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Research paper

Sex differences in health resource utilization, costs and mortality during hospitalization for infective endocarditis in the United States

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Background: Few studies have assessed the association between sex and outcomes among patients with infective endocarditis. The aim of the study was to better understand the association between biologic sex, clinical outcomes and surgical treatment patterns among a contemporary cohort of patients admitted to hospital with infective endocarditis.
Methods: We used the National Inpatient Sample dataset from the Health Care Utilization Project to identify adult patients admitted for infective endocarditis between January and December 2016. We compared outcomes between men and women including inpatient hospital mortality, direct hospital costs, length of stay, and inpatient surgical treatment patterns. Multivariable analyses were performed with adjustment for age, socioeconomic status, and comorbidity burden.
Results: Among 18,702 patients with infective endocarditis, there were 8730 (46.7%) women and 1753 (8.4%) in-hospital deaths. In multivariable analysis, female sex was associated with a trend toward lower in-hospital mortality (adjusted odds ratio (OR) 0.90; 95% confidence interval (CI) 0.80 to 1.01, $p = 0.06$). Additionally, female sex was associated with significantly shorter hospital length of stay (−0.5 days; 95% CI −0.88 to −0.12, $p = 0.009$) and lower hospital costs (−$3035; 95% CI −$4277 to −$1792; $p < 0.001$). Notably, women were less likely to undergo surgical intervention (adjusted OR 0.59; 95% CI 0.52 to 0.67, $p < 0.001$).
Conclusions: In a contemporary, nationally representative cohort of patients admitted for IE in the United States, there were sex-specific differences in management and in-hospital outcomes. Possible sex-based bias in treatment patterns and access to inpatient surgical intervention for infective endocarditis warrants further study.

1. Introduction

Over the past decade, there have been increasing efforts to better understand sex-specific differences in cardiovascular disease [1]. Yet, there is still relatively scarce data in the literature exploring the impact of sex on management and outcomes in patients with infective endocarditis (IE). The few available prior studies have yielded conflicting data on outcomes following IE, such as whether female sex confers an adverse or protective prognosis following hospitalization for IE [2–4]. Women tend to have a higher prevalence of comorbidities such as chronic kidney disease and diabetes, which would confer an adverse prognosis in IE [1,5]. Additionally, lower rates of surgical management of IE have been observed among women, which may also contribute to worse outcomes [2].

The objective of this study was to explore the association of sex and outcomes following hospitalization for IE. Specifically, we sought to assess sex differences in baseline demographics, health resource utilization, costs of care and inpatient mortality in a large national cohort of patients admitted for IE within the United States (US).

2. Methods

This was a retrospective cohort study of hospital discharge data from the Health Care Utilization Project (HCUP) Nationwide Inpatient Sample

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(NIS) dataset, which is a stratified 20% sample of all inpatient discharges from acute care community hospitals in the US and weighted to be nationally representative of all US hospitalizations. Sponsored by the Agency of Healthcare Research and Quality, the HCUP-NIS is the largest publicly available all-payer inpatient care database in the US with data on more than seven million hospital stays per year [6].

We identified hospital admissions among patients 18 years of age or older for IE between January 1, 2016 and December 30, 2016, using the International Classification of Diseases 10th revision (ICD-10-CM) codes: A32.82, A39.51, A52.03, B33.21, B37.6, I01.1, I38, I39, I33.0, or I33.9. The use of ICD-10-CM codes for identifying cases of IE have been previously validated with 90% sensitivity and 100% specificity [7]. Sex (i.e. male or female assigned at birth) was the primary independent variable of interest. Admissions with missing sex entries were excluded from analysis (n = 7).

We also assessed the effects of socioeconomic status (defined by the quartiles of median household income of the ZIP code in which the patient resided: first quartile as the lowest income), race (White/Black/Hispanic/Asian or Pacific Islander/Native American/other), hospital setting and comorbidities on the outcomes of interest. A comorbidity count classifier (0/1–2/3+) of all comorbidities was computed using the HCUP Beta Elixhauser Comorbidity Algorithm (Agency for Healthcare Research and Quality; Rockville, MD) for ICD-10-CM [8,9]. The primary outcome was in-hospital mortality. Secondary outcomes included inpatient cardiac surgical intervention for management of endocarditis, hospital length of stay, and hospitalization costs in US dollars. Surgical management was defined by the ICD-10-PCS codes for intervention on any of the aortic, mitral, pulmonary or tricuspid valves: 02R.F07Z, 02R.F08Z, 02R.F0JZ, 02R.F0KZ, 02R.G07Z, 02R.G08Z, 02R.G0JZ, 02R.G0KZ, 02R.H07Z, 02R.H08Z, 02R.H0JZ, 02R.H0KZ, 02R.J07Z, 02R.J08Z, 02R.J0JZ, 02R.J0KZ, 02Q.F0ZZ, 02Q.G0ZZ, 02Q.H0ZZ, 02Q.J0ZZ, 027.H04Z, 027.H0DZ, 02N.H0ZZ, 027.J04Z, 027.J0DZ, 027.J0ZZ, 02N.J0ZZ, 027.F04Z, 027.F0DZ, 027.F0ZZ, 02N.F0ZZ, 027.G04Z, 027.G0DZ, 027.G0ZZ, and 02N.G0ZZ.

Continuous variables are presented as means and standard deviations, while categorical variables are expressed as frequencies and percentages. The Student *t*-test and Chi-squared test were used to compare differences in continuous variables and categorical variables, respectively. The relationship between sex and outcomes was assessed using logistic regression for in hospital death and surgical intervention, and linear regression for length of stay and costs. The multivariable model included age, geographic location, socioeconomic status and comorbidities in addition to sex and defined a priori. Two-sided p-values <0.05 were considered significant. All analyses were conducted with R 3.6.1.

Data access for this project was approved by the Agency for Healthcare Quality and Research (AHQR). This study was conducted in accordance with the Declaration of Helsinki. Informed consent was waived as this study is based on secondary analysis of deidentified publicly available administrative data through AHQR.

3. Results

18,702 patients hospitalized with IE were included in the analysis and women comprised 47% of the cohort. Baseline characteristics stratified by sex are shown in Table 1. The mean age of the overall cohort was 60.1 years. Men were slightly younger than women (mean age 60.8 years versus 61.4 years, p = 0.04). Women with a hospitalization for IE had lower median household income quartile and a greater proportion of women were on Medicare/Medicaid. There was a higher number of total Elixhauser comorbidities among women. Specifically, previously known valvular disease, fluid and electrolyte disorders, chronic pulmonary disease, heart failure, drug use, and hypothyroidism were more prevalent in women than men. However, there was a greater proportion of hypertension, renal failure, diabetes, and liver disease among men ($p < 0.001$ for all comparisons between men and women).

There were 1753 in-hospital deaths (8.4%) in the overall cohort. The risk of death was higher among men (9.0%) compared to women (7.7%, p = 0.002) (Table 2). Female sex was associated with a lower odds of in-hospital mortality (unadjusted odds ratio (OR) 0.85; 95% confidence interval (CI) 0.76 to 0.94, p = 0.002), although this association was no longer statistically significant after multivariable adjustment for age, socioeconomic status and comorbidities (adjusted OR 0.90; 95% CI 0.80, 1.01, p = 0.06).

Female sex was associated with mean shorter hospital length of stay (LOS) (−0.9 days; 95% CI −1.3 to −0.5, $p < 0.001$) and lower

Table 1
Baseline characteristics of endocarditis hospitalizations stratified by sex.

Characteristic	Male	Female
N	9972	8730
Mean years, years (SD)	60.8 (18.3)	61.4 (21.0)
Ethnicity, no. (%)		
White	6959 (69.8%)	6127 (70.2%)
Black	1172 (11.8%)	1186 (13.6%)
Hispanic	924 (9.3%)	644 (7.4%)
Asian/Pacific Islander	170 (1.7%)	151 (1.7%)
Native American	63 (0.6%)	79 (0.9%)
Other	237 (2.4%)	190 (2.2%)
Median income		
First quartile (lowest)	3199 (32.1%)	3033 (34.7%)
Second quartile	2481 (24.9%)	2298 (26.3%)
Third quartile	2157 (21.6%)	1779 (20.4%)
Fourth quartile (highest)	1889 (18.9%)	1452 (16.6%)
Primary expected payer		
Medicare	5337 (53.5%)	5096 (58.4%)
Medicaid	1856 (18.6%)	1849 (21.2%)
Private insurance	1911 (19.2%)	1186 (13.6%)
Self-pay	507 (5.1%)	399 (4.6%)
No charge	59 (0.6%)	37 (0.4%)
Other	287 (2.9%)	151 (1.7%)
Hospital location/teaching status		
Rural	752 (7.5%)	884 (10.1%)
Urban non-teaching	2358 (23.6%)	2161 (24.8%)
Urban teaching	6862 (68.8%)	5685 (65.1%)
Hospital region		
Northeast	1945 (19.5%)	1575 (18.0%)
Midwest	2021 (20.3%)	1835 (21.0%)
South	4054 (40.7%)	3886 (44.5%)
West	1952 (19.6%)	1434 (16.4%)
Elixhauser comorbidities		
0	153 (1.5%)	92 (1.1%)
1–2	1675 (16.8%)	1285 (14.7%)
≥3	8144 (81.7%)	7353 (84.2%)
Hypertension	5941 (59.6%)	5062 (58.0%)
Fluid and electrolyte disorders	4638 (46.5%)	4119 (47.2%)
Valvular disease	4044 (40.6%)	4168 (47.7%)
Renal failure	3070 (30.8%)	2391 (27.4%)
Diabetes with complications	1393 (14.0%)	1190 (13.6%)
Diabetes without complications	1697 (17.0%)	1390 (15.9%)
Liver disease	1081 (10.8%)	734 (8.4%)
Chronic pulmonary disease	2104 (21.1%)	2145 (24.6%)
Congestive heart failure	2247 (22.5%)	2012 (23.0%)
Drug abuse	1548 (15.5%)	1569 (18.0%)
Hypothyroidism	855 (8.6%)	1568 (18.0%)

NB. All characteristics differed significantly between men and women to a p value of <0.001, except age (p = 0.04).

Table 2
Primary and secondary outcomes stratified by sex.

Outcome	Male (N = 9972)	Female (N = 8730)	P value
In hospital death, no (%)	898 (9.0)	675 (7.7)	0.002
Inpatient surgical intervention, no (%)	919 (9.2)	452 (5.2)	<0.001
Mean length of stay, days ± SD	11.7 ± 14.2	10.8 ± 13.0	<0.001
Hospital costs, 2016 USD			
Mean ± sd	\$33,299 ± \$46,802	\$27,851 ± \$40,573	<0.001
Median (interquartile range)	\$17,815 (\$9032, \$17,815)	\$14,628 (\$7505, \$30,235)	

Table 3
Models assessing the association between female sex and outcomes.

Outcome	Univariate Model	p value	Multivariable Model	p value
In hospital death	0.85 (0.76, 0.94)	0.002	0.9 (0.8, 1.01)	0.06
Inpatient surgical intervention	0.54 (0.48, 0.6)	< 0.001	0.59 (0.52, 0.67)	< 0.001
Mean length of stay	− 0.88 (− 1.27, − 0.49)	< 0.001	− 0.5 (− 0.88, − 0.12)	0.009
Hospital costs	− 5448 (− 6712, − 4183)	< 0.001	− 3035 (− 4277, − 1792)	< 0.001

hospitalization costs (−$5448; 95% CI −$6712 to −$4183, $p < 0.001$) in unadjusted analyses. These associations persisted in adjusted analyses: mean length of stay (−0.5 days; 95% CI 0.9 to 0.1; $p = 0.009$) and costs (−$3035; 95% CI −$4277 to −$1792, $p < 0.001$) among women. Women underwent inpatient cardiac surgery for IE less frequently than men (5.2% vs. 9.2%, $p < 0.001$). This finding persisted after multivariable adjustment (OR 0.6; 95% 0.52 to 0.67, $p < 0.001$) (Table 3).

4. Discussion

Our study explored the association between sex and inpatient mortality, health resource utilization and direct health costs in the current largest nationally-representative cohort of hospitalized patients with IE. Our findings suggest an association between sex and in-hospital outcomes among patients hospitalized for IE. Specifically, female sex was associated with a shorter hospital length of stay and lower in-patient hospital costs. There was a trend toward lower in-hospital mortality and women were less likely to undergo inpatient surgical intervention for IE, even after adjustment for age, socioeconomic status and comorbidities.

Although sex-specific differences in IE costs and health resource utilization have not been fully explored in the literature, a handful of prior studies have assessed the relationship between sex and mortality associated with IE. For example, Sambola et al. followed a cohort of 271 patients with IE enrolled between 2000 and 2008 [10]. The authors found that all-cause mortality was significantly higher in women than men, both in-hospital and at 1-year. Interestingly, when surgery was indicated, women were less likely to undergo the procedure, and after adjustment for surgical intervention, female sex was no longer predictive of in-hospital or one-year mortality [10]. Similarly, in a single-center cohort of prospectively enrolled patients with IE, female sex was associated with higher in-patient mortality than men [2]. However, after adjustment for the higher number comorbidities among women (such as diabetes and renal failure), female sex was not associated with in-hospital mortality. These results are also consistent with a retrospective cohort of 621 patients with left-sided IE enrolled between 1996 and 2007 from three tertiary care centers [3]. Sevilla et al. found trend toward higher in-hospital mortality among women (35%) compared to men (28%; $p = 0.1$); however, the authors did not adjust for potentially important baseline clinical characteristics.

Our study results diverge from these findings where female sex was not associated with a higher risk of in-hospital mortality in the adjusted analyses, and there was a non-significant trend toward decreased mortality. One possible explanation may be selection bias in these smaller cohort studies where patients were solely enrolled from tertiary care centers. Sex-based differences in these mortality rates may be due to differences in management prior to tertiary hospital admission, such as delays to transfer from a non-tertiary care center, or increased severity of endocarditis warranting transfer. Our study evaluated a nationally representative cohort of patients, managed by both tertiary and non-tertiary hospitals, which may have a different risk profile than cohorts solely enrolled tertiary centers. Our results are more consistent with the findings reported from a contemporary United Kingdom population cohort using administrative data [4]. Among patients with predisposing cardiac conditions who were hospitalized for IE, there was higher unadjusted in-hospital mortality rate observed among men compared to women (Odd ratio 1.65; 95% confidence interval 1.53 to 1.77, $P < 0.001$). However, the authors did not further explore the observed sex differences in outcomes, and they did not adjust for known confounders.

Notably, our study found that women were less likely to undergo inpatient surgical intervention even after adjustment for age, comorbidities and socioeconomic status. Prior studies suggest a possible sex-based treatment bias, with less aggressive management of cardiovascular diseases in women, such as access to percutaneous coronary intervention or treatment for dyslipidemia and hypertension [10–12]. With regard to the management of endocarditis, our results complement the findings of Curlier and colleagues, who reported the outcomes of 620 patients from two French registries initiated in 1999 and 2008 [13]. Concordant with our current study, the author found that women were less likely to undergo early valve surgery for endocarditis, and had similar rates of in-hospital mortality. However, when partitioning follow-up time from valve surgery into an early (≤14 days) and late (>14 days) period, women had a 3-fold higher risk of early post-operative mortality compared to men. These differences in outcomes by sex have been observed in other surgical procedures such as coronary artery bypass grafting and valve surgery outside the setting of endocarditis [14,15]. It is unclear if these observations are due to potential sex-related differences in treatment response, or reflect disparities in the treatment pathway leading up to surgical intervention. For example, prior studies have described the association of delayed diagnosis and treatment initiation with poorer outcomes in women in the setting of acute myocardial infarction or coronary artery bypass grafting [16,17]. Nevertheless, the possible sex bias in treatment patterns requires further investigation.

The results of our study need to be interpreted in the context of several limitations including its retrospective, observational nature. Given that the cohort was derived from hospital claims data, there was no information regarding microbiology, antibiotic treatment details, the type of valvular involvement (i.e. left or right sided endocarditis), diagnostic imaging findings, or information regarding complications of IE such as perivalvular abscess. It is possible that differences in these clinical and treatment characteristics may confound our findings. Additionally, lack of follow-up beyond hospitalization limits longitudinal analysis of outcomes and assessment of the possible downstream implications of sex-based differences in referral to cardiac surgery. Notably, we did not have data regarding post-hospital disposition or management decisions where surgical therapy was deemed too high risk. Mortality in the setting of palliative management may be underestimated if patients were transferred to non-hospital facilities and palliation did not occur in the hospital admission. Finally, administrative data is prone to misclassification and missing data, and may not capture the severity of illness as accurately as traditional clinical registries [18]. Potential differences in the proportion of misclassified data between sexes may affect the results of the multivariable regression.

5. Conclusions

In a contemporary, nationally representative cohort of patients admitted for IE in the US, there were sex-specific differences were observed with regard to costs and health resource utilization. Additionally, women were less likely to undergo inpatient surgical intervention compared to men. Possible sex-based bias in long-term outcomes, treatment patterns and access to inpatient surgical intervention for infective endocarditis warrants further study.

CRediT authorship contribution statement

Derek S. Chew: Conceptualization, Methodology, Writing – original draft. **Elissa Rennert-May:** Conceptualization, Methodology, Writing – review & editing. **Shengjie Lu:** Formal analysis, Visualization. **Michael Parkins:** Methodology, Writing – review & editing. **Robert J.H. Miller:**

Methodology, Writing – review & editing. **Ranjani Somayaji:** Conceptualization, Methodology, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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