Association of Autoimmune Connective Tissue Disease and Outcomes in Patients Undergoing Transcatheter Aortic Valve Implantation

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Patients with autoimmune connective tissue disease (CTD) are at higher risk for developing aortic valve pathology, but the safety and value of transcatheter aortic valve implantation (TAVI) in this population has not been investigated. This study evaluated mortality, complication, and readmission rates along with length of stay and total costs after TAVI in patients with CTD. We retrospectively reviewed 47,216 patients who underwent TAVI from the National Readmissions Database between January 2011 and September 2015. Patients with systemic lupus erythematosus, scleroderma, rheumatoid arthritis, and other autoimmune CTD comprised the cohort. The primary outcome was mortality at index hospitalization. The 2,557 CTD patients (5.4%) had a higher Elixhauser co-morbidity index (7.1 vs 6.1, p <0.001) than non-CTD patients. CTD and non-CTD patients had similar mortality (2.8 vs 4.1%, p = 0.052), 30-day readmission (19.3 vs 17.0%, p = 0.077), length of stay (8.2 vs 8.3 days, p = 0.615), and total adjusted costs ($57,202 vs $58,309, p = 0.196), respectively. However, CTD patients were more frequently readmitted for postoperative infection (9.4 vs 5.6%, p = 0.042) and septicemia (8.2 vs 4.5%, p = 0.019). After multivariable adjustment, CTD patients faced lower mortality at index hospitalization (odds ratio [OR] 0.56 [0.38 to 0.82], p = 0.003) but were more frequently readmitted for septicemia (OR = 1.95 [1.10 to 3.45], p = 0.023) and postoperative infection (OR = 3.10 [1.01 to 9.52], p = 0.048) relative to non-CTD patients. In conclusion, CTD is not a risk factor for in-hospital mortality but is an independent risk factor for infectious complications post-TAVI. **(Am J Cardiol 2019;123:1675−1680)**

TAVI has emerged as the procedure of choice for patients with severe aortic stenosis who are at high risk for open surgery.[1,2] Percutaneous femoral access permits aortic valve implantation without requiring general anesthesia or cardiopulmonary bypass, thereby reducing bleeding risk and postoperative complications.[3,4] Although TAVI has been preferred in those over 75 years of age, recent randomized control trials have suggested that TAVI can be offered to patients even at intermediate and low surgical risk.[1,2] Despite widespread adoption of TAVI, its appropriateness for patients with autoimmune connective tissue disease (CTD) remains unclear. Patients with CTD are at higher risk for developing aortic valve pathology.[5−7] Although TAVI was first utilized in a patient with systemic lupus erythematosus (SLE) in 2013, the use of this technology in patients with CTD remains generally uncharacterized.[8] This study evaluated mortality, complications, and readmissions along with length of stay (LOS) and total costs for CTD patients with aortic stenosis who underwent TAVI.

Methods

This was a retrospective study of the National Readmissions Database, a federal, state, and industry partnership maintained by the Healthcare Cost and Utilization Project, which estimates 36 million annual discharges. All adult patients who underwent TAVI from January 2011 to September 2015 were identified, whereas those with endocarditis, previous cardiac surgery, and concurrent procedures were excluded (Figure 1). Primary stratification was based on the presence of an autoimmune connective tissue disorder. In accordance with the CTD definition provided by the Agency for Healthcare Research and Quality, the CTD cohort included patients with SLE, scleroderma, rheumatoid arthritis, dermatomyositis, polymyositis, Sjogren's syndrome, ankylosing spondylitis, and other CTD with autoimmune etiology (ICD-9 codes: 710.0-710.9, 714.0-714.9, and 720.0-720.9).

The primary outcome was mortality at index hospitalization. Secondary outcomes included the rate and causes of 30- and 90-day readmissions, LOS, and total adjusted costs at both index hospitalization and 30-day readmission. The most frequent causes of 30-day readmission among CTD patients were categorized using the Diagnosis Related Group. The proportion of CTD patients readmitted for those causes was subsequently compared with readmission rates for non-CTD patients using univariate analysis.

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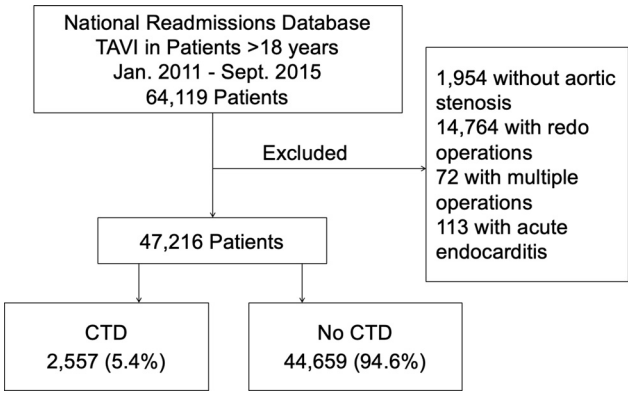

Figure 1. Patient selection criteria. Of 64,119 adult patients who underwent TAVI, 47,216 met inclusion criteria and 2,557 (5.4%) had a CTD diagnosis.

Demographics and co-morbidities were analyzed by the presence of CTD. The Kruskal-Wallis test was used to compare continuous variables, whereas chi-squared analysis was utilized to compare categorical variables. Insurance status was codified as coverage by private insurance, Medicare, Medicaid, and other or unknown payer. Multivariable logistic regression models were used to evaluate the risk of CTD for mortality, as well as 30- and 90-day readmission rates. Adjusted linear regression models were utilized to evaluate causes of readmission, LOS, and adjusted costs. Models were adjusted for differences between CTD and non-CTD cohorts, and included age, gender, Elixhauser co-morbidity index, insurance coverage, diabetes mellitus, systemic hypertension, renal failure, emergent admission, and procedure year. In all comparisons, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA 14.2 (StataCorp LP, College Station, Texas). The study was deemed exempt by the Institutional Review Board at the University of California, Los Angeles.

Results

Of the 47,216 TAVI patients included in the analysis, 2,557 (5.4%) had CTD. Patients with CTD were most likely to have rheumatoid arthritis, followed by systemic lupus erythematosus and scleroderma (Table 1). As shown in Table 2, patients with CTD were more commonly female, had a higher Elixhauser co-morbidity score, but were younger than non-CTD patients. Compared with non-CTD patients, those with CTD were less likely to have chronic kidney disease and diabetes but were otherwise comparable in the rates of congestive heart failure, peripheral vascular disease, and chronic lung disease.

Univariate outcomes between CTD and non-CTD cohorts are depicted in Table 3. Mortality, 30-day readmission, LOS, and total adjusted costs were similar between those with and without CTD. At the 30 day readmission, mortality, LOS, and total costs also were similar between the CTD and the non-CTD cohorts. Stroke rates at index hospitalization or at 30-day readmission were also similar between the groups. Among patients readmitted within 30 days, the principal causes for readmission included congestive heart failure, postoperative infection, septicemia, gastrointestinal hemorrhage, and pneumonia (Figure 2). On univariate analysis, patients with CTD were more frequently readmitted for postoperative infection, septicemia, and pulmonary edema, but less commonly for pacemaker implantation, compared with those without CTD.

The adjusted odds ratios (ORs) for outcomes after multivariable regression analysis are presented in Figure 3. After adjustment, patients with CTD were less likely to die at

Table 1
Connective tissue disease diagnoses

Variable	Number of patients diagnosed	Percentage of CTD cohort with diagnosis (n = 2,557)
Systemic lupus erythematosus	259	10.1%
Scleroderma	204	8.0%
Localized scleroderma	21	0.8%
Diffuse scleroderma	183	7.2%
Sjogren's syndrome	155	6.1%
Dermatomyositis	21	0.8%
Polymyositis	10	0.4%
Other connective tissue disease	12	0.5%
Rheumatoid arthritis	1,933	75.6%
Ankylosing spondylitis	49	1.9%
Multiple diagnoses	290	11.3%
Total diagnoses	2,847	100%

Table 2
Demographics and co-morbidities by CTD status

Variable	Connective tissue disease		p
	No (n = 44,659)	Yes (n = 2,557)	
Women	23,641 (52.9%)	1,892 (74.0%)	<0.001
Age (years)	81.7 ± 0.1	80.7 ± 0.3	0.001
Elixhauser co-morbidity index	6.1 ± 0.05	7.1 ± 0.08	<0.001
Insurance			
Private	2,420 (5.4%)	128 (5.0)	0.629
Medicare	41,027 (91.9%)	2,384 (93.2%)	0.152
Medicaid	422 (0.9%)	10 (0.4%)	0.030
Other	790 (1.8%)	35 (1.4%)	0.267
Hospital bed size			
Small	1,873 (4.2%)	91 (3.6%)	0.373
Medium	6,271 (14.0%)	405 (15.8%)	0.123
Large	36,513 (81.8%)	2,061 (80.6%)	0.376
Income quartile			
1st	8,640 (19.3%)	474 (18.5%)	0.557
2nd	10,921 (24.5%)	587 (22.9%)	0.301
3rd	11,669 (26.1%)	671 (26.3%)	0.937
4th	12,859 (28.8%)	805 (31.5%)	0.064
Co-morbidities			
Congestive heart failure	3,963 (8.9%)	260 (10.2%)	0.206
Renal failure	15,735 (35.2%)	816 (31.9%)	0.036
Diabetes mellitus	11,841 (26.5%)	604 (23.6%)	0.047
Systemic hypertension	35,116 (78.6%)	2,063 (80.7%)	0.145
Liver disease	1,288 (2.9%)	68 (2.6%)	0.646
Chronic lung disease	15,085 (33.8%)	900 (35.2%)	0.372
Coagulation disorder	10,380 (23.2%)	600 (23.5%)	0.879
Pulmonary hypertension	1,286 (2.9%)	76 (3.0%)	0.854
Peripheral vascular disease	12,342 (27.6%)	684 (26.7%)	0.571

CTD = connective tissue disease.

Table 3
Univariate outcomes by CTD status

Outcomes	Connective tissue disease		p
	No (n = 44,659)	Yes (n = 2,557)	
Index hospitalization			
Death	1,823 (4.1%)	73 (2.8%)	0.052
LOS (days)	8.3 ± 0.2	8.2 ± 0.3	0.615
Adjusted cost	$58,309 ± 677	$57,202 ± 1,055	0.196
30-day readmission	7,078 (17.0%)	452 (19.3%)	0.077
90-day readmission	9,557 (26.9%)	587 (29.8%)	0.07
30-day readmission			
Death	403 (5.7%)	23 (5.0%)	0.695
LOS (days)	6.4 ± 0.1	7.9 ± 1	0.125
Adjusted cost	$14,431 ± 361	$17,410 ± 2,779	0.291

CTD = connective tissue disease; LOS = length of stay.

index hospitalization (OR = 0.56 [0.38 to 0.82]) and were not at increased risk for readmission at 30 days (OR = 1.06 [0.89 to 1.27]) or 90 days (OR = 1.05 [0.90 to 1.24]). In addition, patients with CTD had less costly index hospitalizations (β = −$4,554 [−$6,250 to −$3,079]) and shorter LOS (β = −1.3 days [−1.7 to −0.8]) relative to their non-CTD counterparts (Table 4). However, CTD patients were significantly more likely to be readmitted for septicemia (OR = 1.95 [1.10 to 3.45]) and postoperative infection (OR = 3.10 [1.01 to 9.52]) relative to non-CTD patients (Figure 4).

Discussion

Patients with autoimmune CTD are at increased risk of heart valve degeneration. Despite the widespread adoption of TAVI as an alternative to surgical valve replacement in high-risk patients, outcomes of TAVI for patients with CTD have not been previously reported. In this nationwide analysis of TAVI patients, those with CTD were not at increased risk of mortality, readmission, LOS, or costs. However, CTD was an independent risk factor for infectious complications at 30-day readmission.

Since the first in-human report of TAVI over a decade ago, the technology has been adopted for high-risk patients not suitable for surgical aortic valve replacement.[9] Patients with CTD, including rheumatoid arthritis, scleroderma, and SLE, are generally considered high-risk because of their dysregulated immune response and co-morbidities.[5,6] Surgical aortic valve replacement has been previously performed for patients with CTD, including rheumatoid arthritis and SLE.[7,10–12] However, the first successful report of TAVI for severe aortic stenosis in a patient with SLE was not published until 2013.[8] Concern for risks of delayed healing and infection may have been early deterrents to offering TAVI to CTD patients. Despite this concern, the present analysis demonstrates rapid adoption of TAVI in patients with CTD, who comprised over 5% of the TAVI cohort.

Although CTD differs in presentation, valvular involvement is a frequent and shared cardiac manifestation.[13] The mechanisms underlying cardiac valve pathology are uncertain but may relate to vascular inflammation.[10] CTD patients have higher levels of circulating inflammatory markers,[14–16] and osteogenic activation can further predispose patients to the greater aortic and arterial calcification.[10,17,18] Case reports suggest that meticulous attention to leaflet lengths and coronary heights and maintenance of asepsis are critical considerations for TAVI in this population. Our study is the first to examine a national cohort and show TAVI to be feasible and safe in patients with CTD, with no additional risk of mortality or readmission relative to non-CTD patients.[11,12] Although our analysis shows CTD patients to be at decreased risk of mortality, this may represent selection bias. Other considerations for this

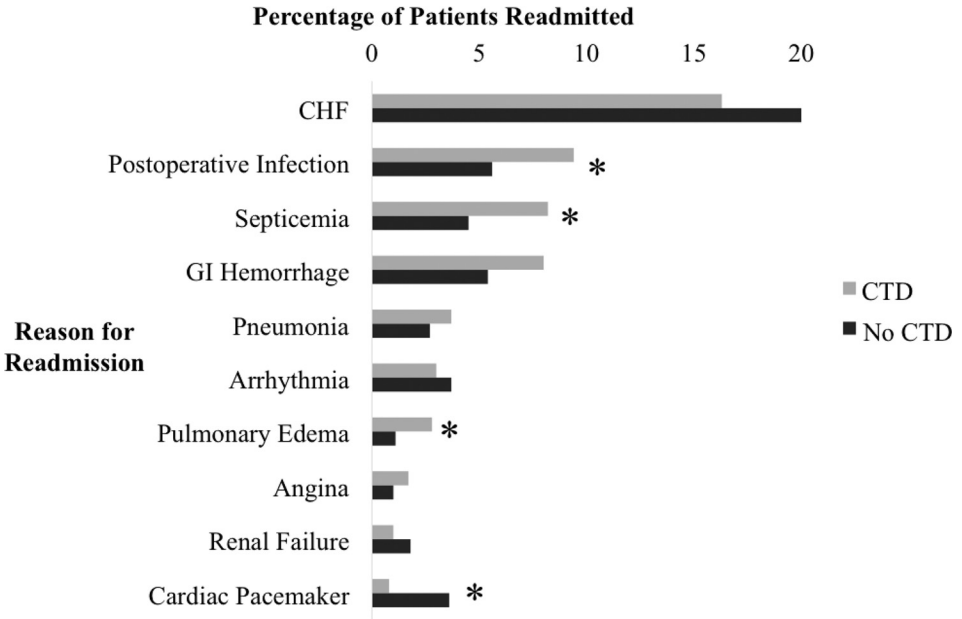

Figure 2. Reasons for 30-day readmission by CTD status. Univariate analysis demonstrates differences in causes of readmission by CTD status. * indicates significance at p <0.05.

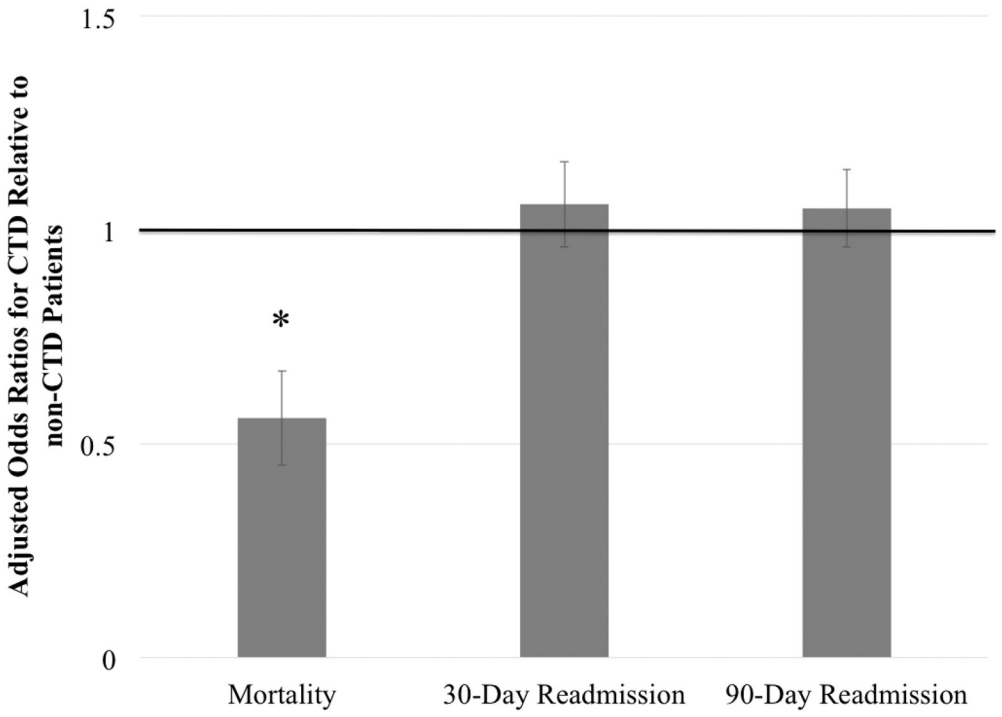

Figure 3. Adjusted odds ratios for CTD patients relative to non-CTD patients at index hospitalization. After adjustment, patients with CTD were less likely to face mortality at index hospitalization (OR = 0.56 [0.38 to 0.82], p = 0.003) and were not at increased risk of 30-day (OR = 1.06 [0.89 to 1.27], p = 0.502) or 90-day (OR = 1.05 [0.90 to 1.24], p = 0.533) readmission. Multivariable regressions were adjusted for age, gender, Elixhauser co-morbidity index, insurance coverage, diabetes mellitus, systemic hypertension, renal failure, emergent admission, and procedure year. * indicates significance at p <0.05.

unexpected finding may include differences in pharmacotherapy, more granular severity index for the aortic valve pathology, or other risk/protective factors not accounted by our analysis.

Our analysis also demonstrated an increased risk of infectious complications in patients with CTD. This outcome supports previous research indicating that patients with Rheumatoid arthritis (RA) and SLE are at increased baseline risk of infection relative to the general population.[19] This increased infection risk may be a direct consequence of immunosuppressive regimens or the result of medication termination leading to disease flares that complicate healing.[19] However, multiple studies have suggested that immunosuppressive regimens can be safely continued throughout invasive surgery without increased infectious complications.[20–22] In fact, the 2017 American College of Rheumatology guidelines suggest that appropriate management of antirheumatic medication in the

Table 4
Multivariable predictors of adjusted cost and LOS by CTD status

	Adjusted cost (USD)		LOS (days)	
Variable	Coefficient (95% CI)	p	Coefficient (95% CI)	p
CTD	−$4,554 (−$6,250 to −$3,079)	<0.001	−1.25 (−1.70 to −0.81)	<0.001
Female	$946 ($51-$1,840)	0.038	0.47 (0.20-0.74)	0.001
Age	$44 (−$33 to $120)	0.262	0.01 (−0.01 to 0.03)	0.307
Elixhauser	$3,611 ($3,228-$3,994)	<0.001	1.10 (1.01-1.18)	<0.001
Insurance				
Private	Ref	Ref	Ref	Ref
Medicare	−$1,186 (−$3,785 to $1,413)	0.371	−0.17 (−0.84 to 0.50)	0.611
Medicaid	$3,843 (−$4,252 to $11,938)	0.352	1.92 (−0.32 to 4.15)	0.092
Other	−$110 (−$4,278 to $4,059)	0.959	−0.25 (−1.28 to 0.77)	0.624
Diabetes	−$4,214 (−$5,348 to −$3,079)	<0.001	−1.38 (−1.67 to −1.09)	<0.001
Systemic hypertension	−$10,532 (−$12,039 to −$9,025)	<0.001	−2.73 (−3.13 to −2.32)	<0.001
Renal failure	$834 (−$220 to $1,887)	0.121	0.37 (0.05-0.70)	0.026
Emergent admission	$13,049 ($10,388 to $15,710)	<0.001	6.42 (5.82-7.04)	<0.001
Operative year	−$1,392 (−$2,500 to −$286)	0.014	−0.81 (−1.02 to −0.59)	<0.001

CTD = connective tissue disease; LOS = length of stay; USD = United States dollar.

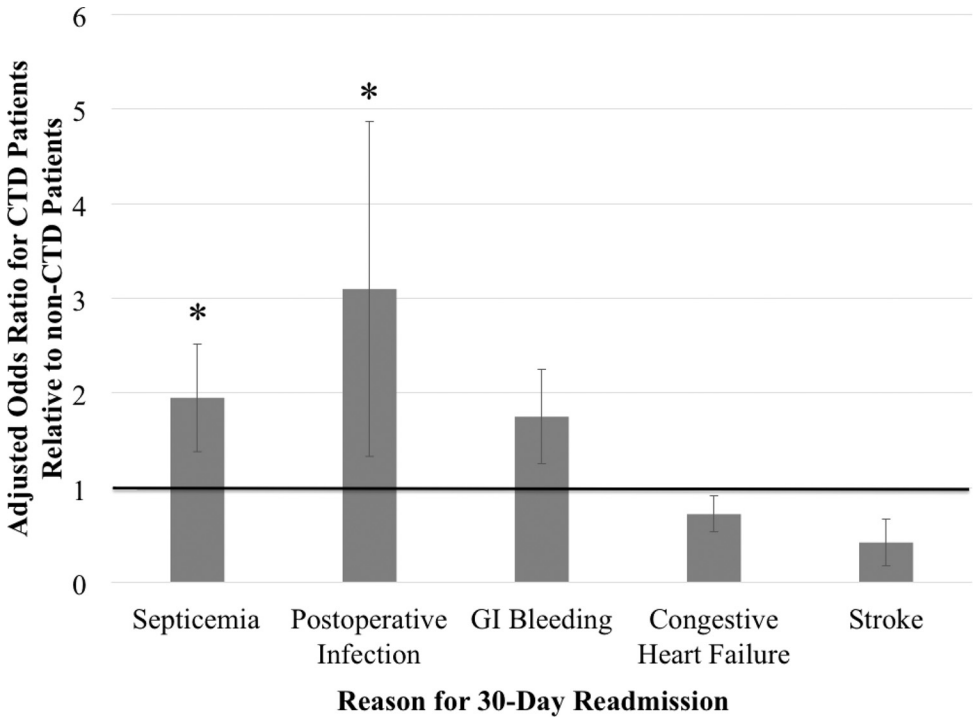

Figure 4. Adjusted odds ratios for CTD patients relative to non-CTD patients. The figure displays the adjusted odds ratios for causes of 30-day readmissions. CTD patients were more likely to be readmitted for septicemia (OR = 1.95 [1.10 to 3.45], p = 0.023) and postoperative infection (OR = 3.10 [1.01 to 9.52], p = 0.048) but not CHF (OR = 0.72 [0.45 to 1.14], p = 0.155), gastrointestinal bleeding (OR = 1.75 [0.99 to 3.07], p = 0.053), or stroke (OR = 0.42 [0.13 to 1.39], p = 0.156). Regressions were adjusted for age, gender, Elixhauser co-morbidity index, insurance coverage, diabetes mellitus, systemic hypertension, renal failure, emergent admission, and procedure year. * indicates significance at p <0.05.

perioperative period may provide an important opportunity to mitigate risk.[23] According to such guidelines for elective orthopedic surgery, nonbiologic therapies can be safely continued, whereas biologic mediations should be discontinued in the perioperative period.[23] Guidance for less-invasive procedures like TAVI remains unclear, but our finding of increased infectious postoperative complications merits further investigation.

Notably, patients with CTD were not at increased risk of stroke after TAVI. Patients with systemic autoimmune diseases, and particularly for those with antiphospholipid syndrome, are at increased risk of stroke at baseline.[24] With a known stroke risk of 3.3% to 6.7% in TAVI patients, the potential for cerebral embolism might present a significant risk to those with CTD.[25] However, our preliminary data do not reflect such risk at index hospitalization or subsequent readmission in CTD patients who underwent TAVI. This may be a function of patient selection for those not in active disease, too few stroke events within 30 days to discern differences between populations, or careful management of patient medications to reduce thrombotic risk.[26–28]

The present study has several important limitations inherent to retrospective studies of administrative databases. First, we were unable to assess medication regimens of patients who underwent TAVI to assess whether termination or continuation of medications was responsible for increased infectious outcomes. Second, we could only ascertain diagnoses, and not the relative activity level of each disease state, at the time of TAVI, which may have significant implications on outcomes. Finally, the outcomes may differ based on the type of CTD, but the sample size of the CTD cohort was too small to further subcategorize based on specific CTD.

In conclusion, our analysis reveals that CTD is an independent risk factor for infectious complications post TAVI and during readmission. However, overall readmission rates, costs, and LOS are similar between those with and without CTD. TAVI appears to be safe for patients despite a diagnosis of CTD and should receive consideration as an effective therapy in such patients. Given the increased risk of postoperative infections and septicemia, perioperative adjustment to immunosuppressive regimens and potential prophylaxis should be further investigated. These results merit further investigations.

Disclosures

The authors have no conflicts of interest to disclose.

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