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Article type: Original article

Received: December 28, 2022

Accepted: June 5, 2023

Early publication date: June 25, 2023

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The impact of gender on in-hospital mortality and long-term mortality in patients undergoing surgical aortic valve replacement: SAVR and SEX Study

Short title: SAVR and SEX Study

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WHAT'S NEW?

Traditionally, women gender is considered as a factor worsening prognosis after heart surgeries. In this analysis based on 4 510 patients undergoing isolated aortic valve replacement, in-hospital and late mortality did not differ significantly between men and women. In propensity score matching analysis, a 5-year survival in women was increased in comparison to men.

ABSTRACT

Background: Surgical aortic valve replacement (SAVR) is among the most commonly performed valve valvular surgeries. Despite many previous studies conducted in this setting, the impact of gender on outcomes in the patients undergoing SAVR is still unclear.

Aims: To define gender differences in short- and long-term mortality in patients undergoing SAVR.

Methods: We analyzed retrospectively all the patients undergoing isolated SAVR from January 2006 to March 2020 in the Department of Cardiovascular Surgery and Transplantology in John Paul II Hospital in Cracow. The primary end point was in-hospital and long-term mortality. Secondary end points included the length duration of hospital stay and perioperative complications. Groups of men and women with regard to the prosthesis type were compared. Propensity score matching was performed to adjust for differences in baseline characteristics.

Results: A total number of 4 510 patients undergoing isolated surgical SAVR were analyzed. A follow-up median (interquartile range [IQR]) was 2120 (1000–3452) days. Females constituted 41.55% of the cohort and were older, displayed more non-cardiac comorbidities and faced a higher operative risk. In both genders, bioprostheses were more often applied (55.5% vs. 44.5%; $P < 0.0001$). In univariable analysis, gender was not associated linked to in-hospital fatality (3.7% vs. 3%; $P = 0.15$) and late mortality (rates) (23.37% vs. 23.52 %; $P = 0.9$). Upon adjustment for baseline characteristics (propensity score matching analysis) and considering 5-year survival, a long-term prognosis proved to be better in women with 86.8% comparing to 82.7% in men ($P = 0.03$).

Conclusions: A key finding from this study suggests that the female gender was not associated with a higher in-hospital and late mortality rate compared to men. Further studies are needed to confirm long-term benefits in women undergoing SAVR .

Key words: gender, mortality, SAVR, TAVI

INTRODUCTION

Surgical aortic valve replacement (SAVR) is among the most commonly performed heart surgeries and most frequently conducted valvular interventions in western countries [1]. The obvious indication for SAVR is aortic stenosis (AS) with equal prevalence in elderly women and men [2]. With the onset of AS symptoms, prognosis dramatically deteriorates as the disorder is immune to pharmacological treatment [3]. On the contrary, surgery for AS reduces mortality and symptoms and increases the quality of life in both genders [4, 5]. Nonetheless, gender differences in outcomes after SAVR are not unequivocally defined because of mixed results of previous studies with more ample evidence of worse prognoses for women [2, 6–11]. Unfavorable outcomes observed in women were explained by smaller anatomical structures rendering the procedure more technically demanding, more frequent frailty syndrome and more comorbidities increasing an operative risk.

Recently, promising results of transcatheter aortic valve implantation (TAVI) in women were achieved [12, 13]. Nonetheless, the accessibility to this technique is not yet sufficient for extending a group of patients with AS and therefore, improving results after SAVR procedure is still of the utmost importance as surgery remains the gold standard of AS and aortic regurgitation (AR) treatment. The aim of the present study is to assess the gender differences in the outcomes after SAVR.

METHODS

We analyzed all patients undergoing SAVR in the single department of cardiac surgery from January 2006 to March 2020. For the purpose of ruling out an impact of other procedures on subjects undergoing TAVI, an annuloplasty and concomitant surgery were excluded. The baseline, clinical and follow-up data were recorded including demographic characteristics, concomitant diseases, a course of the hospitalization with procedural details and possible complications. Late mortality was assessed with the Polish National PESEL database for the highest accuracy. The decision of the type and model of the prosthesis was discussed with a patient. The primary study end points were in-hospital and late mortality. Secondary end points included hospital length of stay (HLoS) and periprocedural complications. Propensity Score Matching was applied for baseline differences adjustment. All included characteristics were listed in the Table 3. The study was conducted in accordance with to the Declaration of Helsinki.

Due to the retrospective nature of the data collected, patient consent was not required and the bioethics committee approval was waived.

Study database

Data for this study was collected retrospectively based on the standardised form of the Polish National Database of Cardiac Surgery Procedures (“KROK” registry; www.krok.csioz.gov.pl). The registry is an ongoing, nation-wide, multi-institutional record of cardiac surgery procedures in Poland, which has been established on the initiative of the Club of Polish Cardiac Surgeons and compiled in cooperation with the Polish Ministry of Health. Centers enrolling patients into the KROK registry are required to transfer the data regarding every cardiac surgery to the central database in the National Centre for Healthcare Information Systems at the Ministry of Health.

The data gathered included age, gender, body mass index (BMI), ejection fraction (EF), previous percutaneous coronary intervention (PCI), Canadian Cardiovascular Society (CCS) class, New York Heart Association (NYHA) class, smoking status, diabetes mellitus (DM), arterial hypertension, hypercholesterolemia, asthma, chronic obstructive pulmonary disease (COPD). The observation time was defined as period to last observation or death. Late mortality was examined with the Polish National PESEL database for the highest possible accuracy.

On the basis of the form of the KROK registry, a computer database was built for further statistical analysis.

Missing data in the database

We decided to exclude patients in case records of outcomes (i.e. mortality/survivors) were missing. The completeness of each patient record was counted: records were only analysed if the percentage of complete data entered was higher than 90%. Records that were lower than 90% were excluded from this analysis. To handle missing data in propensity score matching (PSM), an additional level for the missing values was created for categorical data. In other words, arbitrary value imputation technique was applied for those parameters. Cases with missing data in continuous parameters were excluded from PSM.

Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were expressed as the mean with standard deviation (SD) or the median with the lower and upper quartile (interquartile range [IQR]). Normality was assessed by the Shapiro-Wilk test. Equality

of variances was assessed using the Levene's test. Differences between groups were compared using the Student's or the Welch's t-test depending on the equality of variances for normally distributed variables. The Mann-Whitney U test was used for non-normally distributed continuous variables or for ordinal variables. Categorical variables were compared by the Pearson's χ^2 test or by the Fisher's exact test if 20% of the cells had an expected count less than 5. To evaluate the influence of gender on mortality (overall death), the Cox proportional-hazards model was created and adjusted for baseline covariates (age, prior MI, current or former smoking status, DM, sinus rhythm before procedure, planned or emergency/urgent procedure, EuroSCORE II, hyperlipidemia and NYHA class). The multivariable model was fitted in backward stepwise regression with p-value threshold of 0.05 stopping rule. Survival probabilities were presented using the Kaplan-Meier curves and compared with the log rank test.

To avoid potential influence of the non-randomized design and reduce bias, a propensity score was calculated using a multivariable logistic regression model with gender considered as a dependent variable. The propensity score was calculated based on baseline variables (see Table 3 for details). Covariate balance was assessed using standardized mean differences (SMD) that were less than 5. Pairs of male and female patients were formed using 1:1 caliper matching. Caliper of width equal to 0.07 was used. Unpaired patients were rejected from the analysis. Clinical outcomes (including mortality) for matched samples were compared using the McNemar's test. Additionally, a matched pairs design of the win ratio method was applied for lifetime data [14]. Results of this method were presented on a forest plot (Figure 1).

The level of statistical significance was set at $P < 0.05$. Statistical analyses were performed with JMP®, Version 16.2.0 (SAS Institute INC., Cary, NC, US) and using R, Version 4.1.0 (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria, 2017. <https://www.r-project.org/>).

RESULTS

General characteristics

A total of 5035 consecutive patients undergoing invasive replacement of the aortic valve (AV) were included. Following exclusion, 4510 patients treated with isolated SAVR were analyzed (Supplementary material, Figure S1). Men constituted 58.5 % of the cohort. Women were older (mean age 67.3 years vs. 61.6 years, respectively; $P < 0.001$) and more often overweight or obese (mean body mass index [BMI], 29.2 kg/m² vs. 28 kg/m²; $P < 0.001$) with more non-cardiovascular concomitant diseases. Men were more often smokers (10.6% vs. 4.6%; P

<0.001) and they more often suffered from prior myocardial infarction (11.2% vs. 5.4%; $P < 0.001$). Majority of patients were afflicted with aortic stenosis (85%). Maximal transvalvular (pressure) gradient was higher in women (89.2 vs. 79.4 mm Hg; $P < 0.001$). Men had more often moderate or severe aortic regurgitation. Symptoms assessed by the NYHA functional classification differed significantly in both groups with female dominance in class III. The baseline patient characteristics are shown in the [Table 1](#).

Procedural outcomes

Except for 4 cases, all procedures were performed with the use of the cardioplegic solution. The length of the procedure was longer in men (214 vs. 208 min; $P = 0.002$) and they received bigger prostheses (23.7 vs. 21.3 mm; $P < 0.001$). Also, the average time of extracorporeal circulation was longer in men (113.2 vs. 108.7 min; $P < 0.001$). Bioprostheses were chosen more often in both genders, especially in women (61.6% vs. 51.2%; $P < 0.001$).

Clinical outcomes

A follow-up median (IQR) was 2 120 (1 000–3 452) days, for men 2186 (1 000–3 568) days and for women 2042 (1006–3270; $P = 0.01$) days. Frequency of complications did not differ between genders (10.75% vs. 11.2%; $P = 0.67$). A univariate analysis did not show differences between women and men in terms of in-hospital mortality (3.7% vs. 3%; $P = 0.15$) and late mortality (23.37% vs. 23.52%; $P = 0.9$). Nonetheless, the propensity score analysis disclosed that after a year's observation the mortality rate in men was higher and remained so until the last observation period using the McNemar's test for matched pairs. The Kaplan-Meier estimate did not show significant differences between men and women in long-term observation ([Figure 1](#)). In the win ratio approach, a statistically significant mortality rate difference was observed only for the period of 5 years, however all analyses show similar win ratio results ([Figure 2](#)). For the 5-year observation, women have 33% more wins over death (WR = 1.33; 95% CI, 1.00–1.79; $P = 0.048$). Additionally, the multivariable Cox regression demonstrated/indicated that male gender was associated with a higher risk of death (hazard ratio [HR], 1.22; 95% CI, 1.07–1.39; $P = 0.003$).

DISCUSSION

The key findings of this study led to the conclusion that women do not have higher in-hospital and long-term mortality than men. Traditionally, female gender was associated with worse clinical outcomes after heart surgeries. Female gender is embedded into the STS and

EuroSCORE II risk models as a factor aggravating the prognosis [15]. Nevertheless, it should be pointed out that these scales were designed based on data from CABG procedures and might not accurately define an operative risk for SAVR.

In previous studies, despite more symptoms, females were treated conservatively for a longer period of time and were referred for SAVR more rarely; as a consequence at the time of operation they presented with worse baseline characteristics [2]. Similarly, in our study women were older, more often with diabetes, hypertension and a higher operative risk.

It was postulated that later women presentation for SAVR might be related to delayed development of AS in women. Older studies based on echocardiographic data showed that men are twice as likely to be diagnosed with AS [16]. Nonetheless, data from a large national registry from Sweden showed that the AS is nearly equivalent in elderly women and men [17]. As evidenced by the former, gender discrepancies among patients undergoing SAVR are probably caused by referral bias.

Sex-dependent pathophysiological development of AS was described previously [18]. Women face a greater risk of developing left ventricular concentric geometry in response to AS, ejection fraction and fibrosis. As far as calcifications are concerned, women have lower aortic valve calcium burden than men. Nonetheless, in women calcifications have a more profound impact on AS severity. Therefore, gender is not associated with AS progression [19, 20].

The histogram representing the average 365-day survival for each year of the study period shows the mortality peak in 2015 with consequent tendency to decrease (**Figure 3**). This finding might be attributed to 240 patients who were for TAVI, mostly after 2015 (Supplementary material, *Figure S1*). Their risk profile based on EuroSCORE II was 2.55, higher than of patients undergoing isolated SAVR. Therefore, we might assume that the drain of the sickest patients to TAVI procedures have impacted the outcomes of the SAVR. There are many studies supporting TAVI utilization in high- and medium-risk patients given its favorable outcomes, especially in women. Nonetheless, the majority of TAVI studies were based on octogenarians, which raises doubts as a longer life expectancy of women might influence these outcomes [21–26]. Moreover, the studies assessing gender differences in patients undergoing SAVR of at least 80 years old also revealed better outcomes in the women's group [10, 17]. For all the patients at that age, the newer generation bioprostheses might offer excellent outcomes [27–30]. In post hoc analysis of SURTAVI study van Mieghem et al. did not show significant gender differences between SAVR and TAVI groups in a 2-year follow-up [9]. Similarly, in recent analysis Marzec et al. did not find statistically significant mortality rate difference in 24-months mortality between two methods [31]. Available meta-analyses comparing TAVI and SAVR reveal

distinct benefits of each technique. TAVI seems to reduce an incidence of bleeding, new-onset atrial fibrillation and acute kidney injury with a higher rate of vascular complications, prosthesis-patient mismatch and reinterventions. In terms of all-cause mortality, no significant differences between both methods were found [32, 33]. Noteworthy is the emergence of new surgical techniques that reduce the rate of cerebrovascular events and make SAVR more accessible for patients with COPD, which is a common contraindication for SAVR [34]. Comparable results of TAVI and SAVR in the mentioned studies suggest that the both methods should be considered in patients suffering from aortic valve disease. Our study has demonstrated that SAVR is a reasonable option for women with outcomes comparable to men in short- and long-term observation. There was a trend of better results in women shown in the PSM, but this need to be confirmed in further studies. Also, in the presence of the growing body of evidence suggesting comparable outcomes in men and women after SAVR, the female gender as a risk factor for SAVR should be reconsidered [35].

Limitations

This is a single-center retrospective study. Not all determinants of the outcomes could be recorded. Lack of comprehensive echocardiographic data prevented an assessment of patient-prosthesis mismatch (PPM). In terms of late mortality, it was not possible to distinguish between cardiac and non-cardiac causes of death.

CONCLUSIONS

In the present study crude analysis revealed that women were not associated with higher in-hospital and late mortality rate after SAVR compared to men. Further studies are needed to confirm long-term benefits in women undergoing SAVR.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

Funding: None.

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Table 1. Baseline characteristics before propensity score matching (PSM)

		Women, n = 1874	Men, n = 2636	Total, n = 4510	P-value
Age, years, median (IQR)		69 (62–75)	63 (55–71)	66 (57–73)	<0.001
Body mass index, kg/m ² , median (IQR)		28.8 (25.4– 32.5)	27.7 (24.8– 30.9)	28.1 (25–31)	<0.001
Overweight (BMI ≥25), n (%)		1442 (77.2)	1904 (72.7)	3346 (74.6)	0.006
Obesity (BMI ≥30), n (%)		785 (42.1)	806 (30.8)	1591 (35.5)	<0.001
Body surface area, m ² , median (IQR)		1.8 (1.7–1.9)	2 (1.8–2.1)	1.9 (1.8–2)	<0.001
LVEF, %, median (IQR)		60 (50–65)	55 (45–60)	60 (50–63)	<0.001
AV mean gradient, mm Hg, median (IQR)		86.5 (73–104)	81 (66–96)	84 (70–100)	<0.001
AR	None, n (%)	205 (11)	240 (9.1)	445 (9.9)	<0.001
	Trivial, n (%)	692 (37)	793 (30.2)	1485 (33)	
	Mild, n (%)	649 (34.7)	762 (29)	1411 (31.4)	
	Moderate, n (%)	245 (13.1)	543 (20.7)	788 (17.5)	
	Severe, n (%)	79 (4.2)	287 (10.9)	366 (8.1)	
Smoking	None, n (%)	1604 (85.8)	1878 (71.6)	3482 (77.5)	<0.001
	Former, n (%)	179 (9.6)	469 (17.9)	648 (14.4)	
	Current, n (%)	86 (4.6)	277 (10.6)	363 (8.1)	
Last creatinine level, mg/dl, median (IQR)		0.85 (0.7–1)	0.95 (0.8–1)	0.9 (0.7–1)	<0.001
CCS	N/A, n (%)	144 (7.7)	209 (8)	353 (7.9)	0.77
	I, n (%)	690 (36.9)	962 (36.7)	1652 (36.8)	
	II, n (%)	852 (45.6)	1212 (46.2)	2064 (46)	
	III, n (%)	162 (8.7)	205 (7.8)	367 (8.2)	
	IV, n (%)	21 (1.1)	35 (1.3)	56 (1.3)	
NYHA	N/A, n (%)	21 (1.1)	25 (1)	46 (1)	0.03

	I, n (%)	311 (16.6)	497 (18.9)	808 (18)	
	II, n (%)	856 (45.8)	1255 (47.8)	2111 (47)	
	III, n (%)	606 (32.4%)	719 (27.4%)	1325 (29.5)	
	IV, n (%)	76 (4.1)	128 (4.9)	204 (4.5)	
Prior MI, n (%)		101 (5.4)	294 (11.2)	395 (8.8)	<0.001
Prior PCI, n (%)		56 (6.9)	122 (11.6)	178 (9.5)	0.001
Diabetes mellitus, n (%)		438 (23.4)	478 (18.2)	916 (20.4)	<0.001
IDDM, n (%)		183 (9.8)	200 (7.6)	383 (8.5)	0.01
COPD	None, n (%)	1548 (82.8)	2095 (79.9)	3643 (81.1)	0.04
	Treated, n (%)	320 (17.1)	526 (20.1)	846 (18.8)	
	Non-treated/untreated, n (%)	1 (0.1)	2 (0.1)	3 (0.1)	
Hypertension, n (%)		1585 (84.8)	2118 (80.7)	3703 (82.4)	0.001
Dyslipidemia, n (%)		676 (36.2)	966 (36.8)	1642 (36.6)	0.66
EurosCORE II, median (IQR)		1.2 (0.9–1.6)	0.8 (0.7–1.2)	1 (0.7–1.4)	<0.001

Abbreviations: AV, aortic valve; AR, aortic regurgitation; COPD chronic obstructive pulmonary disease; IDDM, insulin-dependent diabetes mellitus; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention

Table 2. Procedural and clinical outcomes before propensity score matching (PSM)

		Women, n = 1 874	Men, n = 2 636	Total, n = 4 510	P-value
Duration of hospitalization, days, median (IQR)		10 (8–14)	10 (8–14)	10 (8–14)	0.14
Valve type	Bioprosthesis	1155 (61.6)	1349 (51.2)	2504 (55.5)	<0.001
	Mechanical	719 (38.4)	1287 (48.8)	2006 (44.5)	
Valve diameter, mm, median (IQR)		21 (21–23)	23 (23–25)	23 (21–25)	<0.001
Cardioplegia	Crystalloid, n (%)	717 (38.5)	930 (35.5)	1647 (36.8)	0.04
	Blood, n (%)	1145 (61.5)	1689 (64.5)	2834 (63.2)	
Complications, n (%)		200 (10.8)	291 (11.1)	491 (11)	0.67
Re-operation	Re-sternotomy, n (%)	98 (8.5)	161 (9.9)	259 (9.3)	0.21
	Secondary sternal repair, n (%)	19 (1.7)	38 (2.3)	57 (2)	
In-hospital mortality, n (%)		70 (3.7)	78 (3)	148 (3.3)	0.15
Death in operating room/theater, n (%)		6 (0.3)	7 (0.3)	13 (0.3)	0.74

Table 3. Baseline characteristics after propensity score matching (PSM)

		Men, n = 763	Women, n = 763	P-value
Age, years, median (IQR)		67 (58–74)	67 (60–73)	0.73
Body mass index, kg/m ² , median (IQR)		28.2 (25.1–31.5)	28.3 (25.1–32.4)	0.08
Overweight (BMI ≥25), n (%)		574 (75.2)	577 (75.6)	0.86
Obesity (BMI ≥30), n (%)		282 (37)	284 (37.2)	0.91
Body surface area, m ² , mean (SD)		2 (0.2)	1.8 (0.2)	<0.001 ^a
LVEF, %, median (IQR)		60 (50–65)	60 (50–63)	0.22
AV gradient, mm Hg, median (IQR)		81 (66–96)	86.5 (73–104)	0.56
AR	None, n (%)	94 (12.3)	91 (11.9)	0.98
	Trivial, n (%)	281 (36.8)	279 (36.6)	
	Mild, n (%)	255 (33.4)	256 (33.6)	
	Moderate, n (%)	113 (14.8)	115 (15.1)	
	Severe, n (%)	20 (2.6%)	22 (2.9%)	
Smoking	None, n (%)	605 (79.3)	606 (79.4)	0.82
	Former, n (%)	107 (14)	101 (13.2)	

	Current, n (%)	51 (6.7)	56 (7.3)	
Last creatinine level, mg/dl, median (IQR)		0.9 (0.8–1.03)	0.8 (0.7–1)	<0.001 ^a
CCS	N/A, n (%)	62 (8.1)	54 (7.1)	0.86
	I, n (%)	289 (37.9)	294 (38.5)	
	II, n (%)	344 (45.1)	341 (44.7)	
	III, n (%)	63 (8.3)	69 (9)	
	IV, n (%)	5 (0.7)	5 (0.7)	
NYHA	N/A, n (%)	62 (8.1)	54 (7.1)	0.96
	I, n (%)	142 (18.6)	138 (18.1)	
	II, n (%)	374 (49)	370 (48.5)	
	III, n (%)	208 (27.2)	212 (27.8)	
	IV, n (%)	30 (3.9)	34 (4.5)	
Prior MI, n (%)		57 (7.5)	62 (8.13)	0.63
Prior PCI, n (%)		26 (7.8)	32 (9.5)	0.82
Diabetes mellitus, n (%)		171 (22.4)	166 (21.8)	0.76
IDDM, n (%)		72 (9.4)	74 (9.7)	0.86
COPD	None, n (%)	611 (80.1)	615 (80.6)	0.56
	Treated, n (%)	150 (19.7)	148 (19.4)	
	Non-treated/untreated, n (%)	2 (0.3)	0 (0)	
Hypertension, n (%)		645(84.5)	637 (83.5)	0.57
Dyslipidemia, n (%)		290 (38)	280 (36.7)	0.61
EuroSCORE II, median (IQR)		0.9 (0.7–1.4)	1.1 (0.9–1.5)	<0.001 ^a

Abbreviations: see [Table 1](#)

Table 4. Procedural and clinical outcomes after propensity score matching (PSM)

		Women, n = 763	Men, n = 763	P-value
Duration of hospitalization, days, median (IQR)		10 (8–14)	10 (8–14)	0.45
Valve type	Bioprosthesis, n (%)	457 (59.9)	453 (59.4)	0.83
	Mechanical, n (%)	306 (40.1)	310 (40.6)	
Valve diameter, mm, median (IQR)		23 (21-23)	23 (21-23)	0.14
Cardioplegia	Crystalloid, n (%)	469 (61.6)	497 (65.5)	0.11
	Blood, n (%)	293 (38.5)	262 (34.5)	
Re-operation	Re-sternotomy, n (%)	44 (9.4)	36 (7.8)	0.8
	Secondary sternal repair, n (%)	10 (2.2)	6 (1.3)	
Death in operating room/theater, n (%)		1 (0.1)	2 (0.3)	0.56

Continuous variables were expressed as the median with the lower and upper quartile (IQR, interquartile range)

Table 5. In-hospital and late mortality after propensity score matching (McNemar's test)

	Female, n = 763	Male, n = 763	P-value
Procedural complications, n (%)	72 (9.5)	82 (10.8)	0.40
In-hospital mortality, n (%)	26 (3.4)	27 (3.5)	0.89
Death (within 1 year), n (%)	48 (6.3)	66 (8.7)	0.08
Death (within 2 years), n (%)	61 (8)	84 (11)	0.046
Death (within 3 years) , n (%)	72 (9.4)	97 (12.7)	0.04
Death (within 4 years) , n (%)	86 (11.3)	117 (15.3)	0.02
Death (within 5 years) , n (%)	101 (13.2)	132 (17.3)	0.03
Overall death, n (%)	161 (21.1)	186 (24.4)	0.12

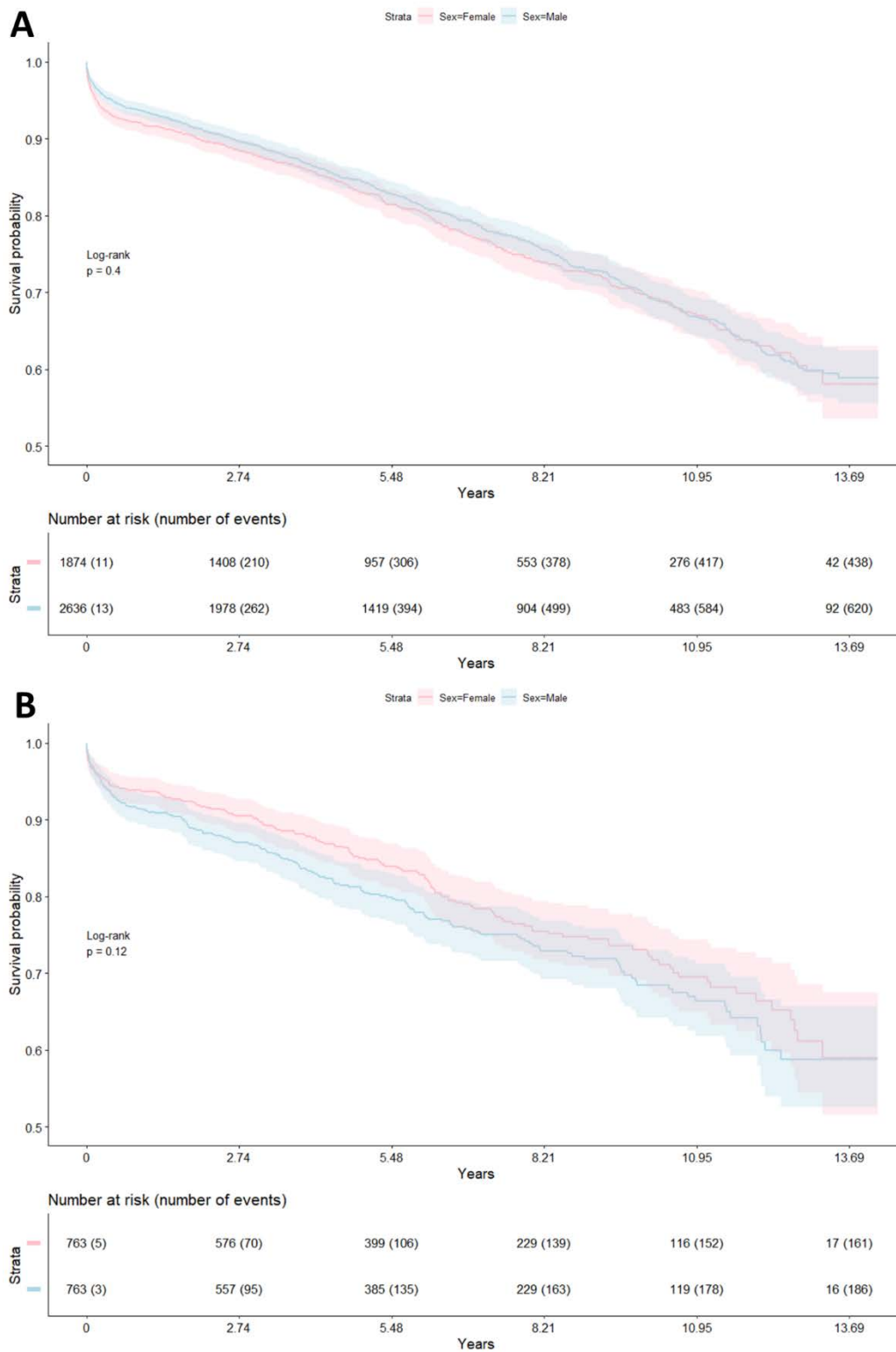


Figure 1. A. The Kaplan-Meier curves before PSM. **B.** The Kaplan-Meier curves after PSM
Abbreviations: see [Table 1](#)

