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ORIGINAL RESEARCH

Sex Differences in the Utilization and Outcomes of Cardiac Valve Replacement Surgery for Infective Endocarditis: Insights From the National Inpatient Sample

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BACKGROUND: The data on the differential impact of sex on the utilization and outcomes of valve replacement surgery for infective endocarditis are limited to single-center and small sample size patient population.

METHODS AND RESULTS: We utilized the National Inpatient Sample database to identify patients with a discharge diagnosis of infective endocarditis from 2004 to 2015 to assess differences in the characteristics and clinical outcomes of patients hospitalized with infective endocarditis stratified by sex. We also evaluated trends in utilization of cardiac valve replacement and individual valve replacement surgeries in women versus men over a 12-year period, and compared in-hospital mortality after surgical treatment in women versus men. A total of 81 942 patients were hospitalized with a primary diagnosis of infective endocarditis from January 2004 to September 2015, of whom 44.31% were women. Women were less likely to undergo overall cardiac valve replacement (6.92% versus 12.12%), aortic valve replacement (3.32% versus 8.46%), mitral valve replacement (4.60% versus 5.57%), and combined aortic and mitral valve replacement (0.85% versus 1.81%) but had similar in-hospital mortality rates. From 2004 to 2015, the overall rates of cardiac valve replacement increased from 11.76% to 13.96% in men and 6.34% to 9.26% in women and in-hospital mortality declined in both men and women. Among the patients undergoing valve replacement surgery, in-hospital mortality was higher in women (9.94% versus 6.99%, $P<0.001$).

CONCLUSIONS: Despite increased utilization of valve surgery for infective endocarditis in both men and women and improving trends in mortality, we showed that there exists a treatment bias with underutilization of valve surgeries for infective endocarditis in women and demonstrated that in-hospital mortality was higher in women undergoing valve surgery in comparison to men.

Key Words: infective endocarditis ■ sex differences ■ underutilization ■ valve replacement

Infective endocarditis (IE) is a lethal and potentially devastating complication of heart valve disease and its incidence has increased from 9.3 per 100 000 population in 1998 to 15 per 100 000 in 2011.[1] Early valve replacement surgery can potentially be lifesaving in a selected group of patients with IE.[2,3] Surgical intervention within 5 to 7 days of clinical presentation should be considered in patients with new-onset heart failure, prosthetic valve endocarditis, tissue invasion and destruction, persistent bacteremia, presence of large mobile vegetations, and for the prevention of recurrent embolization.[2]

Sex-related differences in the incidence, clinical presentation, treatment, and outcomes for various cardiovascular pathologies have been studied extensively. These differences may be attributed to a

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CLINICAL PERSPECTIVE

What Is New?

- Female sex was independently associated with decreased likelihood of valve replacement for infective endocarditis.
- Among the patients undergoing valve replacement surgery, female sex was associated with significantly increased mortality.

What Are the Clinical Implications?

- Treatment bias may account for underutilization of valve surgery in women, which in turn has an adverse impact on the overall outcome.
- More women hospitalized with infective endocarditis should be offered early surgical intervention.

Nonstandard Abbreviations and Acronyms

AVR	aortic valve replacement
AVR+MVR	combined aortic and mitral valve replacement
IE	infective endocarditis
MVR	mitral valve replacement
NIS	National Inpatient Sample

variety of factors including variable risk factors/comorbidities, treatment biases, or inherent physiologic differences. Women are less likely to receive surgical intervention including coronary artery bypass graft,[4] aortic or mitral valve replacement (MVR) than men,[5–7] and when they do, they have worse postoperative outcomes. IE has been shown to be more frequent in men than women, and the presence of estrogen has been proposed to be a protective factor against endothelial damage.[8,9] The data on the differential impact of sex on the utilization and outcomes of valve replacement surgery for IE is, however, limited to a single-center and small sample size patient population.[10–12]

To assess this gap, we utilized a large national database to (1) evaluate differences in the characteristics and clinical outcomes of patients hospitalized with IE stratified by sex from 2004 to 2015, (2) assess trends in utilization of cardiac valve replacement and individual valve replacement surgeries (aortic valve replacement [AVR], mitral valve replacement [MVR], combined aortic and mitral valve replacement [AVR+MVR]) in women versus men over a 12-year period, and (3) analyze in-hospital mortality after cardiac valve replacement in women versus men in the setting of IE.

METHODS

The authors declare that all supporting data are available within the article (and its online supplementary files).

Study Data

We used the Agency for Healthcare Research and Quality's National Inpatient Sample (NIS) database of hospitalized patients in the United States to derive patient-relevant information between January 2004 and September 2015. The NIS is the largest publicly available all-payer administrative claims–based database and contains information about patient discharges from ≈1000 nonfederal hospitals in 45 states. Briefly, the NIS is a random 20% sample of all inpatient hospitalizations in the United States each year. Unweighted, it contains data from more than 7 million hospital stays each year; and weighted, it estimates more than 35 million hospitalizations nationally. Discharges are weighted based on the sampling scheme to permit inferences for a nationally representative population. The Institutional Review Board at Cleveland Clinic exempted the study from board approval and waived the requirement for informed consent because the NIS is a publicly available deidentified database.

Study Population

We used the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 4210, 4211, 4219, 11281, 3642, 9884, 11504, 11514, 11594, 42490, 42491, and 42499 to identify all individuals with the principal diagnosis of IE. We then excluded discharges with missing data on age, sex, and in-hospital death.

Study End Points

The primary end point of the study was cardiac valve replacement in patients hospitalized with IE. The secondary end points were individual valve surgeries (AVR, MVR, AVR+MVR, mitral valve repair, tricuspid valve replacement, and tricuspid valve repair), in-hospital mortality, acute stroke, length of stay, and hospitalization charges.

Statistical Analysis

Outcome analyses were performed using the actual unweighted sample available in the NIS, whereas trend analysis was performed utilizing the national estimate.[13] Continuous variables are described as medians and interquartile ranges. Categorical variables are described as percentages. To compare the baseline characteristics, Mann–Whitney test/Wilcoxon rank sum test were used for continuous variables, and Pearson χ^2 tests were used for categorical variables. Temporal

Table 1. Baseline Patient Characteristics Stratified by Sex for Infective Endocarditis Hospitalizations From 2004 to 2015

Characteristics	Men (N=45 640)	Women (N=36 302)	*P* value
Age, mean (SD), y	59.85 (17.85)	62.58 (19.62)	<0.001
Elective admission	15.17%	15.93%	0.003
Organisms/microbiology			
Staphylococcus aureus endocarditis	27.92%	26.04%	<0.001
Streptococcus endocarditis	27.66%	17.99%	<0.001
Gram-negative endocarditis	7.69%	4.84%	<0.001
Enterococcus endocarditis	4.03%	3.18%	<0.001
Fungus endocarditis	0.82%	0.67%	0.02
Unknown organism	19.6%	28.2%	<0.001
Risk factors and comorbidities			
Drug abuse	19.73%	15.54%	<0.001
Congenital heart disease	5.22%	3.16%	<0.001
Hepatitis C	12.69%	11.39%	<0.001
Chronic rheumatic heart disease	8.83%	9.16%	0.099
Infection of cardiac device/implant (prosthetic valve endocarditis)	9.02%	5.01%	<0.001
Prior valve replacement	7.00%	5.32%	<0.001
Prior PCI	2.58%	1.94%	<0.001
Prior CABG	6.73%	3.68%	<0.001
Congestive heart failure	32.75%	32.09%	0.046
Cardiac arrhythmias	34.26%	31.84%	<0.001
Atrial fibrillation	21.13%	20.40%	0.009
Coronary artery disease	23.05%	18.61%	<0.001
Liver cirrhosis	3.75%	2.34%	<0.001
Coagulopathy	11.85%	9.55%	<0.001
Diabetes controlled	16.48%	18.12%	<0.001
Diabetes uncontrolled	5.58%	5.62%	0.91
Hypertension controlled	29.27%	33.51%	<0.001
Hypertension uncontrolled	18.55%	17.90%	0.018
Peripheral vascular disease	6.46%	5.64%	<0.001
Smoking	6.16%	3.97%	<0.001
Solid tumor without metastasis	2.91%	2.41%	<0.001
Metastatic cancer	1.29%	1.28%	0.98
Malnutrition disorder	7.47%	7.47%	0.99
Cardiogenic shock	1.72%	1.08%	<0.001
Myocardial infarction	3.95%	3.50%	0.005
Mechanical ventilation	3.64%	3.36%	0.035
Blood transfusion	17.67%	17.62%	0.86
Demographics			
Race/ethnicity			
White	74.05%	73.50%	<0.001*
Black	12.72%	14.60%	
Hispanic	8.09%	6.81%	
Hospital bed size			
Small	13.98%	15.39%	<0.001
Medium	23.21%	24.56%	
Large	62.80%	60.05%	

(*Continued*)

Table 1. Continued

Characteristics	Men (N=45 640)	Women (N=36 302)	*P* value
Hospital region			
Northeast	22.90%	21.68%	<0.001
Midwest	20.21%	21.23%	
South	38.76%	41.30%	
West	18.12%	15.76%	

CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.
**P* value applies to all three races.

trends in overall cardiac valve replacement, AVR, MVR, AVR+MVR, in-hospital mortality, and length of stay were examined and were further stratified by sex. Temporal trends over time for cardiac valve replacement, AVR, MVR, AVR+MVR, and in-hospital mortality were assessed using Cochrane Armitage trend test, whereas length of stay trend was assessed by multivariable linear regression using log-transformed length of stay as the dependent variable and year as a continuous variable.

The outcomes including the utilization of cardiac valve replacement, in-hospital mortality, and stroke were evaluated using the multivariable logistic regression, whereas the length of hospital stay was analyzed using multivariable negative binomial regression. Multivariable regression analysis was used to adjust for baseline differences between men and women by adjusting for univariate predictors of examined outcomes ($P<0.05$). The following variables were included in the multivariable regression adjustment model: age, elective admission, organisms (*Staphylococcus aureus* endocarditis, *Streptococcus* endocarditis, gram-negative endocarditis, *Enterococcus* endocarditis, fungal endocarditis, and unknown organism), comorbidities (drug abuse, congenital heart disease, hepatitis C, infection of cardiac device/implant, prior valve replacement, prior percutaneous coronary intervention, prior coronary artery bypass graft, congestive heart failure, cardiac arrhythmias, atrial fibrillation, liver cirrhosis, coagulopathy, diabetes, hypertension, peripheral vascular disease, smoking, solid tumor without metastasis, cardiogenic shock, myocardial infarction, acute renal failure, and mechanical ventilation), race/ethnicity and hospital characteristics (hospital bed size, and region). Odds ratio and 95% CI were used to report logistic regression, whereas incidence rate ratios and 95% CI were used for negative binomial regression. Further adjustments were made using the Bonferroni correction method to account for multiple comparisons. All statistical tests were 2-sided, and a *P* value of <0.05 was considered to be statistically significant. Statistical analyses were performed with SPSS software (version 25.0; IBM Corp, Armonk, NY) and R version 4.0.3.

RESULTS

A total of 81 942 (weighted national estimates: 405 386) hospitalizations were identified with a primary diagnosis of IE from 2004 to 2015, of which 36 302 (44.31%) were female.

Baseline Characteristics

Baseline characteristics for hospitalizations with IE stratified by sex are shown in Table 1. Men were younger

Table 2. In-Hospital Outcomes Stratified by Sex for Infective Endocarditis Hospitalizations From 2004 to 2015

In-hospital outcomes	Men (N=45 640)	Women (N=36 302)	*P* value
Cardiac valve replacement	12.12%	6.92%	<0.001
Aortic valve replacement	8.46%	3.32%	<0.001
Mitral valve replacement	5.57%	4.60%	<0.001
AVR+MVR	1.81%	0.85%	<0.001
Mitral valve repair	0.25%	0.31%	0.772
Tricuspid valve replacement	0.32%	0.36%	0.990
Tricuspid valve repair	0.63%	0.65%	0.990
In-hospital mortality	6.36%	6.09%	0.990
Acute stroke	7.47%	7.06%	0.314
Length of stay, mean (SD), d	11.13 (12.12)	10.16 (10.78)	<0.001
Total charges, mean (SD), $	88 409 (121 179.3)	71 196 (118 723.2)	<0.001

AVR+MVR indicates combined aortic and mitral valve replacement.

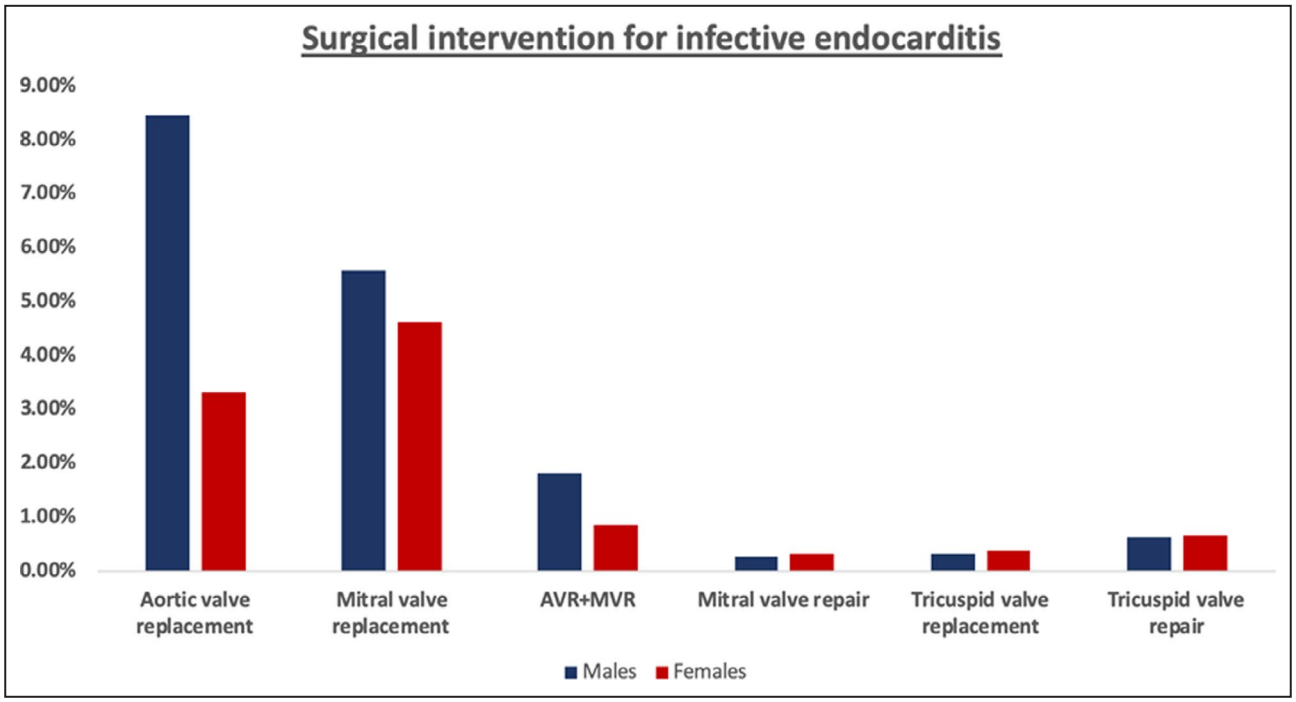

Figure 1. Surgical intervention for patients hospitalized with infective endocarditis stratified by sex.
AVR+MVR indicates combined aortic and mitral valve replacement.

(59.85 [17.85] versus 62.58 [19.62] years) and had increased prevalence of risk factors and comorbidities as compared with women. Men had higher rates of drug abuse, congenital heart disease, hepatitis C, history of prior procedures/interventions including valve replacement, percutaneous coronary intervention, coronary artery bypass graft, congestive heart failure, cardiac arrhythmias, coronary artery disease, liver cirrhosis, coagulopathy, peripheral vascular disease, smoking, uncontrolled hypertension, and solid tumors. Also, there was a higher incidence of infected cardiac device or implant (prosthetic valve endocarditis) (9.02% versus 5.01%, $P<0.001$), myocardial infarction (3.95% versus 3.50%, $P=0.005$), cardiogenic shock (1.72% versus 1.08%, $P<0.001$), and need for mechanical ventilation (3.64% versus 3.36%, $P=0.035$) among men.

Table 3. Unadjusted and Adjusted Association Between Sex and Likelihood of Undergoing Valve Replacement, In-Hospital Mortality, and Stroke

Variables	Unadjusted association	*P* value	Adjusted association	*P* value
Cardiac valve replacement	0.540 (0.514–0.568)	<0.001	0.614 (0.578–0.652)	<0.001
Aortic valve replacement	0.371 (0.347–0.397)	<0.001	0.422 (0.390–0.456)	<0.001
Mitral valve replacement	0.818 (0.768–0.871)	<0.001	0.963 (0.894–1.036)	0.314
AVR+MVR	0.473 (0.415–0.539)	<0.001	0.559 (0.481–0.648)	<0.001
Mitral valve repair	1.280 (0.987–1.660)	0.062		
Tricuspid valve replacement	1.163 (0.919–1.470)	0.208		
Tricuspid valve repair	1.052 (0.885–1.248)	0.563		
In-hospital mortality	0.958 (0.905–1.015)	0.143		
Acute stroke	0.942 (0.893–0.993)	0.027	0.909 (0.856–0.966)	0.002

Adjusted for the following variables: age, elective admission, *Staphylococcus aureus* endocarditis, *Streptococcus* endocarditis, Gram-negative endocarditis, *Enterococcus* endocarditis, fungal endocarditis, unknown organism, drug abuse, congenital heart disease, hepatitis C, infection of cardiac device/implant (prosthetic valve endocarditis), prior valve replacement, prior PCI, prior CABG, congestive heart failure, cardiac arrhythmias, atrial fibrillation, liver cirrhosis, coagulopathy, diabetes controlled, hypertension controlled, hypertension uncontrolled, peripheral vascular disease, smoking, solid tumor without metastasis, cardiogenic shock, myocardial infarction, acute renal failure, mechanical ventilation, race, hospital bed size, and region. AVR+MVR indicates combined aortic and mitral valve replacement; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.

Table 4. Baseline Patient Characteristics and In-Hospital Outcomes Stratified by Sex for Infective Endocarditis Hospitalizations Undergoing Cardiac Valve Replacement Surgery From 2004 to 2015

	Men (N=5529)	Women (N=2518)	*P* value
Characteristics (%)			
Mean age, y	52.83	52.97	0.38
Elective admission	19.15%	19.91%	0.44
Organisms			
Staphylococcus endocarditis	22.96%	27.14%	<0.001
Streptococcus endocarditis	34.90%	29.65%	<0.001
Gram-negative endocarditis	8.86%	7.19%	0.013
Enterococcus endocarditis	3.94%	2.65%	0.005
Fungus endocarditis	1.20%	1.18%	>0.99
Risk factors and comorbidities			
Drug abuse	20.62%	18.75%	0.056
Congenital heart disease	13.07%	10.57%	<0.001
Hepatitis C	10.82%	13.04%	0.005
Chronic rheumatic heart disease	16.30%	19.91%	<0.001
Infection of cardiac device/implant (prosthetic valve endocarditis)	12.16%	10.57%	0.040
Prior valve replacement	1.86%	1.47%	0.246
Prior PCI	1.13%	0.96%	0.526
Prior CABG	1.94%	1.02%	0.004
Congestive heart failure	45.93%	46.85%	0.455
Cardiac arrhythmias	43.12%	39.60%	0.003
Atrial fibrillation	22.73%	18.76%	<0.001
Coronary artery disease	18.16%	14.12%	<0.001
Liver cirrhosis	2.46%	1.28%	0.001
Coagulopathy	18.63%	22.11%	0.003
Diabetes controlled	10.93%	11.28%	0.665
Diabetes uncontrolled	3.23%	3.89%	0.153
Hypertension controlled	21.77%	19.84%	0.054
Hypertension uncontrolled	15.58%	18.06%	0.006
Peripheral vascular disease	5.83%	4.60%	0.027
Smoking	5.52%	3.39%	<0.001
Solid tumor without metastasis	1.12%	0.86%	0.370
Metastatic cancer	0.42%	0.44%	>0.99
Malnutrition disorder	11.54%	14.70%	<0.001
Cardiogenic shock	8.78%	8.37%	0.590
Myocardial infarction	6.39%	5.53%	0.147
Mechanical ventilation	10.20%	14.41%	<0.001
Blood transfusion	38.99%	41.13%	0.071
Demographics			
Race/ethnicity			
White	72.25%	70.73%	0.002*
Black	13.13%	16.45%	
Hispanic	8.99%	6.98%	
Hospital bed size			
Small	5.56%	5.38%	0.576
Medium	17.64%	18.56%	
Large	76.60%	76.02%	

(*Continued*)

Table 4. Continued

	Men (N=5529)	Women (N=2518)	*P* value
Hospital region			
Northeast	22.82%	21.97%	0.005
Midwest	21.34%	18.57%	
South	36.46%	39.60%	
West	19.36%	16.57%	
In-hospital outcomes			
Mortality	6.99%	9.94%	<0.001
Stroke	13.34%	14.22%	0.307
Length of stay, mean (SD), d	20.87 (15.84)	23.21 (17.49)	<0.001

CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.
**P* value applies to all three races.

Study Outcomes

Women were less likely to undergo overall cardiac valve replacement (6.92% versus 12.12%, *P*<0.001), AVR, MVR, and AVR+MVR. There were no significant difference in the rates of mitral valve repair, tricuspid valve surgery, in-hospital stroke, and mortality rates. In addition, the mean length of stay (11.13 [12.12] versus 10.16 [10.78] days, *P*<0.001) and hospitalization charges (88 409 [121 179.3] $ versus 71 196 [118 723.2] $, *P*<0.001) were higher in men (Table 2).

Utilization of Valve Replacement Surgery Stratified by Sex

Figure 1 shows the utilization of individual valve surgeries by sex (AVR: 8.46% versus 3.32%, *P*<0.001, MVR: 5.57% versus 4.60%, *P*<0.001, AVR+MVR: 1.81% versus 0.85%, *P*<0.001, mitral valve repair: 0.25% versus 0.31%, *P*=0.07, tricuspid valve replacement: 0.32% versus 0.36%, *P*=0.23, tricuspid valve repair: 0.63% versus 0.65%, *P*=0.59).

Table 3 shows the relationship between sex and likelihood of undergoing valve replacement surgery, in-hospital mortality, and stroke. After adjustment with multivariable logistic regression analysis, female sex remained associated with less likelihood of overall cardiac valve replacement (0.614 [95% CI, 0.578–0.652], *P*<0.001), AVR (0.422 [95% CI, 0.390–0.456], *P*<0.001), and AVR+MVR (0.559 [95% CI, 0.481–0.648], *P*<0.001); however, there was no difference in the mitral valve replacement rates (0.963 [95% CI, 0.894–1.036], *P*=0.314).

In addition, there were no significant differences in mortality; however, female sex was associated with decreased stroke rates. Furthermore, after multivariable negative binomial regression adjustment, female sex was not associated with the length of stay (incidence rate ratio, 1.001 [95% CI, 0.986–1.015], *P*=0.766) in patients hospitalized with IE.

Characteristics and Outcomes of Hospitalizations Undergoing Valve Replacement Surgery

Table 4 shows the baseline characteristics and in-hospital outcomes of IE admissions who underwent cardiac valve replacement surgery stratified by sex. Among hospitalized patients who underwent valve replacement surgery, women were more likely to have *Staphylococcal* bacteremia, chronic rheumatic heart disease, coagulopathy, uncontrolled hypertension, malnutrition disorder, and require mechanical ventilation during the hospitalization. Of the admissions undergoing cardiac valve replacement, 11.67% (12.16% in men and 10.57% in women, *P*=0.040) had an infection of cardiac device/implant (prosthetic valve endocarditis). The overall in-hospital mortality rates were significantly higher in women who underwent valve replacement surgery in comparison to men (9.94% versus 6.99%, *P*<0.001).

Table 5 shows the significant predictors of in-hospital mortality in those undergoing valve replacement surgery. We note that after adjustment with multivariable logistic regression analysis, female sex remained independently associated with increased in-hospital mortality (1.312 [95% CI, 1.092–1.575], *P*=0.003). Other factors associated with increased mortality in patients undergoing surgery included fungal endocarditis, infected cardiac device/implant, presence of coagulopathy, uncontrolled hypertension, liver cirrhosis, myocardial infarction, need for mechanical ventilation, and combined aortic and mitral valve replacement.

In addition, among the patients undergoing valve replacement surgery, there were no significant differences in the adjusted length of stay based on sex (incidence rate ratio, 0.998 [0.978–1.083], *P*=0.832).

Table 5. Predictors of In-Hospital Mortality in Patients Undergoing Cardiac Valve Replacement Surgery

Characteristics (%)	Unadjusted	*P* value	Adjusted	*P* value
Mean age, y	1.027 (1.021–1.032)	<0.001	1.027 (1.020–1.034)	<0.001
Female sex	1.470 (1.243–1.735)	<0.001	1.312 (1.092–1.575)	0.003
Elective admission	0.537 (0.416–0.683)	<0.001	0.649 (0.497–0.836)	<0.001
Organisms/microbiology				
Staphylococcus endocarditis	1.399 (1.170–1.667)	<0.001	1.102 (0.901–1.345)	0.341
Streptococcus endocarditis	0.491 (0.401–0.597)	<0.001	0.685 (0.538–0.865)	0.001
Gram-negative endocarditis	0.411 (0.264–0.608)	<0.001	0.635 (0.389–0.996)	0.057
Enterococcus endocarditis	1.122 (0.721–1.671)	0.589		
Fungus endocarditis	2.358 (1.323–3.947)	<0.001	2.352 (1.265–4.140)	0.004
Risk factors and comorbidities				
Drug abuse	0.328 (0.242–0.434)	<0.001	0.499 (0.361–0.676)	<0.001
Congenital heart disease	0.513 (0.368–0.696)	<0.001	0.753 (0.530–1.044)	0.100
Hepatitis C	1.000 (0.770–1.281)	0.998		
Chronic rheumatic heart disease	0.809 (0.641–1.010)	0.066		
Infection of cardiac device/implant (prosthetic valve endocarditis)	1.987 (1.607–2.441)	<0.001	1.840 (1.457–2.309)	<0.001
Prior valve replacement	0.991 (0.502–1.759)	0.976		
Prior PCI	0.412 (0.101–1.104)	0.132		
Prior CABG	1.048 (0.531–1.865)	0.881		
Congestive heart failure	1.192 (1.014–1.402)	0.033	1.033 (0.865–1.233)	0.720
Cardiac arrhythmias	0.825 (0.698–0.974)	0.024	0.661 (0.550–0.793)	<0.001
Atrial fibrillation	0.887 (0.721–1.083)	0.246		
Coronary artery disease	0.775 (0.610–0.974)	0.032	0.784 (0.605–1.007)	0.061
Liver cirrhosis	2.385 (1.546–3.551)	<0.001	2.886 (1.810–4.466)	<0.001
Coagulopathy	1.928 (1.611–2.300)	<0.001	1.594 (1.313–1.930)	<0.001
Diabetes controlled	0.699 (0.516–0.927)	0.016	0.918 (0.665–1.245)	0.593
Diabetes uncontrolled	0.955 (0.590–1.465)	0.843		
Hypertension controlled	0.338 (0.253–0.443)	<0.001	0.464 (0.340–0.622)	<0.001
Hypertension uncontrolled	1.956 (1.618–2.354)	<0.001	1.349 (1.093–1.658)	0.004
Peripheral vascular disease	1.182 (0.833–1.633)	0.328		
Smoking	0.265 (0.126–0.485)	<0.001	0.406 (0.191–0.755)	0.009
Solid tumor without metastasis	0.578 (0.176–1.394)	0.286		
Metastatic cancer	2.011 (0.682–4.781)	0.150		
Malnutrition disorder	1.164 (0.916–1.462)	0.203		
Cardiogenic shock	1.900 (1.493–2.395)	<0.001	1.125 (0.862–1.455)	0.376
Myocardial infarction	2.562 (1.981–3.277)	<0.001		
Mechanical ventilation	4.076 (3.383–4.898)	<0.001	2.764 (2.252–3.383)	<0.001
Blood transfusion	0.726 (0.611–0.861)	<0.001		
Race	1.022 (0.944–1.102)	0.576		
Hospital bed size	0.971 (0.845–1.123)	0.690		
Hospital region	0.990 (0.915–1.071)	0.799		
Aortic valve replacement	1.002 (0.848–1.186)	0.985		
Mitral valve replacement	1.511 (1.283–1.782)	<0.001	1.044 (0.851–1.279)	0.678
AVR+MVR	1.926 (1.578–2.339)	<0.001	1.844 (1.446–2.347)	<0.001
Mitral valve repair	0.755 (0.417–1.256)	0.313		
Tricuspid valve replacement	0.655 (0.370–1.069)	0.114		
Tricuspid valve repair	1.283 (0.806–1.945)	0.265		
Acute stroke	1.752 (1.425–2.141)	<0.001	1.486 (1.184–1.853)	<0.001

Adjusted for variables with $P<0.05$ on univariate analysis. AVR+MVR indicates combined aortic and mitral valve replacement; CABG, coronary artery bypass graft; and PCI, percutaneous coronary intervention.

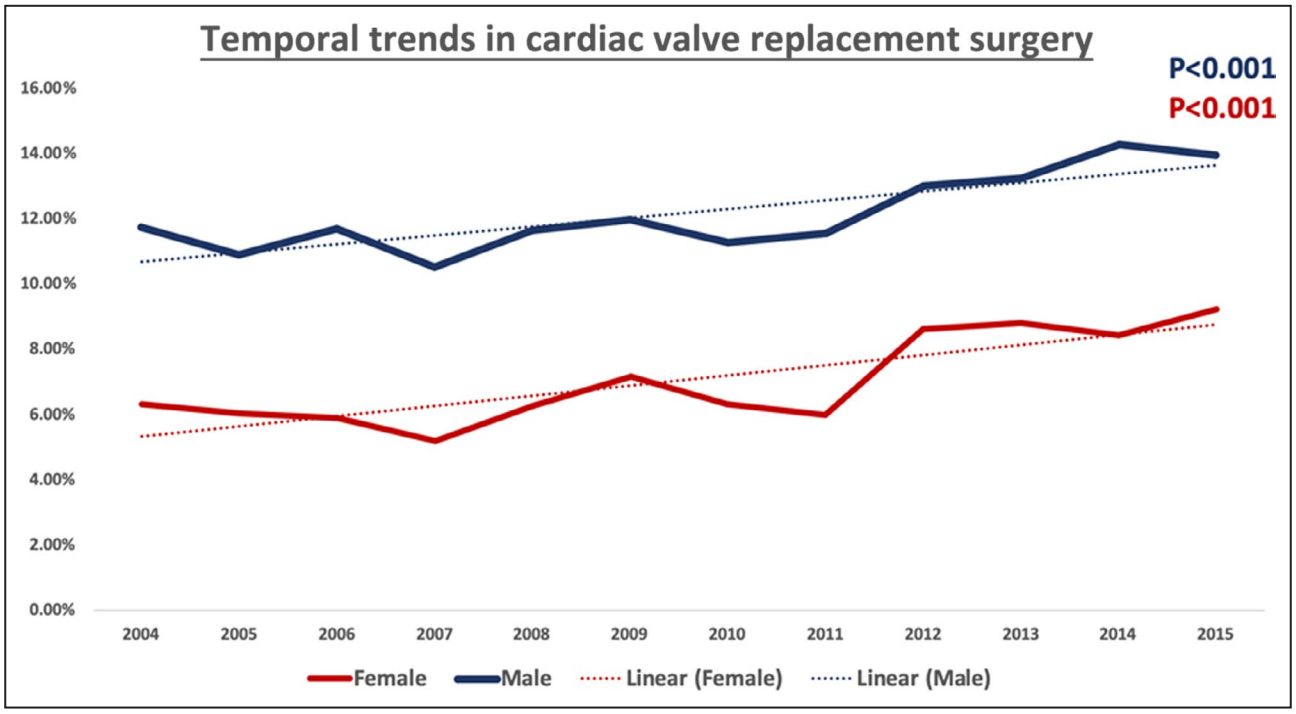

Figure 2. Temporal trends in overall cardiac valve replacement by sex for patients hospitalized with infective endocarditis from 2004 to 2015.

Temporal Trends in Utilization of Valve Replacement Surgery and In-Hospital Mortality

There was an increase in the utilization of valve replacement surgeries for IE during the study period (Figures 2 and 3, Tables S1 through S4). The overall rates of cardiac valve replacement in the setting of endocarditis increased from 11.76% to 13.96% (P<0.001) in men and 6.34% to 9.26% (P<0.001) in women; AVR increased from 7.88% to 9.55% (P<0.001) in men and 2.87% to 4.11% (P<0.001) in women; MVR increased from 5.47% to 6.45% (P<0.001) in men and 4.25% to 5.92% (P<0.001) in women; combined AVR+MVR increased from 1.54% to 1.94% (P<0.001) in men and 0.68% to 1.02% (P<0.001) in women. However, there continued to exist a significant sex difference with decreased utilization of surgery in women. A significant decline in in-hospital mortality rates for both of the sexes (men, 8.24%–4.90% and women, 7.85%–4.99%) was observed during the study period. Among the hospitalizations undergoing valve replacement surgery, the difference in in-hospital mortality rates between the 2 groups declined over the time period, with a greater reduction of mortality in women (15.36%–7.50%, P<0.001) in comparison to men (9.46%–5.84%, P<0.001) (Figure 4) (Tables S5 and S6). The trends in the length of stay are shown in Figure S1. The predictors of undergoing valve replacement surgery are shown in Table S7.

DISCUSSION

We conducted an analysis exploring the clinical outcomes in the setting of IE and utilization rates of surgery stratified by sex. The salient finding is that female sex was associated with a decreased likelihood of undergoing overall cardiac valve replacement. However, the lower rates of surgery in women did not translate into higher observed in-hospital mortality. Women selected to undergo surgery had significantly higher in-hospital mortality rates than their male counterparts. The overall rates of surgery for endocarditis rose during the period of observation but there continued to exist a gap between the 2 sexes. Finally, although in-hospital mortality rates for IE surgery decreased during the study period, women continued to experience higher in-hospital mortality.

In line with previous studies,[10,12] IE was more common in men. Women hospitalized with IE were older; however, men had more comorbid conditions including history of surgical interventions (valve replacement, coronary artery bypass graft, and percutaneous coronary intervention) and concurrent prosthetic valve endocarditis, liver cirrhosis, coagulopathy, uncontrolled hypertension, and coronary artery disease, but diabetes was more common in women.[14]

Our study shows that men were almost twice as likely to undergo valve replacement surgery (12.12% versus 6.92%). In our NIS cohort, women were older than men

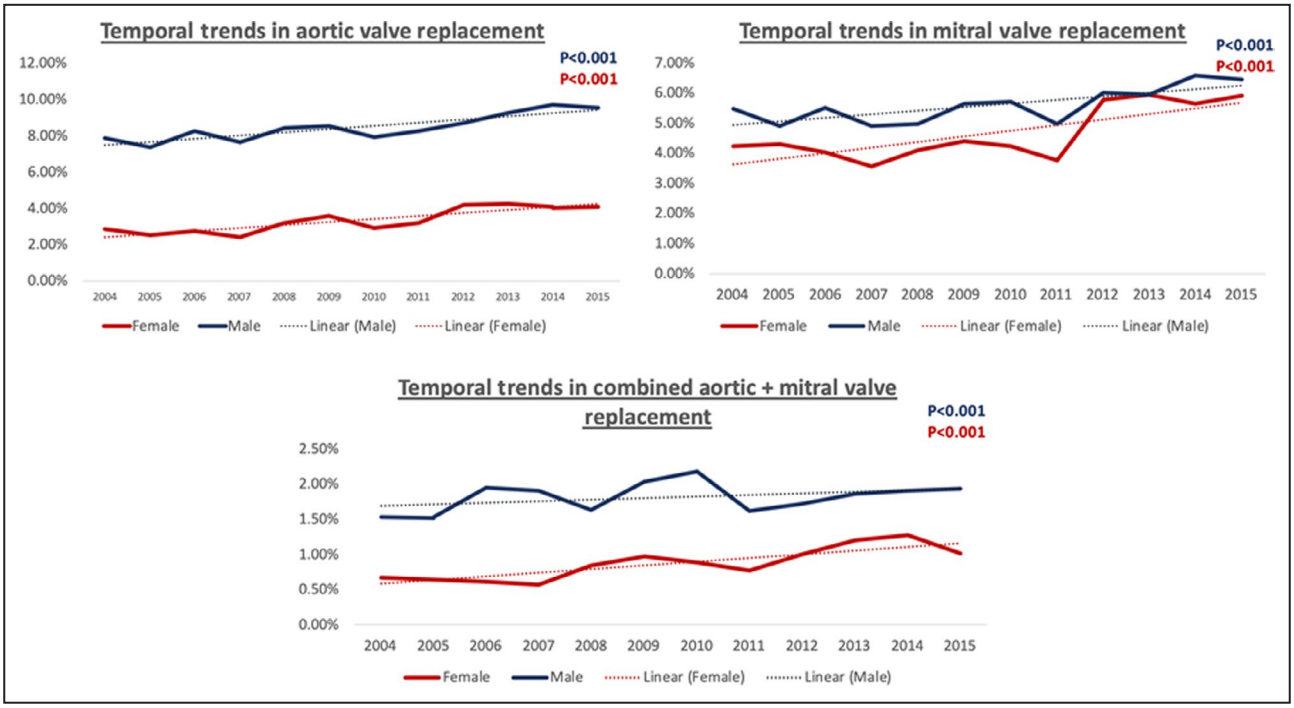

Figure 3. Temporal trends in individual valve replacement surgeries (aortic valve replacement, mitral valve replacement, and aortic+mitral valve replacement) by sex for patients hospitalized with infective endocarditis from 2004 to 2015.

and since age is 1 of the predominant factors that influence the decision of surgery, one might attribute the decreased likelihood of surgical intervention in women to that. In addition, the potential indications of surgical intervention that could be identified from the nationwide cohort including congestive heart failure, *S aureus* endocarditis, fungal endocarditis, cardiogenic shock, prosthetic valve endocarditis, and others were more common in men, and that could be attributed as the reason for increased rates of utilization of surgery for IE in men. However, in our study, we demonstrated that after multivariable adjustment of all the mentioned variables, female sex was independently associated with a decreased likelihood of utilization of cardiac valve replacement surgery with a significant margin (adjusted odds ratio of 0.61 [95% CI, 0.58–0.65]), suggesting the presence of treatment bias. The existence of implicit bias among cardiology physicians has been reported in previous studies.[15] It is possible that the decision to operate more on men might have been influenced partly by the fact that IE was more often found to affect the aortic valve in men, which is associated with increased paravalvular complications, thus necessitating surgical intervention.[2] There were significant differences in overall cardiac valve replacement, AVR, and AVR+MVR; however, after adjustment there was no difference in MVR rates between men and women. This could be because the mitral valve is affected more often in women and because of increased prevalence of rheumatic heart disease in women.[16]

Some prior studies have shown female sex to be an independent predictor of mortality after valve replacement surgery whereas others have not. Using the Society of Thoracic Surgeons database between 1994 and 2003, Rankin et al[17] demonstrated female sex to be an independent predictor of operative mortality. Similar results with sex disparities were shown by Chaker et al[18] among the patients undergoing surgical AVR using the NIS database. In contrast, Saxena et al[19] showed no difference in the incidence of early and late mortality between men and women after surgical aortic valve replacement. However, there are only small, single-center studies that have evaluated the sex differences in operative outcomes for patients with IE.[10,12,20] In our large nationwide study, women undergoing valve replacement surgery had about 1.5 times (9.94% versus 6.99%) higher likelihood of in-hospital mortality in comparison to men. Early surgery for IE within 48 hours has been shown to have a favorable outcome with reduction in composite end point of death and embolic events.[3] The most common cause of mortality in patients with IE is because of congestive heart failure. Decreased survival in women undergoing valve replacement surgery could be secondary to late presentation and delayed surgical intervention, which increases the risk of having congestive heart failure. The smaller body size and anatomy of women further makes surgical interventions technically more difficult and frequently require the use of smaller prosthetic

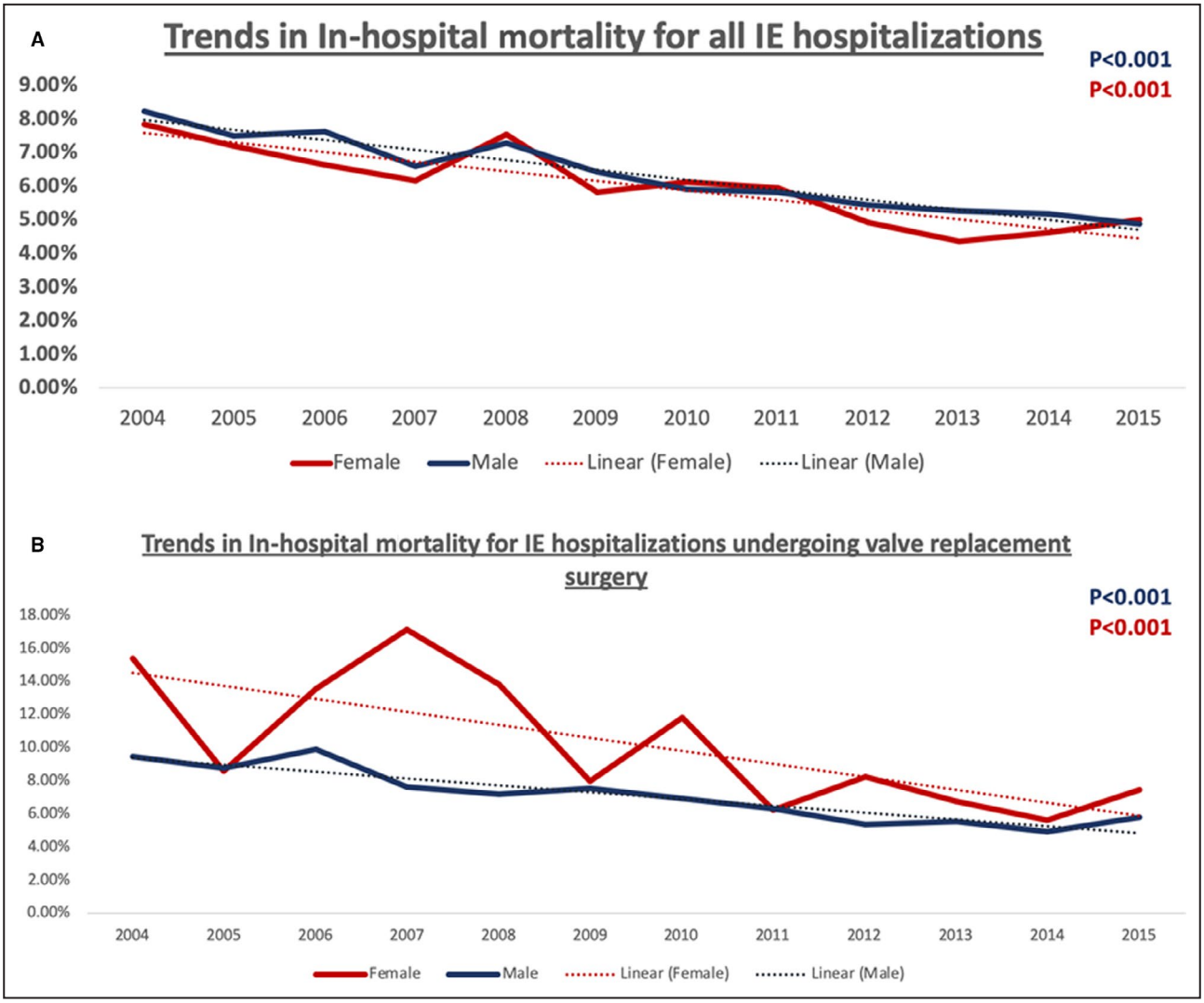

Figure 4. Temporal trends in in-hospital mortality stratified by sex for (A) all patients hospitalized with infective endocarditis from 2004 to 2015, and (B) patients with infective endocarditis who underwent cardiac valve replacement surgery from 2004 to 2015. IE indicates infective endocarditis.

valves, which is associated with worse postoperative outcomes.[21,22]

Treatment bias may account for underutilization of valve surgery in women, which in turn has an adverse impact on the overall outcome. In line with previous investigations, more women hospitalized with IE should be offered early surgical intervention. It is encouraging to find that the rates of valve replacement surgeries have increased from 2004 to 2015 and more importantly, the gap in the in-hospital mortality rates between men and women has narrowed over the mentioned time period.

Study Limitations

Our study has several limitations. First, the NIS is an administrative database that collects data for billing purposes and is subject to erroneous coding. However, we used *ICD-9 CM* code for IE that has been well-validated and shown to have high predictive value. Second, the NIS provides detailed data on in-hospital mortality, morbidity, and cost but lacks the echocardiographic, laboratory, and outcomes data beyond hospital discharge. Vegetation size has been shown to be an independent predictor of early mortality. Third, the non-procedural codes are not associated with specific dates in this administrative database, thus introducing the uncertainties about the timing of certain morbidities. For example, *ICD* codes are unable to distinguish whether acute stroke, blood transfusion, mechanical ventilation, or cardiogenic shock were the reason or a complication of valve replacement surgery. Fourth, we could not determine the indication of valve replacement surgery from

the database. Fifth, in our study we did not use the *ICD* code for methicillin-resistant *S aureus*. This is because the *ICD* coding for methicillin-resistant *S aureus* was introduced in 2008 and we looked at the time period from 2004 to 2015. Sixth, using the *ICD-9* codes, we are unable to determine with certainty which valve is affected with IE. Thus, for example, in hospitalizations undergoing combined aortic and mitral valve replacement, it is possible that the mitral valve is infected and the aortic valve is replaced secondary to other reasons. Also, we are unable to ascertain the presence or severity of valvular dysfunction secondary to IE. Seventh, the potential for unmeasured confounders may bias the outcome results; however, we believe that our rigorous multivariable adjustment for the variables adequately addressed the selection bias.

CONCLUSIONS

Despite increased utilization of valve surgery for IE in both men and women and improving trends in mortality, in this large, multicenter, population-based observational study, we showed that there exists a possible treatment bias with underutilization of valve surgeries for IE in women, and observed that in-hospital mortality was higher in women undergoing valve surgery in comparison to men.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S7
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Year wise utilization of cardiac valve replacement surgery in hospitalizations stratified by sex.

Year	Cardiac valve replacement in females	No cardiac valve replacement in females	Cardiac valve replacement in males	No cardiac valve replacement in males
2004	963	14205	2072	15547
2005	858	13367	1967	16089
2006	960	15209	2182	16428
2007	802	14604	1860	15758
2008	1098	16294	2339	17724
2009	1201	15489	2382	17520
2010	972	14334	2226	17484
2011	1000	15621	2401	18387
2012	1210	12764	2455	16365
2013	1250	12925	2620	17115
2014	1155	12495	2765	16585
2015 Sep	1000	9815	2150	13265

Table S2. Year wise utilization of aortic valve replacement in hospitalizations stratified by sex.

Year	Aortic valve replacement in females	No aortic valve replacement in females	Aortic valve replacement in males	No aortic valve replacement in males
2004	437	14732	1388	16231
2005	358	13868	1329	16727
2006	445	15724	1538	17071
2007	370	15036	1350	16270
2008	562	16830	1698	18365
2009	605	16085	1699	18203
2010	454	14852	1564	18147
2011	533	16088	1722	19067
2012	590	13385	1645	17175
2013	605	13570	1830	17905
2014	560	13090	1880	17470
2015 Sep	445	10370	1470	13945

Table S3. Year wise utilization of mitral valve replacement in hospitalizations stratified by sex.

Year	Mitral valve replacement in females	No mitral valve replacement in females	Mitral valve replacement in males	No mitral valve replacement in males
2004	644	14524	965	16654
2005	614	13611	888	17169
2006	654	15514	1028	17582
2007	548	14858	867	16750
2008	717	16675	998	19065
2009	737	15953	1125	18777
2010	647	14658	1129	18581
2011	627	15994	1037	19751
2012	810	13164	1135	17685
2013	845	13329	1175	18560
2014	770	12880	1275	18075
2015 Sep	640	10175	995	14420

Table S4. Year wise utilization of combined aortic + mitral valve replacement in hospitalizations stratified by sex.

Year	Combined AVR + MVR in females	No combined AVR+ MVR in females	Combined AVR + MVR in males	No combined AVR+ MVR in males
2004	103	15064	272	17347
2005	93	14132	274	17783
2006	100	16068	365	18244
2007	89	15317	226	17281
2008	145	17246	329	19734
2009	164	16525	406	19496
2010	137	15169	433	19277
2011	128	16493	337	20451
2012	140	13834	325	18495
2013	170	14004	370	19364
2014	175	13475	370	18980
2015 Sep	110	10705	300	15115

Table S5. Year wise Mortality in hospitalizations undergoing valve replacement surgery stratified by sex.

Year	Mortality in hospitalizations undergoing valve replacement surgery, females	No mortality in hospitalizations undergoing valve replacement surgery, females	Mortality in hospitalizations undergoing valve replacement surgery, males	No mortality in hospitalizations undergoing valve replacement surgery, males
2004	148	815	194	1873
2005	72	771	171	1786
2006	130	825	215	1966
2007	135	655	141	1719
2008	152	945	169	2171
2009	95	1100	179	2203
2010	115	857	154	2058
2011	62	934	152	2235
2012	100	1110	130	2315
2013	85	1165	145	2475
2014	65	1090	135	2625
2015 Sep	75	925	125	2020

Table S6. Year wise mortality in infective endocarditis hospitalizations stratified by sex.

Year	Mortality in IE hospitalizations, females	No mortality in IE hospitalizations, females	Mortality in IE hospitalizations, males	No mortality in IE hospitalizations, males
2004	1189	13970	1450	16130
2005	1024	13150	1353	16683
2006	1073	15063	1421	17179
2007	947	1443	1159	16446
2008	1311	16062	1460	18578
2009	972	15713	1281	18613
2010	935	14366	1166	18495
2011	990	15582	1207	19535
2012	690	13280	1020	17780
2013	620	13544	1040	18670
2014	630	13005	1005	18330
2015 Sep	540	10270	755	14645

Table S7. Predictors of cardiac valve replacement surgery in patients hospitalized with infective endocarditis from 2004-2015.

Characteristics (%)	**Unadjusted**	**p-value**	**Adjusted**	**p-value**
Mean age, years	0.978 (0.977-9.979)	<0.001	0.973 (0.971-0.974)	<0.001
Elective admission	1.354 (1.276-1.436)	<0.001	2.009 (1.866-2.164)	<0.001
Female	**0.540 (0.514-0.568)**	**<0.001**	**0.586 (0.552-0.622)**	**<0.001**
Organisms/Microbiology				
Staphylococcus endocarditis	0.858 (0.813-0.905)	<0.001	0.755 (0.704-0.810)	<0.001
Streptococcus endocarditis	1.737 (1.653-1.825)	<0.001	1.583 (1.472-1.701)	<0.001
Gram negative endocarditis	1.370 (1.258-1.490)	<0.001	0.996 (0.888-1.116)	0.941
Enterococcus endocarditis	0.964 (0.849-1.089)	0.56		
Fungus endocarditis	1.708 (1.366-2.114)	<0.001	1.279 (0.969-1.669)	0.076
Risk factors and co-morbidities				
Drug abuse	1.132 (1.068-1.199)	<0.001	0.955 (0.885-1.030)	0.232
Congenital heart disease	3.758 (3.474-4.061)	<0.001	2.046 (1.846-2.265)	<0.001
Hepatitis C	0.934 (0.868-1.003)	0.061		
Chronic rheumatic heart disease	2.405 (2.257-2.562)	<0.001	1.986 (1.834-2.150)	<0.001
Infection of cardiac device/implant	1.805 (1.676-1.943)	<0.001	1.548 (1.409-1.698)	<0.001
Prior valve replacement	0.244 (0.205-0.288)	<0.001	0.303 (0.250-0.363)	<0.001
Prior PCI	0.438 (0.350-0.540)	<0.001	0.622 (0.480-0.795)	<0.001
Prior CABG	0.274 (0.229-0.325)	<0.001	0.376 (0.306-0.458)	<0.001
Congestive heart failure	1.917 (1.830-2.009)	<0.001	1.917 (1.803-2.037)	<0.001
Cardiac arrhythmias	1.524 (1.454-1.597)	<0.001	1.805 (1.697-1.919)	<0.001
Atrial fibrillation	1.046 (0.989-1.106)	0.114		
Coronary artery disease	0.741 (0.697-0.787)	<0.001	1.264 (1.163-1.372)	<0.001
Liver cirrhosis	0.636 (0.542-0.744)	<0.001	0.500 (0.413-0.600)	<0.001

Coagulopathy	2.245 (2.114-2.383)	<0.001	1.609 (1.490-1.736)	<0.001
DM controlled	0.569 (0.530-0.612)	<0.001	0.807 (0.739-0.881)	<0.001
DM uncontrolled	0.575 (0.507-0.650)	<0.001	0.672 (0.579-0.776)	<0.001
HTN controlled	0.565 (0.534-0.597)	<0.001	0.975 (0.907-1.049)	0.500
HTN uncontrolled	0.864 (0.812-0.919)	<0.001	0.816 (0.751-0.885)	<0.001
Peripheral vascular disease	0.878 (0.793-0.970)	0.011	1.215 (1.075-1.370)	0.001
Smoking	0.925 (0.830-1.027)	0.150		
Solid tumor without metastasis	0.358 (0.285-0.442)	<0.001	0.525 (0.400-0.678)	<0.001
Metastatic cancer	0.301 (0.210-0.417)	<0.001	0.368 (0.235-0.553)	<0.001
Malnutrition disorder	1.926 (1.792-2.069)	<0.001	1.513 (1.381-1.656)	<0.001
Cardiogenic shock	14.242 (12.659-16.035)	<0.001	7.811 (6.738-9.060)	<0.001
Myocardial infarction	1.800 (1.628-1.986)	<0.001	1.247 (1.096-1.415)	<0.001
Mechanical ventilation	4.773 (4.397-5.179)	<0.001	2.502 (2.248-2.783)	<0.001
Blood transfusion	3.655 (3.480-3.838)	<0.001	3.336 (3.141-3.544)	<0.001
Acute stroke	2.228 (2.077-2.389)	<0.001	2.143 (1.959-2.341)	<0.001
Race	1.053 (1.030-1.077)	<0.001	0.990 (0.964-1.016)	0.456
Hospital bed size	1.836 (1.765-1.911)	<0.001	1.747 (1.667-1.832)	<0.001
Hospital region	1.001 (0.979-1.024)	0.903		

Figure S1. Trends in the mean length of stay for patients hospitalized with infective endocarditis stratified by sex.