Original Article

Sex differences in 30-day readmission rates, etiology, and predictors after transcatheter aortic valve replacement

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ABSTRACT

Background: The aim of this study is to analyze sex-specific readmission rates, etiology, and predictors of readmission after transcatheter aortic valve replacement (TAVR). Readmissions after TAVR are common, contributing to increased health care utilization and costs. Many factors have been discovered as predictors of readmission; however, sex-specific disparities in readmission rates are limited.
Methods: Between January 2012 and September 2015, adult patients after TAVR were identified using appropriate international classifications of diseases, ninth revision, clinical modification from the National Readmission Database. Incidence of unplanned 30-days readmission rate was the primary outcome of this study. In addition, this study includes sex-specific etiology and predictors of readmissions. Multivariate logistic regression was performed to analyze adjusted readmission rates. Hierarchical 2-level logistic models were used to evaluate predictors of readmission.
Results: Readmission rate at 30 days was 17.3%, with slightly higher readmission rates in women (OR 1.09; CI: 1.01—1.19, $p < 0.001$) after multivariate adjusted analysis. Noncardiac causes were responsible for most readmissions in both genders. Etiologies for readmissions such as arrhythmias, pulmonary complications, and infections were slightly higher in women, whereas heart failure and bleeding complications were higher in men. History of heart failure, atrial fibrillation, prior pacemaker, and renal failure significantly strongly predicted readmissions in both genders.
Conclusion: Women undergoing TAVR have slightly higher 30-day all-cause readmission rates. These results indicate that women require more attention compared to men to prevent 30-day readmission. In addition, risk stratification for men and women based on predictors will help identify high-risk men and women for readmissions.
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1. Introduction

The transcatheter aortic valve replacement (TAVR) has been increasingly utilized as an intervention for the management of symptomatic intermediate- and high-risk severe aortic stenosis, and with utilization rates expected to increase exponentially worldwide.[1,2] Several factors have led to better outcomes in TAVR in recent years, including the increase in procedural volume and operator experience, the technical and procedural refinements,

besides improved patient's selection.[3] However, there is an ongoing urge for further improvements in outcomes, specifically readmission rates, as readmissions are associated with higher financial burden and adversely affects quality of life.[4] Thirty-day readmission rate is an important quality metric measure used for cardiovascular diseases and procedures such as heart failure, myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting.[5] A recent study by Kolte et al demonstrated 30-day readmission rates for TAVR was estimated to be 17.9%; however, gender-specific readmission rates were not shown.[4] In addition, Khera et al have generated the risk tool to predict a 30-day readmission rate for TAVR patients, which once validated, we believe it would be of a great value especially in patient's selection.[6] Although nine factors including anemia, atrial

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fibrillation, chronic liver disease, chronic lung disease, chronic kidney disease, end-stage renal disease on dialysis, length of stay 5 days or more, acute kidney injury, and discharge disposition were used to generate the aforementioned risk tool, other important factors such as the effect of gender on outcomes was left behind.[6] Gender was an important factor for readmission and was included in predictions of readmission with other interventional procedures.[7]

In this study, we analyzed sex-specific difference in readmission rates after TAVR. In addition, we studied sex-specific differences in etiology and predictors to better understand target high-risk patients. This study can potentially help reduce readmission rates and associated financial burdens.

2. Methods

2.1. Data source

This study utilized Nationwide Readmission Database (NRD) from January 2012 to September 2015. The NRD is part of the all-payer databases established by the Agency for Healthcare Research and Quality for the Healthcare Cost and Utilization Project. The NRD represents ~50% of all US hospitalizations. It includes discharge records of patients treated in the 21 states of the US hospitals, excluding rehabilitation and long-term acute care facilities. Discharge weights are provided to calculate national estimates. The NRD contains verified patient linkage numbers that could be used to track a patient across hospitals within a state. However, the patient linkage numbers do not track the same person from 1 year into the following year. Patients were tracked using variable "NRD_visitlink," and time between 2 admissions was calculated by subtracting variable "NRD_Days-ToEvent." This study was deemed exempt by the Institutional Review Board as the NRD is a publicly available data that contains deidentified database. More details regarding NRD data have been published earlier.[4,8]

2.2. Study population

We identified patients who underwent TAVR procedure using *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) procedure codes 35.05 and 35.06 from the NRD database, which has been utilized previously.[4,9] We included hospitalizations from January 2012 to September 2015 as ICD-10-CM codes were utilized after September 2015. Hospitalization records were excluded if (1) discharge month was December for years 2012—2014 and September for year 2015 because 30-day readmission data would not be available; (2) subject died during the index hospitalization; and (3) age <18 years, and 4) subjects with missing age, gender, and death information (Supplement Figure 1). Similar methods were used previously.[4,8]

2.3. Outcomes

The primary outcome was the rate of all-cause unplanned readmission within 30 days of hospitalization with TAVR in men and in women. We reviewed the primary diagnosis of each readmission record for men and women and grouped them into clinically meaningful categories to determine the main cause of readmission. This strategy has been utilized previously.[4] Causes of readmissions were classified as cardiac and noncardiac. We also examined secondary in-hospital outcomes such as length of stay and disposition in both men and women cohort.

2.4. Patient and hospital characteristics

Baseline patient characteristics included demographics such as age, median household income by ZIP code, primary expected payer, weekend versus weekday admission, and other relevant comorbidities (e.g., obesity, congestive heart failure, hypertension, diabetes, smoking, dyslipidemia, known coronary artery disease, prior percutaneous coronary intervention, prior myocardial infarction, prior coronary artery bypass grafting, atrial fibrillation, prior permanent pacemaker, prior implantable cardioverter defibrillator, renal failure, chronic liver disease, chronic lung disease) and in-hospital procedures such as coronary angiography, percutaneous coronary intervention, and mechanical circulatory support. We used "cm_" variables provided by Healthcare Cost and Utilization Project to identify different comorbidities which use ICD-9-CM diagnoses and the diagnosis-related group in effect on the discharge date. These comorbidities are not directly related to the principal diagnosis or the main reason for admission and are likely to have originated before the hospital stay.[10] ICD-9-CM codes used to identify other comorbidities and in-hospital procedures are given in Supplementary Table 1. Hospital-related characteristics, such as bed size (small, medium, and large), location (urban vs rural), and teaching status, were also included.

2.5. Statistical analysis

Baseline patient and hospital characteristics, comorbidities, in-hospital procedures, and in-hospital outcomes were compared between patients with and without 30-day readmission using Pearson χ^2 test for categorical variables and Student's *t*-test for continuous variables.

SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used for analyses. Categorical variables were presented as frequencies and percentages, whereas continuous variables as mean ± standard deviations or median (interquartile range) depending on their distribution. Hierarchical 2-level logistic models with hospital ID as random effect were used to evaluate predictors of readmission for men and women. Multivariate models for readmission included patient-level variables such as age, median household income (higher income quartile vs lowest income quartile), primary payer (private insurance [including Health Maintenance Organization] and self-pay versus Medicaid/Medicare), all comorbidities, in-hospital procedures, and all hospital level variables as explained previously. A 2-sided value of $p < 0.05$ was set for statistical significance in all analyses.

3. Results

Between January 2012 and September 2015, a total of 26,233 patients were included in this study. Prevalence of TAVR was comparable in men and in women (53% vs. 47%). From the study population, 4532 (17.2%) patients were readmitted. Total readmission rate trended down from 2012 to 2015 (19.3%—16.1%, $P_{trend}<0.001$). Total readmission rate was slightly higher in women (17.1% in men and 18% in women, $p < 0.001$). This readmission rate trended down in men (19.1%—15.5%, $P_{trend}<0.001$) as well in women (19.4%—16.8%, $P_{trend}<0.001$) (Fig. 1).

Cardiac causes were responsible for 38.3% of the readmissions in men and 35.8% in women, among which heart failure was the most prevalent (23.5% in men vs. 21.9% in women), followed by arrhythmias (6.2% in men vs. 6.8% in women). Other common reasons for readmissions were pulmonary complications and infections, both slightly higher in women than men. Bleeding and renal complications were also among the major reasons for readmission to the hospital (Supplement Figure 2 and 3).
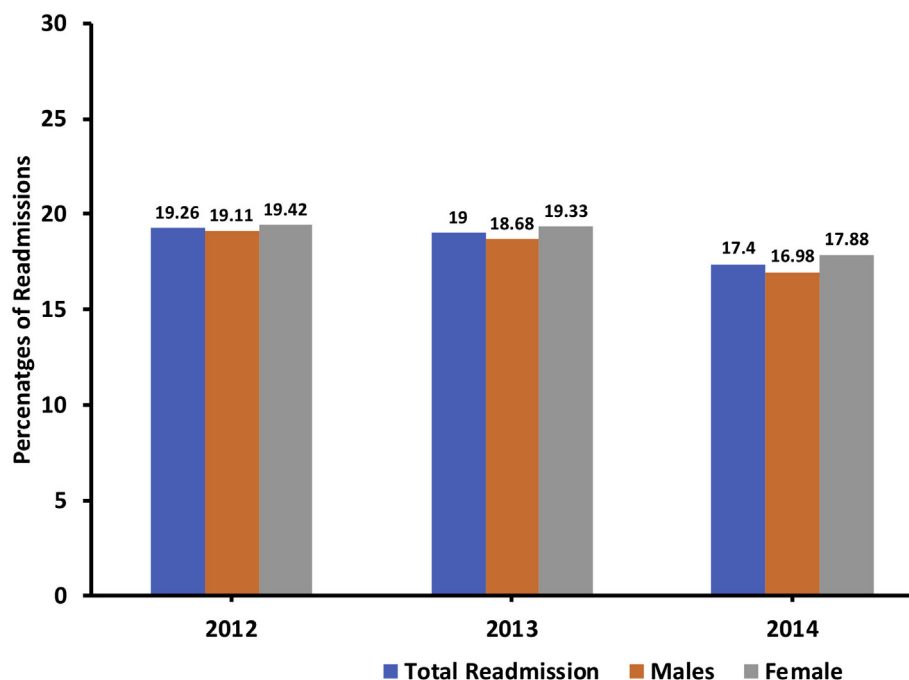
Fig. 1. All-cause readmission rates in overall TAVR patients and further stratified by men and women. P_{trend} value for all <0.001. TAVR, transcatheter aortic valve replacement.

Women were slightly older in this study (80.6 vs. 81.8 years, $p < 0.001$). There were differences in baseline characteristics in men and in women. Women have higher prevalence of obesity (13.9% vs 18.2%, $p < 0.001$), heart failure (6.8% vs 7.5%, $p = 0.003$), and hypertension (80% vs. 80.8%, $p = 0.006$), whereas other comorbidities were higher in men. Women more frequently underwent TAVR using transapical approach as opposed to transfemoral approach and required more blood transfusions than men (15.6% vs 23.4%, $p < 0.001$). However, men required more mechanical circulatory support (1.6% vs. 1.0%, $p < 0.001$). No statistically significant difference was noted in the utilization of coronary angiography and percutaneous coronary intervention (PCI) rates between both groups (Table 1). Supplementary Table 2 demonstrated gender differences based on whether they were readmitted to the hospital.

There were 3 cardiac conditions associated with increased risk of readmission including heart failure (OR 3.44 in men, 3.65 in women), followed by the presence of prior permanent pacemaker (OR 1.39 in men, 1.32 in women), and atrial fibrillation (OR 1.17 in men, 1.36 in women), $p < 0.001$ for all. Concerning noncardiac causes, renal failure (OR 1.41 in men, 1.26 in women, $p < 0.001$ for both) and the need for blood transfusion (OR 1.31 in men, 1.14 in women, $p < 0.001$ for both) predicted readmission in both genders. While diabetes predicted readmissions only in women (OR 1.19, $p < 0.001$), chronic lung disease (OR 1.24, $p < 0.001$) predicted readmissions only in men (Table 2).

After multivariate adjustment, odds of 30-day readmission were significantly higher in women (OR 1.09; CI: 1.01–1.19, $p < 0.001$). After index admissions, women had higher odds of discharge to short- or long-term facilities (OR 1.61, $p < 0.001$) rather than home. Women also had higher odds of hospital stay for more than five days (OR 1.61; CI: 1.50–1.72 $p < 0.001$). Table 3 displays the adjusted outcomes based on gender (Table 3).

4. Discussion

All-cause readmission rates at 30-days were slightly higher in women as compared with men who underwent TAVR from 2012 to 2015 in the United States. This study demonstrated that all-cause readmission rates associated with TAVR has been slowly decreasing in men as well as in women as expected. This analysis also highlighted that cardiac etiology, infections, pulmonary etiology, and bleeding were not the most common reasons for readmissions. Cardiac etiology and bleeding were more common in men as compared with women, whereas pulmonary etiology and infections were more common in women as compared with men. In different cardiac etiologies for readmissions, heart failure and arrhythmias were the most common reasons for readmissions in both genders. History of heart failure, atrial fibrillation, prior pacemaker, and renal failure significantly predicted readmissions in both genders. Readmissions rates were significantly lower in patients with private insurance, and patients admitted to the large-bed hospitals or teaching hospitals in men as well in women. This is the all-comers, largest-to-date analysis comparing readmission rates in male and female patients who underwent TAVR.

Patients in both genders presented with different risk profile on index admission. Women presented with slightly higher age as compared with men. More women were obese and had higher heart failure and hypertension. Women more commonly underwent TAVR using transapical approach when compared with men. We are not entirely sure about higher transapical approach in women. These results are in line with previous studies showing higher prevalence of NYHA III/IV class and utilization of non-transfemoral approaches for TAVR in women; however, this study had few women with renal failure undergoing TAVR.[11] Aligned with previous data, readmission rates within 30 days were ~17% with TAVR possibly due to reduction in complication rates and improvement in technology.[4,12,13] Nearly, two-fifth patients were readmitted with cardiac cause which is comparable with previously published studies.[14,15] Infections and pulmonary causes were the other most common reasons for readmission in men and in women which is shown by previous studies.[15] Readmission rates were slightly higher in women at 30 days, which is in contrast to a previously published study which showed no difference at 30-days readmission rates between men and women.[16] The difference was

Table 1
Demographics and baseline characteristics for patients undergoing transcatheter aortic valve replacement: Stratified by gender.

Variables	Men (*n* = 13,922)	Women (*n* = 12,301)	Total (*n* = 26,223)	*p* value
Weighted Frequency	**28,432**	**25,685**	**54,117**	<0.001
Mean age	80.6 ± 12.6	81.8 ± 11.7		
Comorbidities				
Obesity	13.94	18.17	15.95	<0.001
Heart failure	6.82	7.46	7.12	0.004
Hypertension	79.98	80.85	80.39	0.011
Diabetes mellitus	37.79	32.32	35.19	<0.001
Smoking	32.78	18.41	25.96	<0.001
Dyslipidemia	65.41	62.61	64.08	<0.001
History of coronary artery disease	76.33	59.07	68.14	<0.001
Prior myocardial infarction	15.37	9.27	12.48	<0.001
Prior percutaneous coronary intervention	22.57	17.07	19.96	<0.001
Prior coronary artery bypass grafting	30.64	10.99	21.31	<0.001
Atrial fibrillation	46.23	44.55	45.43	<0.001
Prior permanent pacemaker	11.71	9.49	10.66	<0.001
Prior implantable cardioverter defibrillator	4.6	1.22	3	<0.001
Renal failure	40.37	30.09	35.49	<0.001
Chronic liver disease	2.97	2.24	2.62	<0.001
Chronic lung disease	33.96	32.97	33.49	0.015
Procedural details				
Coronary angiography	23.13	23.68	23.39	0.13
Percutaneous coronary intervention	3.62	3.49	3.56	0.42
Mechanical circulatory support	1.64	0.99	1.33	<0.001
Transfemoral approach	84.48	81.7	83.16	<0.001
Transapical approach	15.68	18.47	17	<0.001
Blood transfusion	15.6	23.35	19.28	<0.001
Median household income category for patient's zip code				
0-25th percentile	19.93	20.14	20.03	0.01
26-50th percentile	24.52	25.24	24.86	
51-75th percentile	26.52	26.1	26.32	
76-100th percentile	27.63	27.4	27.52	
Primary payer				
Medicare/Medicaid	90.74	94.17	92.37	<0.001
Private insurance	6.39	4.85	5.66	
Self-pay/others	2.78	0.92	1.89	
Admission type				
Emergency/urgent	21.96	22.86	22.39	0.01
Elective	78.04	77.14	77.61	
Hospital-level characteristics				
Hospital bed size				
Small	4.17	4.16	4.17	0.07
Medium	13.64	14.33	13.96	
Large	82.19	81.51	81.87	
Hospital teaching status				
Non-teaching	9.1	9.04	9.07	0.80
Teaching	90.9	90.96	90.93	
Admission day				
Weekdays	94.13	94.51	94.31	0.057
Weekend	5.87	5.49	5.69	

The bold items are the major variables which has sub-variables.

minimal and we are not sure if this is clinically important. Nonetheless, there are several reasons for this: 1) In previous studies, women were deemed to be frailer than men by heart teams.[11] Poor frailty is significantly associated with morbidity and mortality.[17] This study did not include frailty score as we do not control for variables. 2) In line with previously published articles, more women underwent transapical approach which is associated with worse outcomes as compared with transfemoral approach.[11,18] Typically, patients undergoing transapical TAVR are sicker and they have complex peripheral vascular disease which was not captured in this study.[4] 3) Need for blood transfusion was significantly higher in women than in men. Smaller body surface area, smaller peripheral arteries in women, and sheath to femoral artery ratio more than 1 in small peripheral vessels may contribute to it.[11,19] Previous studies demonstrated higher 30-day vascular complications and major bleeding in women undergoing TAVR.[16,20] Postprocedure blood transfusion was an independent predictor of readmission of patients with heart failure who underwent TAVR in previous studies.[14,21]

Heart failure on presentation significantly predicted readmissions rates in men and in women, prevalence of which was slightly higher in women on index admission. These patients have heart failure partly due to pressure-overload—induced left-sided cardiac hypertrophy.[22] However, pulmonary hypertension—developed secondary to severe aortic stenosis could play a role in progression of heart failure even after TAVR.[23] NYHA class III/IV is independently associated with 1-year mortality as well.[24] Presence of kidney disease was associated with higher readmission rates, which was demonstrated in multiple previous studies.[14,15] We recommend a nephrology consultation, limited use of contrast agent, and elimination of nephrotoxic agents to reduce readmissions. Atrial fibrillation and permanent pacemaker were another significant predictor for readmission in both genders. Atrial fibrillation is shown to be an independent predictor to increase morbidity and mortality.[14,21,25] Atrial fibrillation can contribute to myocardial remodeling and fibrosis which can accelerate ventricular aging and ultimately readmissions.[26] Chronic lung disease in men was shown to be an independent predictor and diabetes in

Table 2
Predictors of readmissions for transcatheter aortic valve replacement: Stratified by gender.

Variables	Men				Women			
	Odds ratio	Lower limit	Upper limit	*p* value	Odds ratio	Lower limit	Upper limit	*p* value
Age	0.99	0.99	1.00	0.51	0.99	0.98	0.99	0.04
Obesity	0.81	0.70	0.93	0.004	0.77	0.68	0.87	<0.001
Heart failure	3.44	3.01	3.93	<0.001	3.65	3.15	4.22	<0.001
Hypertension	0.78	0.69	0.87	<0.001	0.85	0.75	0.95	0.005
Diabetes mellitus	1.06	0.95	1.20	0.29	1.19	1.08	1.31	<0.001
Smoking	0.94	0.85	1.04	0.25	0.94	0.83	1.07	0.35
Dyslipidemia	0.75	0.68	0.82	<0.001	0.85	0.78	0.93	<0.001
History of coronary artery disease	0.89	0.80	0.98	0.023	0.97	0.88	1.06	0.51
Prior myocardial infarction	0.87	0.77	0.97	0.015	1.06	0.89	1.26	0.50
Prior percutaneous coronary intervention	1.10	0.97	1.24	0.13	1.09	0.95	1.26	0.22
Prior coronary artery bypass grafting	0.96	0.87	1.07	0.49	0.97	0.81	1.15	0.72
Atrial fibrillation	1.17	1.07	1.29	<0.001	1.36	1.23	1.50	<0.001
Prior permanent pacemaker	1.39	1.24	1.57	<0.001	1.32	1.16	1.49	<0.001
Prior implantable cardioverter defibrillator	1.20	0.98	1.48	0.08	1.00	0.72	1.40	0.99
Renal failure	1.41	1.29	1.55	<0.001	1.26	1.13	1.40	<0.001
Chronic liver disease	1.14	0.88	1.46	0.32	1.13	0.77	1.65	0.52
Chronic lung disease	1.24	1.13	1.36	<0.001	1.08	0.98	1.20	0.11
Procedural details								
Coronary angiography	0.62	0.55	0.70	<0.001	0.55	0.48	0.63	<0.001
Percutaneous coronary intervention	1.00	0.76	1.32	0.98	0.81	0.62	1.07	0.13
Mechanical circulatory support	0.78	0.55	1.11	0.17	0.87	0.54	1.340	0.56
Blood transfusion	1.31	1.16	1.48	<0.001	1.14	1.15	1.17	<0.001
Transfemoral approach vs. transapical approach	0.62	0.53	0.71	<0.001	0.57	0.49	0.66	<0.001
Median household income category for patient's zip code								
0-25th percentile	Reference	Reference	Reference		Reference	Reference	Reference	
26-50th percentile	0.96	0.82	1.13	0.64	0.96	0.82	1.12	0.59
51-75th percentile	1.03	0.88	1.21	0.68	0.90	0.77	1.05	0.17
76-100th percentile	1.00	0.86	1.18	0.97	0.97	0.83	1.14	0.76
Primary payer								
Medicare/Medicaid	Reference	Reference	Reference		Reference	Reference	Reference	
Private insurance	0.79	0.66	0.96	0.015	0.83	0.63	1.09	0.17
Self-pay/others	0.53	0.39	0.73	<0.001	0.88	0.60	1.28	0.51
Hospital-level characteristics								
Hospital bed size								
Small	Reference	Reference	Reference		Reference	Reference	Reference	
Medium	0.80	0.60	1.05	0.11	0.75	0.58	0.98	0.033
Large	0.61	0.47	0.79	<0.001	0.65	0.52	0.82	<0.001
Hospital teaching status								
Nonteaching	Reference	Reference	Reference		Reference	Reference	Reference	
Teaching	0.47	0.40	0.56	<0.001	0.51	0.43	0.61	<0.001

women was shown to be an independent predictor in this study, and the reason for this difference is largely unknown. Chronic lung disease and chronic kidney disease have shown to be independent predictors of poor outcomes in previous studies.[4,27] As mentioned previously, nontransfemoral approach has been associated with higher readmissions.[4,14] Postprocedure blood transfusion in both genders predicted readmission as demonstrated in multiple previous studies.[14,24] Readmission rates were lower in male patients with private insurance when compared with Medicare/Medicaid.

Table 3
Adjusted outcomes for transcatheter aortic valve replacement.

Outcomes	Odds ratio	Lower limit	Upper limit	*p* value
30 days readmission				
Men	Reference	Reference	Reference	Reference
Women	1.09	1.01	1.19	<0.001
Disposition				
Home				
Men	Reference	Reference	Reference	Reference
Women	0.62	0.58	0.67	<0.001
Long-/short-term facility				
Men	Reference	Reference	Reference	Reference
Women	1.61	1.51	1.72	<0.001
Length of stay during index hospitalization >5 days				
Men	Reference	Reference	Reference	Reference
Women	1.61	1.50	1.72	<0.001

Finally, readmission rates were lower in men as well as women who were admitted to the teaching and large-bed hospital.

To improve 30-day readmission rates, a multidisciplinary approach may help based on the comorbidity present on admission which can predict short- and long-term readmission rates as shown in this study and previous studies.[11,14,24] In addition, we propose performing this procedures at higher volume centers as they tend to have better outcomes and lower readmissions rates.[28] Early postdischarge follow-up for high-risk men and women can reduce readmission rates. More prospective studies are needed demonstrating long-term readmission incidence and etiology in these patients to confirm these results. Better understanding of predictors may help reducing readmission rates associated with TAVR in the future.

There are several limitations which might affect the results of this study. First, this is a retrospective study using NRD which may have coding errors, and readmission to a hospital in another state was not tracked. Second, we do not have information on the severity or frailty as we do not have Society of Thoracic Surgeons score or Kansas City Cardiomyopathy Questionnaire (KCCQ12), valve type, or medical therapy after discharge. Third, no information is available on the type of valve which can impact outcomes and readmissions.[29] Fourth, we do not have information on longitudinal outcomes; however, previous study demonstrated better 1-year survival rates in women as compared with men.[11,16]

This might be associated with less baseline comorbidities on presentation which is demonstrated in our study. Fifth, we have included data up to 2015 which mainly utilized first-generation valves with larger sheath size. This might be one of the reasons for higher complications as this is almost obsolete in 2019. Nonetheless, this is the all-comers, largest till-date study demonstrating sex-specific differences in patients undergoing TAVR.

In conclusion, women undergoing TAVR have slightly higher 30-day all-cause readmission rates. These results indicate that women require slightly more attention compared to men to prevent 30-day readmission rates. In addition, risk stratification for men and women based on predictors will help identify high-risk men and women for readmissions.

Conflicts of interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.09.004.

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