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MAJOR ARTICLE

Obesity as a Risk Factor Among Hospitalized Patients with Infective Endocarditis

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Objective. Obesity contributes to diagnostic and management challenges for many hospitalized patients. The impact of obesity on in-hospital outcomes in patients with infective endocarditis has not been studied and was the focus of this investigation.

Method. We used the 2013 and 2014 Nationwide Inpatient Sample to identify adults ≥18 years of age with a principle diagnosis of endocarditis. We divided the sample into 2 groups based on presence of absence of obesity. Multivariate linear and logistic regression analysis was used to compare in-hospital mortality, valvular replacement, length of stay (LOS), and hospitalization charges.

Results. A total of 24 494 adults 18 years and older were hospitalized with infective endocarditis, of which 2625 were classified as obese. Patients with obesity were older (mean age, 57.8 ± 0.3 vs 54.3 ± 0.6 years; $P < .01$), more likely to be female (50.1% vs 36.1%; $P < .01$), and had more comorbidities (Charlson comorbidity score ≥ 3, 50.6% vs 28.8%; $P < .01$). Multivariate regression analysis found no differences between the 2 groups for mortality or repairs or replacements for any valve. On evaluation of resource utilization, patients with obesity had longer average LOS (13.9 days; confidence interval [CI], 12.7–15.1 vs 12.4 days; CI, 12.0–12.8; $P = .016$) and higher total hospital charges (US $160 789.90; CI, $140.922.40–$180 657.50 vs US $130 627.20; CI, $123 916.70–$137 337.70; $P <.01$). After adjustment for LOS for total hospital charges, there was no observed difference $11436.26 (CI, -$6649.07–$29521.6; $P = .22$).

Conclusions. Obesity does not significantly impact in-hospital mortality or surgical valvular interventions among patients hospitalized with infective endocarditis, but obesity is associated with increased utilization of hospital resources.

Key Words: endocarditis; hospitalizations; large database; mortality; obesity.

INTRODUCTION

Infective endocarditis (IE) is a relatively uncommon yet serious infection of heart valves caused by bacteria or fungi that can lead to devastating end-organ damage and, ultimately, death if ineffectively managed [1]. Acutely ill patients presenting with IE may develop heart failure, heart block, valvular abscesses, or have persistently positive blood cultures despite management with appropriate antimicrobials. When complications such as these develop or patients deteriorate, surgical intervention with either valvular repairs or replacements may be indicated. Earlier surgical intervention for patients who do not improve with antimicrobials or develop major complications from IE have shown to improve in in-hospital mortality [2]. Diagnostic delays early in the disease course is not uncommon, because nonspecific symptoms can make the diagnosis of IE challenging [1, 3]. In particular, obesity can shroud the typical signs and symptoms, not to mention reduce the reliability of the diagnostic tests.

Obesity may lead to poor quality echocardiogram imaging [4], which may negatively impact rapid and adequate assessment of heart valves. Diagnostic delays in the setting of IE in turn may delay indicated surgical valvular interventions and increase the chances of suboptimal clinical outcomes [5]. Patients with obesity have been found to have higher mortality in the setting of fungemia [6]; obese status may translate into antibacterial dosing challenges and ineffectual management of IE [7].

Given these clinical realties, we hypothesized that patients with obesity and IE would have higher mortality, lower surgical interventions, and higher resource utilization because of greater comorbidity, diagnostic reasoning challenges, and management complexities compared with IE patients without obesity. To test this hypothesis, we compared in-hospital mortality, heart valve repairs or replacements, length of stay (LOS) and hospital charges between patients with and without obesity in the

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United States for pooled years 2013–2014 using the National Inpatient Sample (NIS) database.

METHODS

Setting

Pooled data from years 2013–2014 were assessed in the NIS database. Created by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project (HCUP), the NIS was a federal- and state-industry partnership [8]. It is the largest national all-payer inpatient care database and was designed as a stratified probability sample meant to represent all nonfederal acute-care inpatient hospitalizations in the United States. Hospitals in the NIS are stratified by the following features: hospital size, academic status, localization to rural or urban areas, and ownership. A 20% probability sample of discharges from hospitals within each stratum is collected, and information about patient demographics, diagnoses, and resource utilization are obtained. Every discharge is weighted to make the NIS nationally representative. All data are de-identified to protect the privacy of patients, physicians, and hospitals as required by data sources and the Health Insurance Portability and Accountability Act (HIPAA). Multiple admissions for a single patient are considered separate discharges. For the years of 2013 and 2014, the NIS included over 7 million discharges yearly from more than 4300 unique hospitals across 44 states in the United States [8].

Study Population

Patients were included in the study if they had a principal diagnosis of IE during the study period 2013–2014. Patients were excluded if they were younger than 18. The following International Classification of Diseases, 9th revision, Clinical Modification (ICD-9 CM) codes were used to identify eligible admissions for infective endocarditis: 421.0 (acute and subacute bacterial endocarditis); 421.1 (acute and subacute bacterial in diseases classified elsewhere); 421.9 (acute endocarditis, unspecified); 424.9 (endocarditis, valve unspecified); 093.2 (syphilitic endocarditis); 0.9884 (gonococcal endocarditis); 0.74.22 (coxsackie endocarditis); 0.3642 (meningococcal endocarditis); 391.1 (acute rheumatic endocarditis); 112.81 (candida endocarditis); 115.04 (histoplasma capsulatum endocarditis); 115.14 (histoplasma duboisii endocarditis); and 115.94 (histoplasma unspecified endocarditis).

All such admitted patients were categorized further based on the presence or absence of a secondary diagnosis of obesity. Obese patients were obtained by using the body mass index (BMI). The National Institutes of Health defines obesity as a BMI >30 kg/m^2 [9]. We used the following ICD-9 CM codes to include obese patients in the study by their BMI in kg/m^2: BMI, 30–31.9 (ICD-9, V85.30–V85.31); BMI, 32–33.9 (ICD-9, V85.32–V85.33); BMI, 34–35.9 (ICD-9, V85.34–V85.35); BMI, 36–37.9 (ICD-9, V85.36–V85.37); BMI, 38–39.9 (ICD-9, V85.38–V85.39); BMI, 40–49.9 (ICD-9, V85.41–V85.42); BMI ≥ 50 (ICD-9, V85.43–V85.45); and 278.01 (noted morbid obesity).

Study Outcomes

The primary outcome was in-hospital mortality. Secondary clinical outcomes were: (1) combined aortic valve repairs or replacements (ICD-9, 35.11, 35.22, 35.22), (2) combined mitral valve repairs or replacements (ICD-9, 35.12, 35.23, 35.24), and (3) combined tricuspid valve repairs or replacements (ICD-9, 35.14, 35.27, 35.28). Resources utilization outcomes included LOS and total hospital charges.

Patient and Hospital Characteristics

The main independent variable was obesity status. All patient and hospital demographics were collected and adjusted for in the analysis as potential confounders. Variables used for adjustment included patient level (age [in years], gender [only male and female], median household income in patients' zip code, and insurance and comorbidities measured using the Charlson comorbidity index) [8] and hospital level (size [bed count], academic status [teaching vs nonteaching], location [urban vs rural], and geographic region).

The Johns Hopkins University School of Medicine's Institutional Review Board assessed the study proposal and categorized the study as "exempt" from detailed review (https://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/guidelines/exempt_research.html; https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=&SID=83cd09e1c0f5c6937cd9d7513160fc3f&pitd=20180719&n=pt45.1.46&r=PART&ty=HTML#se45.1.46_1104.).

Statistical Analyses

The statistical software used for this study was Stata version 15.0 (Stata Corp, College Station, TX). We accounted for survey design complexity using analytic guidelines that were outlined by the HCUP and the NIS through inclusion of sampling weights, primary sampling units, and strata into the analyses [8–10]. Consequently, population estimates of proportions, means, and regression coefficients were made (*svy* commands). Standard errors were estimated using Taylor series linearization. Patient demographics, comorbidities, and hospital characteristics were compared among the groups (obese vs nonobese) using χ^2 test for categorical variables and one-way analysis of variance for continuous variables. Adjusted odds ratios (aOR) and mean differences (aMD) using multivariate logistic and linear regression analysis were established. Multivariate regression models were built by including all potential confounders that were significantly associated with outcomes on univariate analysis with a *P* value cutoff of .2. Logistic regressions were used to study the binary outcomes (mortality and valvular repairs or replacements). Linear regression analysis assessed the continuous outcomes (LOS and total hospital charges). All *P* values were 2-sided and type I error was set at .05.

RESULTS

In 2013 and 2014, there were 25 059 patients with IE were hospitalized. After removing 565 patients who were <18 years of age, the remaining sample consisted of 24 494 patients. Of these, 21 869 were not obese and 2625 were classified as obese. Compared to the nonobese patients, patients with obesity were significantly older (mean age, 57.8 ± 0.3 vs 54.3 ± 0.6 years; $P < .01$), more likely to be female (50.1% vs 36.1%; $P < .01$), and had more comorbidities (Charlson comorbidity score ≥ 3; 50.6 vs 28.8%; $P < .01$), Table 1. Patients with obesity also were less likely to be uninsured (3.7% vs 10.3%; $P < .01$) or have Medicaid insurance (16.9% vs 22.7%; $P = .01$). Aside from having a higher proportion of Hispanic patients among the obese, the racial makeup was similar between patients with and without obesity. There were no differences in annual income based on obesity status (Table 1).

In-hospital Mortality and Valvular Repairs or Replacements

The proportion of inpatient mortality between patients without and with obesity was similar: 1071 (4.9%) vs 136 (5.2%), respectively; $P = .82$. Patients without obesity had a lower proportion of aortic valve repairs or replacements: 2668 (12.2%) versus 454 (17.3%); $P < .01$. The proportion of mitral valve repairs or replacements were similar between nonobese and obese patients: 2602 (11.9%) versus 332 (12.3%); $P = .76$. The proportion of tricuspid valve repairs or replacements also was similar for patients who were obese compared with those who were not: 1328 (2.8%) versus 68 (2.6%); $P = .80$.

Using multivariate regression analyses to adjust for multiple confounders, we found no significant differences in any of the study outcomes for obese compared with nonobese patients: in-hospital mortality (odds ratio [OR], 0.85; confidence interval [CI], 0.51–1.4; $P = .52$), repairs or replacements of mitral valves (OR, 0.85; CI, 0.61–1.2; $P = .8$) tricuspid valves (OR, 0.82; CI, 0.34–1.9; $P = .66$), and aortic valves (OR, 1.3; CI, 0.98–1.8; $P = .06$) (Table 2). The proportion of obese and nonobese patients receiving tricuspid valve repairs or replacements was much less common when compared with aortic and mitral valve interventions.

Resource Utilization

Compared to nonobese patients, the mean LOS in 2013 and 2014 was longer for patients with obesity (13.9 days; CI, 12.7–15.1) than nonobese patients (12.4 days; CI, 12.0–12.8; $P = .016$). Upon adjusting for confounders, LOS remained higher in patients with obesity (adjusted mean difference, 1.4 days; CI, 0.046 days–2.7 days; $P = .04$). Average hospital charges also were higher for patients with obesity (US $160 789; CI, $140.922.40–$180 657.50) than nonobese patients (US $130 627.20; CI, $123 916.70–$137 337.70; $P < .01$).

Following adjustment for confounders, average hospital charges were higher in patients with obesity (adjusted mean difference, US $23 673.40; CI, US $2315.71–$45031.08; $P = .03$). When we adjusted for LOS as a confounder in the model for total charges, there were no significant differences in total hospital charges (US $11 436.26; CI, US -$6649.07–$29 521.60; $P = .22$).

DISCUSSION

This study evaluated in-hospital mortality valvular surgical interventions and resource utilization among patients with and without obesity admitted with IE and found no significant differences in clinical outcomes, but it did find longer LOS and hospital charges in patients with obesity. Obesity is associated with high morbidity and mortality [11], and, as obesity rates continue to soar worldwide [12], the numbers of patients IE who are obese also can be expected to rise. Between 1996 and 2009, obesity as a secondary discharge diagnosis significantly increased in hospitals throughout the United States [13]. Additionally, the heroin epidemic and its associated risk for IE worsened in 2010 and the impact continued well into 2014 [14]. Further, isolated state data has shown that hospitalizations due to endocarditis increased from 2010–2015 [15]. Our results suggest that the mortality from surgical interventions performed in the context of IE do not appear to be significantly negatively impacted by obesity. However, healthcare charges and hospital stays were both significantly adversely impacted by obesity among patients hospitalized with IE.

The findings seen in our analyses are similar to other studies that investigated the impact of obesity on in-hospital clinical and resource outcomes. However, patients with obesity in our study had higher hospital charges and higher LOS compared with those patients without obesity. The increased hospital charges in obese patients were mainly driven by increased LOS, as the difference in total charges became nonsignificant after adjusting for LOS. Abougergi et al found no difference in in-hospital mortality based on obesity status for patients who presented with nonvariceal upper gastrointestinal hemorrhage [16]. Patients with obesity in that study were found to utilize more resources and had higher hospital costs and charges as well as longer LOS. Similarly, other studies using large population databases found that patients with obesity who presented with either acute heart failure or chronic obstructive pulmonary disease exacerbations also were not found to have higher in-hospital mortality [17, 18]. Our previous study that looked at patients with diabetic foot ulcers and diabetic foot infections (DFUs/DFIs) found that mortality was similar compared with

Table 1. Demographic Data Among Patients Ages 18 Years and Older Hospitalized With Infective Endocarditis Stratified by Obesity and No Obesity From the National Inpatient Sample (2013–2014)

Characteristics	Nonobese patients (N = 21 869)	Patients with obesity (N = 2625)	*P* value
Patient			
Age (years) (mean ± SE)	54.3 ± 0.3	57.8 ± 0.6	<.01
Female, n (%)	7894 (36.1)	1315 (50.1)	<.01
Race, n (%)			
White	16 314 (74.6)	1911 (72.8)	.38
Black	2733 (12.5)	312 (11.9)	.67
Hispanic	1640 (7.5)	301 (11.5)	<.01
Asian or Pacific Islander	371 (1.7)	42 (1.6)	.78
Charlson comorbidity score, n (%)			
0	7173 (32.8)	309 (11.8)	<.01
1	5008 (22.9)	464 (17.7)	<.01
2	3345 (15.3)	519 (19.8)	.01
3 or more	6298 (28.8)	1328 (50.6)	<.01
Comorbidities			
Chronic lung disease	4002 (18.3)	658 (25.1)	<.01
Complicated diabetes mellitus	1159 (5.3)	522 (19.9)	<.01
Drug use	5817 (26.6)	278 (10.6)	<.01
History of hypertension	10 497 (48.0)	1874 (71.4)	<.01
History for valvular disease	3848 (17.6)	399 (15.2)	.68
Acute renal failure	4111 (18.8)	682 (26.0)	<.01
Acute heart failure	2186 (10.1)	525 (20.1)	<.01
History of heart block	1159 (5.3)	199 (7.6)	.05
Septic emboli	4264 (19.5)	399 (15.2)	<.01
Sepsis	2974 (13.6)	315 (12.0)	.26
Stroke	2974 (13.6)	404 (15.4)	.28
History of HIV	284 (1.3)	18 (0.7)	.19
Median income in patient's zip code, n (%)			
US $1–$38 999	6538 (29.9)	845 (32.2)	.29
$39 000–$47 999	5510 (25.2)	677 (25.8)	.76
$48 000–$62 999	4986 (22.8)	590 (22.5)	.89
$63 000 or more	4789 (21.9)	506 (19.3)	.13
Insurance, n (%)			
Medicare	9119 (41.7)	1336 (50.9)	<.01
Medicaid	4964 (22.7)	443 (16.9)	.01
Private	5489 (25.1)	742 (28.3)	.13
Uninsured	2252 (10.3)	97 (3.7)	<.01
Hospital			
Hospital bed size, n (%)			
Small	2908 (13.3)	254 (9.7)	<.01
Medium	5357 (24.5)	603 (23.0)	.42
Large	13 558 (62.0)	1764 (67.2)	.01
Hospital region, n (%)			
Northeast	5008 (22.9)	538 (20.5)	.22
Midwest	4111 (18.8)	619 (23.6)	.01
South	8638 (39.5)	1029 (39.2)	.87
West	4067 (18.6)	433 (16.5)	.24
Teaching hospital, n (%)			
Nonteaching	2252 (10.3)	312 (11.9)	.33
Teaching	19 594 (89.6)	2310 (88.0)	.33

Abbreviation: N, population size; n, number; SE, standard error.

nonobese patients although patients with obesity had a lower prevalence of amputations [19]. Further, patients with obesity and DFUs/DFIs were less likely to be discharged home after hospitalization, had longer LOS, and had more hospital charges compared with those who were not obese. Fewer surgical interventions in patients with obesity were similar to findings by Ludhwani and Wu, who studied patients with obesity with peripheral vascular disease [20].

Table 2. Odds Ratios for Hospital Outcomes in Infective Endocarditis for Patients Ages 18 Years and Older With and Without Obesity From the National Inpatient Sample (2013–2014)

Weight Status (2013–2014)	Multivariable Unadjusted Odds Ratio (95% CI)	*P* value	Multivariable Adjusted Odds Ratio (95% CI)	*P* value
Mitral Valve Repairs or Replacements				
Nonobese (ref)	1.0		1.0	
Obese	1.0 (0.79–1.3)	.34	0.85 (0.61–1.2)	.80
Aortic Valve Repairs or Replacements				
Nonobese (ref)	1.0		1.0	
Obese	1.5 (1.1–1.9)	.01	1.3 (0.98–1.8)	.06
Tricuspid Valve Repairs or Replacements				
Nonobese (ref)	1.0		1.0	
Obese	0.9 (0.5–1.6)	.81	0.82 (0.34–1.9)	.66
In-hospital mortality				
Nonobese (ref)	1.0		1.0	
Obese	1.0 (0.69–1.5)	.82	0.85(0.51–1.4)	.52

Abbreviations: CI, confidence interval; ref, reference.

Variables adjusted for confounders in multivariate analysis include age, gender, median household income, insurance and comorbidities measured using the Charlson comorbidity index, hospital bed size, teaching status, urban location, and region. A modified Charlson comorbidity index that dropped duplicate confounding variables and excluded factors unlikely to lead to mortality or valve repair or replacement as a result of infective endocarditis (such as depression) also was used. Variables included for Charlson comorbidity index were alcohol use, AIDS, anemia, rheumatoid arthritis, blood loss, chronic lung disease, coagulopathy, diabetes with and without complications, drug use, hypertension, liver disease, lymphoma, metastatic disease, electrolyte abnormalities, peripheral vascular disease, and disorders of the pulmonary circulatory system.

Obesity is an established and important risk factor for diagnostic and management barriers among hospitalized patients [21]. What is more, patients with obesity tend to have more comorbidities compared with nonobese patients [22]; these include heart failure and strokes—both of which are possible adverse outcomes or sequelae of IE. Our study affirmed that patients with obesity had a higher in-hospital prevalence of comorbidities compared with nonobese patients. Research has shown that obesity is a risk factor for surgical site and nosocomial infections following surgery [23, 24]. Prior research also established that patients with obesity and infections are generally more ill [19, 25] and have higher intensive care unit in-hospital mortality compared with normal weight individuals [26]. However, higher mortality was not observed in our population of patients with obesity.

Because *Staphylococcus aureus* is the leading pathogen in IE [27], management for both methicillin-resistant and -sensitive *S. aureus* (MRSA and MSSA, respectively) infections likely comprised a large component in our study population. Effective antibiotic prescribing with recommended medications, such as vancomycin and nafcillin, may be more complicated among obese patients given higher potentials for more dose modifications [28, 29]. Similarly, azoles used in the management of fungemia-associated IE also may need dose adjustments in the setting of obesity [30].

Several limitations of this study should be considered. First, the NIS is an administrative database that relies heavily on accuracy of ICD-9 and ICD-10 CM codes. It is possible that some codes were missed or incorporated inaccurately [31]. Specifically, the undercoding of obesity is possible; thus, some patients with obesity may have been misclassified as being nonobese. With regards to clinical outcomes, it is possible that a type II error occurred leading to false negative findings. Although this possibility could not be entirely eliminated, given that our study captured thousands of patients who had obesity explicitly coded as a secondary diagnosis, we suspect that we were sufficiently powered to limit the impact of a type II error. Also, the NIS is limited in its ability to track hospitalizations for given medical conditions while abiding to HIPAA; therefore, we could not track individual patients to determine their readmission for the same diagnosis. Further, because there was almost certainly undercoding for multidrug-resistant organisms, we were unable to adjust for this as a possible confounder in multivariate analysis of valvular repairs or replacements. The NIS does not have data on patient laboratory results, imaging studies, or medications administered, nor could we compare echocardiographic findings between patients with and without obesity, such as the size of vegetations or the presence of perivalvular abscesses. Finally, as true with any observational study, though we attempted to control for many factors, it is possible that residual confounding from unmeasured variables remained. However, we targeted confounders that have previously been described using the NIS and adjusted for these as well as making adjustments for hospital-level factors, such as facility size, academic status, rural or urban location, and geographic region.

In conclusion, the data suggests that there were not significant differences in in-hospital mortality or valvular interventions among patients admitted to the hospital with IE based on obesity status. Despite real diagnostic and management challenges that may be expected in obese patients presenting with IE, patient outcomes were similar to those without obesity. The care of patients with IE rarely is easy or straightforward, which may have eliminated the disparities in care outcomes that we expected to find between the groups. However, despite similar clinical outcomes, resource utilization was higher in patients with obesity and future studies to investigate causative factors are needed.

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