a prosthetic valve. In our population, no statistically significant differences were observed between the sexes in terms of other outcomes, specifically with similar ventilation time ($p = 0.881$), ICU stay duration ($p = 0.413$), and hospital death ($p = 1.000$). In cases of prosthetic aortic valve endocarditis, females had worse outcomes regarding dialysis incidence ($p = 0.029$) and length of ICU stay, which was double that of males ($p = 0.024$). Despite this, there were no statistically significant differences in death ($p = 0.478$), although it was higher in females. In order to assess whether gender, male or female, and the microbial agent play a role in in-hospital death incidence, a multivariable logistic regression analysis was performed and revealed that 30-day death was influenced solely by preoperative dialysis and extracorporeal circulation time (Figure 4); all other covariates (as reported in Table 1) did not show to be independent predictors of death; in particular, we did not find association between death and sex, period, native/prosthetic valves, microbial agents, age.

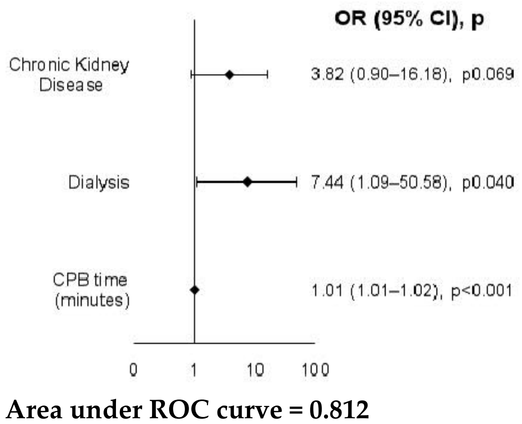

Figure 4. Multivariable logistic regression analysis for 30-day death, in order to assess whether gender, male or female, and the microbial agent play a role.

4. Discussion

In this study, we conducted a comprehensive retrospective analysis of 15 years of data on patients diagnosed with aortic valve endocarditis, encompassing both native and prosthetic valves, who underwent cardiac surgery. The primary aim of this analysis was to elucidate the potential roles of gender differences and microbial agents in influencing patient outcomes. To minimize confounding factors, we systematically examined the temporal trends in the characteristics of patients with isolated aortic valve endocarditis, specifically focusing on those with native (n = 137) and prosthetic (n = 137) valves. To date, numerous publications have addressed gender differences in the context of cardiovascular diseases [13] and infectious diseases; however, few studies have specifically targeted patients suffering from endocarditis who are subjected to cardiac surgery. In this context, it is noteworthy that the majority of existing studies primarily concentrate on infective endocarditis (IE) affecting all cardiac valves across multiple centers, often aggregating a diverse array of valve types and patient populations into a singular analysis [10]. In contrast, our study hones in on aortic valve endocarditis, focusing exclusively on cases involving both native and prosthetic aortic valves within a specific geographic region. By narrowing the scope to aortic valve IE, this study aims to address a critical gap in the current literature.

Our findings confirm the well-established observation that females present for cardiac surgery at an older age and with a higher surgical risk as quantified by the EuroSCORE. This phenomenon has recently been documented by the CAMPAIGN study group, which indicated that female patients exhibit a greater burden of comorbidities and higher surgical risk, ultimately resulting in poorer postoperative outcomes characterized by prolonged ventilation times, extended stays in the intensive care unit, increased rates of new-onset dialysis, and elevated 30-day death rates [10]. In addition, the finding that women are referred to surgery later than men is well-documented and has been reported in several publications [14,15].

However, our results reveal several intriguing aspects that diverge from the existing literature. Firstly, regarding preoperative characteristics, gender differences appear to diminish when comparing patients with native aortic valves to those with prosthetic aortic valve endocarditis. This observation suggests that the presence of a prosthetic valve may play a more significant role in predisposing patients to endocarditis, thereby mitigating the influence of gender differences. Furthermore, we found that postoperative outcomes were not significantly worse for females, particularly in the context of native valve endocarditis. While poorer outcomes associated with prosthetic valve endocarditis are well-documented [16], there is limited data concerning the role of female gender in this context. Importantly, our findings indicate that female patients do not experience higher hospital death rates, contrary to some reports in the literature [10]. Notably, gender was not identified as a risk factor in our multivariable logistic regression analysis as showed in Figure 4; instead, 30-day death in our population was predominantly influenced by preoperative dialysis status and the duration of extracorporeal circulation, aligning with findings from other studies [17].

Moreover, in our study population, we observed a statistically significant increase in the incidence of endocarditis compared to the broader cardiothoracic surgical population (Figure 2A), expressed as a percentage of the total number of patients operated on. This increase remains statistically significant even when the population is stratified by sex, with both males and females showing significant rises in incidence. Furthermore, as illustrated in Figure 2, when we focus exclusively on patients diagnosed with endocarditis and stratify them by gender, we observe a statistically significant increase in the proportion of males, accompanied by a corresponding decrease in females, within our cohort of native valve endocarditis cases ($p = 0.024$) as already reported in other studies [18,19]. Conversely, when considering patients with aortic valve prostheses, the influence of gender on the incidence of endocarditis appears to diminish. In this subgroup, no statistically significant differences are observed between males and females ($p = 0.356$). These findings suggest that while gender seems to play a significant role in native valve endocarditis, it is less impactful in the context of prosthetic valve endocarditis.

In addition to analyzing the role of gender in isolated aortic valve endocarditis, we also aimed to investigate the microbial agents involved and to evaluate trends over time. The shift in the underlying microbiology of infective endocarditis, characterized by an increasing prevalence of *Staphylococcus* species compared to *Streptococcus* species as the predominant causative pathogens, has been well-documented in the literature [20,21]. Specifically, *Staphylococcus aureus* has emerged as the primary causative agent of native valve endocarditis [22], while coagulase-negative Staphylococci is more frequently associated with prosthetic valve endocarditis [23]. This evolution in microbial etiology can be attributed to several epidemiological shifts within the populations affected by infective endocarditis. Factors such as an aging population, the rising incidence of degenerative valvular diseases, and the increasing utilization of prosthetic heart valves are recognized as significant predisposing risk factors for the development of this condition [24]. In our study population, when comparing microbiological agents, we observed a significantly higher incidence of coagulase-negative staphylococci (CoNS) in early prosthetic valve endocarditis, with a statistically significant difference ($p = 0.001$), confirming the data from the literature. Conversely, in late prosthetic valve endocarditis, a statistically significant difference was noted in the higher incidence of Streptococcus species ($p = 0.044$).

On the other hand, in our study population, we did not observe any gender-related differences in the microbiological agents responsible for infections in native valves; indeed, *Streptococcus* species were identified as the predominant etiological agents. However, we noted a notable gender difference in cases of prosthetic valve endocarditis. Specifically, females predominantly exhibited infections caused by *Streptococcus* species, akin to those seen in native valve infections, whereas males had a higher percentage of coagulase-negative *Staphylococci* as the primary causative organisms. These findings diverge from those previously reported in the CAMPAIGN population [10], where *Staphylococcus* species were more frequently identified as causative microorganisms among female patients, while Streptococcus species and *Enterococcus* species were more prevalent among male patients. Despite these findings, the literature does not reach a consensus regarding the correlation between sex and microbial etiology in infective endocarditis. For instance, a study by Polishchuk et al. [25] reported a higher prevalence of coagulase-negative staphylococcal infections in males and a greater incidence of culture-negative endocarditis in females, with no significant differences observed for other pathogens. These observations align with those from a recent large meta-analysis [26], which indicated that while *Staphylococcus aureus* remains the most common microorganism implicated in infective endocarditis, females were more likely to present with culture-negative infections, whereas males were more frequently infected with *Streptococcus viridans*. Nevertheless, our findings present a contrasting perspective. Additionally, our study sought to evaluate the evolution of the microbial etiology of infective endocarditis within our population by categorizing the data into three 5-year intervals. The analysis suggests no statistically significant differences in the microbial etiology of prosthetic valve endocarditis over time, although there was a suggestive trend towards an increased incidence of Streptococcus infections ($p = 0.074$). Conversely, our data corroborated the statistically significant rise in *Staphylococcus aureus* as the etiological agent of native valve endocarditis, aligning with previous reports in the literature [27]. These results underscore the complexities associated with the microbial landscape of infective endocarditis, particularly in relation to gender and the type of valve affected. The evolving patterns of causative pathogens highlight the need for continuous surveillance and further research to elucidate the factors contributing to these trends and to enhance the management of patients with infective endocarditis.

Limitations

This study has several limitations that must be considered. Firstly, it is non-randomized in design, and the data were collected retrospectively, which may introduce biases and limit the ability to establish causal relationships. Furthermore, the analysis focuses on a specific subset of patients with endocarditis—those who had a surgical indication and were subsequently treated. As such, the findings may not fully represent the broader population of patients with endocarditis, thereby offering only a limited perspective on the overall clinical landscape. Additionally, the study is based on the experiences and outcomes from a single surgical center, which may affect the generalizability of the results to other institutions or populations. Moreover, there was no formal sample size calculation, which raises concerns regarding the statistical power of the findings. In addition, we were unable to provide the exact number of patients who underwent previous dental procedures. This information was not systematically documented, and therefore, we cannot draw conclusions regarding its prevalence or potential association with the outcomes observed. It is also important to highlight that the low incidence of fungal infections does not appear to be related to limitations in identification methods; however, this cannot be confirmed with certainty. The VITEK® 2 system, which utilizes VITEK-2 cards for species identification based on biochemical profiling supported by an extensive database, was employed. Additionally, the system includes antifungal susceptibility testing cards, allowing for accurate assessments of susceptibility. These factors highlight the need for cautious interpretation of the results and suggest that further research is necessary to validate and expand upon these findings.

5. Conclusions

This study analyzes 15-year trends in isolated aortic valve endocarditis requiring surgery. We show a significant rise in the incidence of endocarditis affecting aortic valves, expressed as a percentage of the total number of surgical procedures performed, observed in both sexes. The trend analysis suggests that male patients increasingly predominate in native valve endocarditis across the years, but this gender disparity trend disappears in prosthetic valve cases, likely due to differing risk factors.

Key findings in our patient population include the following:

- Postoperative outcomes and hospital death rates are comparable between sexes.
- Females seems to develop aortic valve endocarditis later than men.
- While female patients have higher overall death rates, this difference is not statistically significant, though female sex is a EuroSCORE risk factor.
- No significant sex-based differences were found in the microbiological profile of endocarditis.

An increasing incidence of *Staphylococcus aureus* in native valves was noted. However, neither sex nor microbial etiology independently predicts death. These results suggest that while sex influences incidence and age of onset, it does not significantly affect mortality or infection profile.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/microbiolres16020033/s1, Table S1. Distribution of microbial etiological agents according to early/late prosthetic valve endocarditis.

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Informed Consent Statement: Patients enrolled provided written consent for data collection as part of clinical routine practice, quality assessment and for scientific research purposes. Data protection and privacy regulations were strictly observed in capturing, forwarding, processing, and storing patient data.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to data protection directive 95/46/EC.

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