In-Hospital Outcomes in Patients With a History of Malignancy Undergoing Transcatheter Aortic Valve Implantation

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A history of malignancy is incorporated in the Society of Thoracic Surgeons score to assess presurgical risk in patients undergoing surgical aortic valve replacement, however data on the prognostic importance in those undergoing transcatheter aortic valve implantation (TAVI) remains limited. We sought to investigate the utilization and in-hospital outcomes of TAVI in patients with a history of malignancy. The National Inpatient Sample Database was queried from 2012 to 2017 to identify patients who underwent TAVI using International Classification of Diseases (ICD) 9 and ICD-10 procedure codes. Between 2012 and 2017, there were 123,070 patients who underwent TAVI, of these 23,670 patients (19.2%) had a previous history of malignancy. The proportion of patients undergoing TAVI with a history of malignancy trended upward between 2012 and 2017. Patients with a history of malignancy were similar in age to those without (81.1 ± 7.9 vs 80.1 ± 6.7 years old, p <0.001), with a higher prevalence of tobacco use and major depressive disorder (p <0.001 for both). Patients with a history of malignancy had higher rates of post-TAVI pacemaker implantation (p <0.001), otherwise periprocedural complication rates were similar to those without. Using a multivariate logistic regression model to adjust for confounding factors, a history of malignancy was predictive of decreased odds of death in patients underwent TAVI (OR: 0.67, 95% CI, 0.60 to 0.76, p <0.001) and higher odds of pacemaker implantation (OR: 1.14, 95% CI, 1.09 to 1.19, p <0.001). In conclusion, with time the proportion of TAVI patients with a history of malignancy trended upward. Despite a greater prevalence of previous tobacco use and major depressive disorder, patients with a history of malignancy had TAVI safely with a low in-hospital all-cause mortality, yet greater cost of hospitalization and more frequent implantation of pacemaker devices. **(Am J Cardiol 2021;142:109−115)**

The prevalence of aortic stenosis (AS) is 0.4% in the general population and increases with age (1.7% in those 65 years of age and older).[1] Age also remains a major risk factor for the development of malignant tumors.[2] However, as treatment options for malignancies improve, patients are living longer, and those with AS may be more at risk for death from their valvular heart disease as opposed to their malignancy history.[3] Previous randomized controlled trials investigating outcomes in transcatheter aortic valve implantation (TAVI) patients have excluded patients with a history of malignancy, however, investigating the interplay between a history of malignancy and aortic valve implantation remains important in this group of patients. TAVI is currently an accepted therapy for symptomatic patients with severe AS who have low to intermediate or greater surgical risk as assessed by the heart team.[4] Previous observational studies have shown patients with a history of malignancy to have higher rates of complications (transfusions, reintubation, pneumonia, and septicemia) when undergoing surgical aortic valve replacement (SAVR) but comparable mortality rates to those without a history of malignancy.[5−7] However, at present only a small number of studies have evaluated outcomes specific to TAVI.[8−11] We sought to evaluate nationwide in-hospital utilization and outcomes of TAVI in persons with a history of malignancy.

Methods

The National Inpatient Sample (NIS) offers the largest database of hospitalizations, representing a 20% random, stratified, sample of hospital discharges in the United States. To identify the study population, International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) and ICD-10-CM diagnostic and procedural codes were used. Institutional review board approval was not needed, as all patient information is de-identified within

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the NIS. All the data under NIS are publicly available. Detailed methods used for statistical analyses are presented under the Data Supplement, which can be used for replication of our results.

From January 1, 2012 to September 15, 2017, a total of 42,914,653 discharge records comprised the NIS for the US adult population (age ≥18), corresponding to a national estimate of 214,573,207 hospitalizations across the country. We identified all patients aged ≥18 undergoing Transcatheter Aortic Valve Implantation using ICD-9 Procedure Coding System code of 35.05 and 35.06, or ICD-10 Procedure Coding System code of 02RF37H, 02RF38H, 02RF3J, 02RF3KH, 02RF37Z, 02RF38Z, 02RF3JZ or 02RF3KZ in any procedure field. Our final study cohort comprised 24,615 patients undergoing TAVI, which, using NIS-provided trend discharge weights, corresponds to an estimated 123,070 overall TAVI hospitalizations during this time period. We separated patients into 2 cohorts, those with a history of malignancy (see data supplement for ICD codes) and those without. Within the data supplement, Table 1 lists the ICD codes for covariates and patient co-morbidities, as well as the ICD-9 and ICD-10 codes used to define post-TAVI complications.

Our primary outcome of interest was post-TAVI all-cause inpatient mortality. Secondary outcomes of interest were rates of postoperative cardiogenic shock, permanent pacemaker insertion, acute kidney injury, major bleeding, postoperative ischemic stroke, total cost of hospitalization and length of hospital stay. Detailed methods, including covariate ascertainment, are included under the Data Supplement. As recommended by the Agency for Healthcare

Table 1
Baseline characteristics of persons with and without a history of malignancy who underwent transcatheter aortic valve implantation

Variable	History of malignancy		p Value
	YES (n = 23,670)	NO (n = 99,400)	
Age (years)	81.1 ± 7.9	80.1 ± 6.7	**<0.001**
GENDER			
Men	13,425 (56.7%)	52,540 (52.9%)	**<0.001**
Women	10,245 (43.3%)	46,860 (47.1%)	
Race			
White	20,360 (90.0%)	81,165 (86.4%)	**<0.001**
Black	755 (3.3%)	4,120 (4.4%)	
Hispanic	690 (3.0%)	4,355 (4.6%)	
Asian/Pacific Islander	165 (0.7%)	1,280 (1.4%)	
Primary expected payer			
Medicare	21,520 (91.0%)	89,395 (90.1%)	**<0.001**
Medicaid	160 (0.7%)	1275 (1.3%)	
Private Insurance	1,620 (6.8%)	6,705 (6.8%)	
Self-Pay	85 (0.4%)	440 (0.4%)	
Other	270 (1.1%)	1370 (1.4%)	
Median household income (percentile)			
0-25th	4,325 (18.6%)	21,285 (21.8%)	**<0.001**
26th-50th	5,375 (23.1%)	25,405 (26.0%)	
51st-75th	6,355 (23.1%)	25,515 (26.1%)	
76th-100th	7,235 (31.1%)	25,530 (26.1%)	
Diabetes mellitus	7,395 (31.6%)	36,180 (36.7%)	**<0.001**
Hypertension	17,585 (81.1%)	71,655 (79.6%)	**<0.001**
Hyperlipidemia	16,710 (73.6%)	66,905 (70.6%)	**<0.001**
Coronary artery disease	16,410 (69.3%)	68,675 (69.3%)	0.919
Heart failure	17,120 (72.3%)	73,535 (74.0%)	**<0.001**
Atrial fibrillation	8,845 (37.4%)	39,915 (40.2%)	**<0.001**
Peripheral arterial disease	4,845 (21.5%)	20,780 (21.7%)	0.416
Chronic kidney disease	7,805 (33.3%)	36,180 (36.4%)	**<0.001**
Renal replacement therapy	540 (2.3%)	3,890 (3.9%)	**<0.001**
Prior stroke	420 (1.8%)	2,090 (2.1%)	0.001
Chronic obstructive pulmonary disease	6,045 (25.8%)	25,125 (25.6%)	0.390
Obesity	3,140 (13.3%)	16,575 (16.7%)	**<0.001**
Smoker	10,060 (42.5%)	33,480 (33.7%)	**<0.001**
Alcohol drinker	250 (1.1%)	1005 (1.0%)	0.538
Illicit drug use	75 (0.3%)	475 (0.5%)	0.001
Chronic liver disease	430 (1.9%)	2,665 (2.7%)	**<0.001**
Anemia	1,075 (5.8%)	5,000 (6.5%)	**<0.001**
Thrombocytopenia	3,530 (14.9%)	15,400 (15.5%)	0.026
Dementia	1,130 (4.8%)	5,610 (5.7%)	**<0.001**
Major depressive disorder	1,920 (8.2%)	7,305 (7.4%)	**<0.001**
Malnutrition	65 (0.3%)	520 (0.5%)	**<0.001**

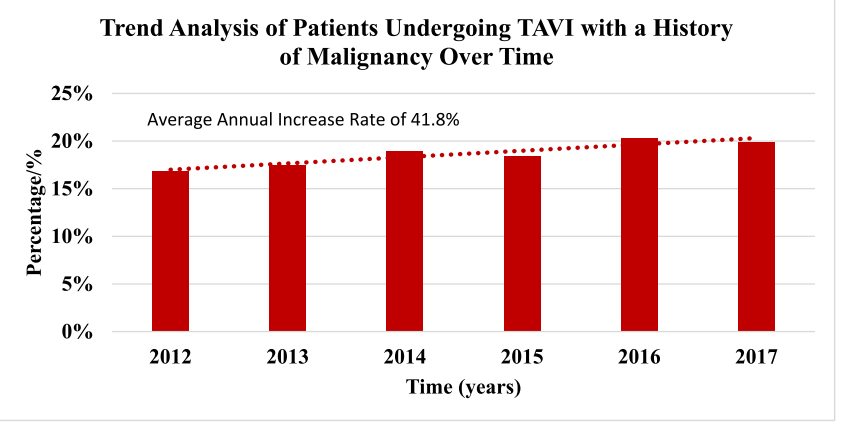
and Research and Quality (AHRQ), weighted data were used for all statistical analyses. Baseline characteristics and post-TAVI outcomes were compared using the Pearson Chi-Squared (χ^2) tests for categorical variables, independent samples T-testing for parametric continuous variables and Mann-Whitney's test for nonparametric continuous variables with a p-value of <0.001 deemed statistically significant. Categorical patient characteristics included hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, atrial fibrillation, alcohol use, smoking history, anemia, and thrombocytopenia (Table 1). Continuous variables of interest included mean age, total cost of hospitalization and length of stay. The association between a history of malignancy, and post-TAVI mortality, major bleeding, pacemaker implantation, and thrombotic complications (such as ischemic stroke) were analyzed using multivariable logistic regression. All multivariable regression models were created using generalized estimating equations with a p value of <0.05 deemed statistically significant. Missing data for race were handled using multiple imputation as recommended by the HCUP. Missing primary payer status in patients ≥65 years of age was imputed to Medicare, whereas missing data for all other variables were imputed to the dominant category. All statistical analyses were performed using SPSS (IBM SPSS Statistics for Mac, Version 26.0. Armonk, New York: IBM Corp.).

Results

A total of 24,615 hospitalizations for TAVI secondary to severe AS were identified corresponding to a weighted estimate of 123,070 hospitalizations for TAVI during the years 2012 to 2017 (Table 1). Women (n = 57,105) comprised 56.1% of the total population. Of the total population, there were 23,670 patients with a history of malignancy (19.2%) and 99,400 patients without a history of malignancy (80.8%). The proportion of patients undergoing TAVI with a history of malignancy trended upward from 16.8 to 19.9%, with an average annual increase rate of 41.8% between 2012 and 2017, see Figure 1. Baseline characteristics are displayed in Table 1.

In-hospital all-cause mortality (1.7% vs 2.7%, p <0.001), hospital length of stay (4.9 ± 5.0 vs 6.0 ± 6.8 days, p <0.001), major bleeding (7.5% vs 9.1%, p<0.001), gastrointestinal bleeding (1.3% vs 1.8%, p<0.001), postoperative ischemic stroke (3.6% vs 4.8%, p <0.001) and mechanical circulatory use (1.0% vs. 1.6%, p <0.001) occurred less in patients with a history of malignancy than those without, see Table 2. Over the period analyzed, in-hospital mortality was comparatively lower in each year in those with a history of malignancy when compared to those without a history of malignancy, except in 2013 and 2017 where there was no significant difference,

(A)



(B)

Calendar year	Proportion of Patients with a History of Malignancy (%)	Percentage change
2012	1215 (16.8)	
2013	2255 (17.5)	85.6
2014	3580 (19)	58.8
2015	4875 (18.4)	36.2
2016	7890 (20.3)	61.8
2017	9835 (19.9)	24.7

Figure 1. Showing the change per year *(A)* and the average annual change rate *(B)* in patients with a history of malignancy undergoing transcatheter aortic valve implantation.

Table 2
Outcomes and complications post-transcatheter aortic valve implantation by the presence of a malignancy history

Outcomes	History of malignancy		p Value
	YES (n = 23,670)	NO (n = 99,400)	
In-hospital mortality	410 (1.7%)	2,655 (2.7%)	**<0.001**
Length of stay (days)	4.9 ± 5.0	6.0 ± 6.8	**<0.001**
Total cost of hospitalization (US dollars, $)	220,507 ± 147,098	207,701 ± 125,002	**<0.001**
Ventricular fibrillation	195 (0.8%)	895 (0.9%)	0.257
Ventricular tachycardia	710 (3.0%)	3,615 (3.6%)	**<0.001**
Postoperative cardiogenic shock	60 (0.3%)	270 (0.3%)	0.627
Intraoperative cardiac arrest	330 (1.4%)	1,895 (1.9%)	**<0.001**
Intra-aortic balloon pump use	130 (0.5%)	1,135 (1.1%)	**<0.001**
Extracorporeal membrane oxygenation	35 (0.1%)	325 (0.3%)	**<0.001**
Mechanical circulatory use	230 (1.0%)	1,590 (1.6%)	**<0.001**
Pacemaker implantation	1795 (7.6%)	6,735 (6.8%)	**<0.001**
Paravalvular leak	210 (0.9%)	1,045 (1.1%)	0.024
Acute kidney injury	2,370 (10.1%)	13,870 (14.0%)	**<0.001**
Septicemia	155 (0.7%)	1,420 (1.4%)	**<0.001**
Postoperative infections	35 (0.1%)	180 (0.2%)	0.271
Major bleeding	1,770 (7.5%)	9,020 (9.1%)	**<0.001**
Gastrointestinal bleeding	315 (1.3%)	1,770 (1.8%)	**<0.001**
Intra and postoperative hemorrhage or hematoma	660 (2.8%)	4,160 (4.2%)	**<0.001**
Transfusion of any blood product	2,610 (11.0%)	12,210 (12.3%)	**<0.001**
Transfusion of packed red blood cells	2,495 (10.5%)	11,650 (11.7%)	**<0.001**
Transfusion of platelets	300 (1.3%)	1,570 (1.6%)	**<0.001**
Transfusion of fresh frozen plasma	165 (0.7%)	1,040 (1.0%)	**<0.001**
Postoperative deep vein thrombosis/pulmonary embolism	655 (2.8%)	3,080 (3.1%)	0.007
Postoperative ischemic stroke	840 (3.6%)	4,715 (4.8%)	**<0.001**
Palliative care consultation	270 (0.6%)	2,675 (0.9%)	**<0.001**
Do Not Resuscitate (DNR%) status	520 (1.1%)	2,920 (1.0%)	0.014
Discharge disposition			
Routine*	12,630 (53.4%)	50,815 (51.1%)	**<0.001**
Short term hospital	105 (0.4%)	625 (0.6%)	
Skilled nursing Facility/Intermediate care facility	4,130 (17.5%)	19,800 (19.9%)	
Home health care	6,385 (27.0%)	25,425 (25.6%)	

* Routine- defined as discharged to home/self-care or with court/law enforcement.

see Figure 3. Total cost of hospitalization ($220,507.0 ± 147,098.2 vs $207,701.0 ± 125,002.5, p <0.001) and pacemaker implantation (7.6% vs. 6.8%, p <0.001) were greater in patients with a history of malignancy than those without. Rates of postoperative deep vein thrombosis/pulmonary embolism (2.8% vs. 3.1%, p = 0.007), paravalvular leaks (0.9% vs 1.1%, p = 0.024) and postoperative infections (0.1% vs 0.2%, p = 0.271) were similar between groups. Using a multivariate logistic regression model to adjust for confounding factors such as age, gender, race, diabetes mellitus, hypertension, chronic kidney disease, atrial fibrillation, smoking history, and obesity revealed that a history of malignancy was predictive of decreased major bleeding (adjusted odds ratio: 0.82, 95% CI, 0.78 to 0.87, p <0.001), acute kidney injury (adjusted odds ratio: 0.76, 95% CI, 0.72 to 0.80, p <0.001), in-hospital all-cause mortality (adjusted odds ratio: 0.67, 95% CI, 0.60 to 0.76, p <0.001) and postoperative ischemic stroke (adjusted odds ratio: 0.73, 95% CI, 0.67 to 0.80, p <0.001) in patients with a history of malignancy, whereas a history of malignancy was predictive of increased odds of pacemaker implantation (adjusted odds ratio: 1.14, 95% CI; 1.09 to 1.19, p <0.001), see Table 3 and Figure 2. Patients with a history of malignancy had less palliative care consultations (0.6% vs 0.9%, p <0.001) during their hospitalization, however there was no difference regarding Do Not Resuscitate orders (1.1% vs 1.0%, p = 0.014).

Discussion

The purpose of this study was to evaluate the nationwide in-hospital utilization and outcomes of transcatheter aortic valve implantation in persons with a history of malignancy. Among major findings which warrant further discussion, patients with a history of malignancy had (1) increased TAVI utilization between 2012 and 2017 (2) a higher prevalence of tobacco use and major depressive disorder; (3) lower in-hospital all-cause mortality; (4) comparable rates of paravalvular leaks and postoperative deep vein thrombosis/pulmonary embolism; and (5) a higher total cost of hospitalization and pacemaker implantation, when compared to patients without a history of malignancy. To our knowledge, this is the largest retrospective observational study investigating early nationwide in-hospital outcomes of TAVI in patients with a history of malignancy. Historically, a history of malignancy or chest radiation has been implicated in the Society of Thoracic Surgeons score to assess presurgical risk in patients undergoing SAVR due to the

Table 3
Multivariate logistic regression model to assess the relationship between a history of malignancy and post transcatheter aortic valve implantation outcomes. Values reported for regression model using inpatient mortality as an outcome and a history of malignancy as a primary independent variable

Outcome	Model	Odds ratio	Confidence interval	p Value
Inpatient mortality	Unadjusted	0.61	0.57-0.65	**<0.001**
	Adjusted	0.67	0.60-0.76	**<0.001**
Acute kidney injury	Unadjusted	0.72	0.70-0.74	**<0.001**
	Adjusted	0.76	0.72-0.80	**<0.001**
Major bleeding	Unadjusted	0.82	0.79-0.85	**<0.001**
	Adjusted	0.82	0.78-0.87	**<0.001**
Red blood cell transfusion	Unadjusted	0.92	0.90-0.95	**<0.001**
	Adjusted	0.95	0.90-0.98	**0.038**
Pacemaker implantation	Unadjusted	1.29	1.24-1.35	**<0.001**
	Adjusted	1.14	1.09-1.19	**<0.001**
Paravalvular leak	Unadjusted	0.65	0.59-0.73	**<0.001**
	Adjusted	0.96	0.80-1.15	0.676
Gastrointestinal bleeding	Unadjusted	0.75	0.69-0.81	**<0.001**
	Adjusted	0.92	0.81-1.04	0.176
Postoperative cardiogenic shock	Unadjusted	0.53	0.44-0.64	**<0.001**
	Adjusted	0.79	0.55-1.14	0.211
Postoperative ischemic stroke	Unadjusted	0.74	0.70-0.78	**<0.001**
	Adjusted	0.73	0.67-0.80	**<0.001**
Postoperative deep vein thrombosis/pulmonary embolism	Unadjusted	0.90	0.86-0.94	**<0.001**
	Adjusted	0.94	0.86-1.03	0.202

A p-Value <0.05 was considered as statistically significant (bold).

Major bleeding, gastrointestinal bleeding and red blood cell transfusion were adjusted for age, gender, anemia, atrial fibrillation, alcohol use and chronic kidney disease.

All other outcomes were adjusted for age, gender, race, diabetes mellitus, hypertension, chronic kidney disease, atrial fibrillation, smoking history and obesity.

greater degree of periprocedural complications.[12] These worsened outcomes have been suggested to be secondary to a cardiopulmonary bypass invoked inflammatory reaction, including an increased release of cytokines (interleukin-1, interleukin-6, interleukin-8, and tumor necrosis factor-alpha).[2] Some of these cytokines had also been involved in the immunologic defense against tumor cell formation, invasion, and metastasis.[13] On this background, we investigated early nationwide outcomes of TAVI in patients with a history of malignancy.

The popularity of TAVI has steadily increased over the last decade and through both rapidly increasing clinical experience and progressive improvement in TAVI devices, TAVI outcomes have improved. Gastrointestinal, prostate, hematological and breast malignancies have been reported as the most common previous malignancies in past TAVI studies.[10,14] There was a trend toward decreased in-hospital all-cause mortality and similar periprocedural complications (paravalvular leaks and postoperative deep vein thrombosis/pulmonary embolism) in patients with a history

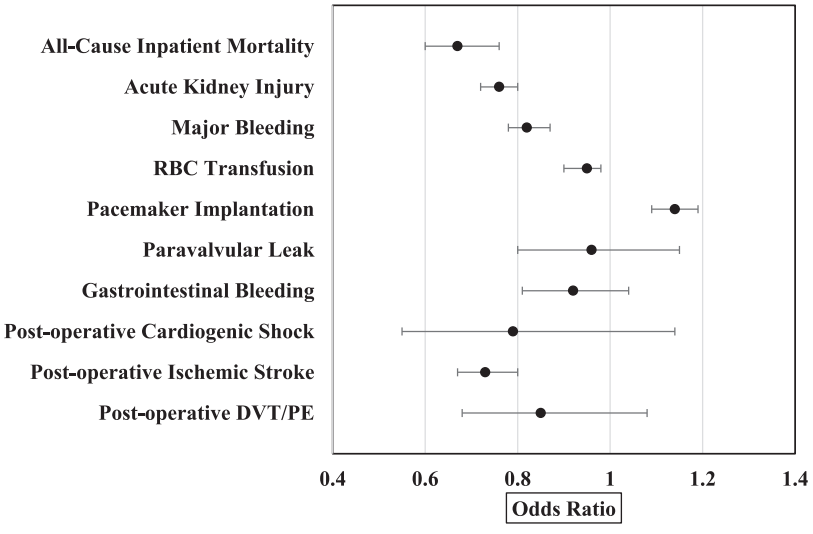
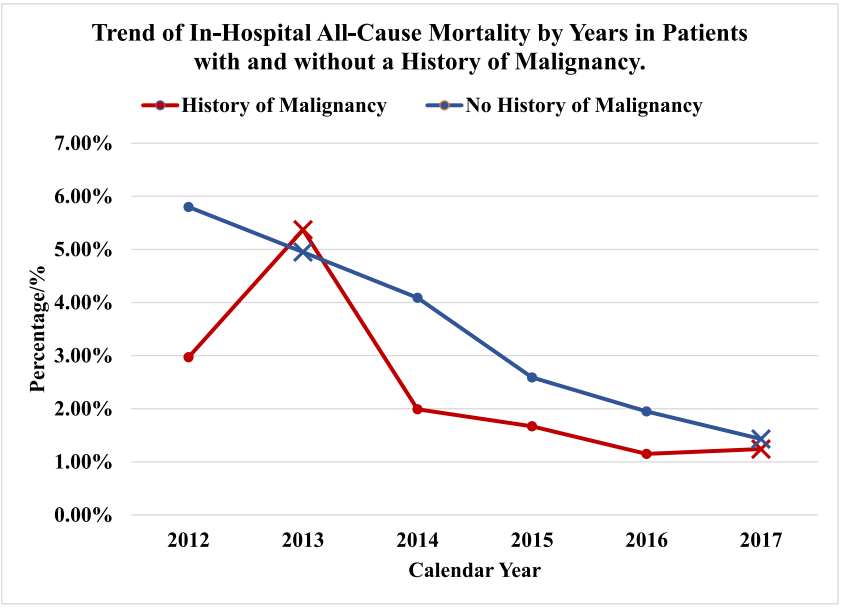


Figure 2. Box plot showing the odds ratios of in-hospital outcomes post transcatheter aortic valve implantation in patients with a history of malignancy.



X- non-significant p value (2013 and 2017); otherwise p<0.05 for all other years.

Figure 3. Showing the trend of in-hospital all-cause mortality post transcatheter aortic valve implantation by years in patients with and without a history of malignancy. X- nonsignificant p value (2013 and 2017); otherwise p <0.05 for all other years.

of malignancy. This is consistent with the findings of recent studies. Notably, the TAVI population with a history of malignancy had less anemia and malnutrition. First, a recent meta-analysis of seven observational studies (n = 628 patients) by Murphy et al. reported a trend toward lower short−term all−cause mortality in patients with a history of cancer (relative risk [RR]: 0.61, 95% CI, 0.36 to 1.01; p = 0.06) with no significant differences in the rates of periprocedural complications including acute kidney injury, bleeding, or pacemaker implantation.[11] Second, utilizing the TAVI in Oncology Patients with severe AS (TOP-AS) registry, TAVI in active cancer patients was associated with similar short-term outcomes and periprocedural complications (stroke, myocardial infarction, and kidney injury).[10] Given the less invasive nature of TAVI when compared to SAVR, malignancy history appears to factor less in periprocedural outcomes, supporting increased consideration of TAVI in this population. This association appears similar when investigating the long-term outcomes (>1 year) in patients with a past history of malignancy, however in patients with active malignancy TAVI was associated with worsened long-term outcomes.[10] Long-term mortality appeared to be mainly driven by cancer, with progressive malignancy a strong predictor of mortality.[10] Treatment decisions should be individualized, with greater emphasis on a history of active malignancy and malignancy stage when considering patient outcomes.

The association between depression and cancer incidence, mortality and survival has been well documented.[15] Consistent with previous literature, our cohort of patients with a history of malignancy had a higher prevalence of major depressive disorder. Furthermore, approximately 40% of patients with a history of malignancy had a history of tobacco use. Although neither depression nor tobacco use was predictive of worsened outcomes in our analysis, this finding highlights the need for further emphasis on multidisciplinary/heart team approaches before TAVI. Inclusion of psychology, psychiatry, cognitive behavioral therapy, and oncology/cardio-oncology services in the care of patients with malignancy undergoing TAVI may be beneficial. Particularly, we found that a history of malignancy was associated with greater post-TAVI pacemaker implantation. This was in keeping with the results of a recent 2020 meta-analysis of 5,162 patients investigating TAVI outcomes in patients with severe AS and a history of active cancer.[14] The significantly higher need for a postprocedural pacemaker in patients with cancer in this study might be explained by the well-known arrhythmogenic impact of various antineoplastic therapies (e.g., methotrexate, 5-fluorouracil and cisplatin), putting patients with cancer at a higher risk for such a complication (by increasing vulnerability of cardiac conductive tissue to mechanical injury imposed by the TAVI procedure).[16] Perhaps an increased focus regarding specific chemotherapy regimen, the time since last treatment and cancer stage may be predictive of pacemaker implantation in this group.

Our study has notable strengths and limitations that warrant discussion. Utilization of the NIS provides us with an opportunity to analyze a large number of TAVI recipients, from hundreds of centers nationwide, across a 6-year timeframe (weighted estimate of 123,070 TAVI procedures). However, as the NIS represents hospitalizations and not individual patients, there is a possibility that patients undergoing TAVI may feature more than once in the data set. One major limitation of our study, by the nature of the database, is the inability to stratify patients based on the presence of active malignancy or malignancy stage. Given the cross-sectional and associative nature of our analyses, no causality can be established. These analyses were also limited by the lack of clinical (New York Heart Association

Class) laboratory, echocardiographic data (including ejection fraction) and device (self-expending versus balloon-expandable), as we used a code-based database.

In conclusion, in patients with severe AS undergoing TAVI, the proportion of patients with a history of malignancy trended upward between 2012 and 2017. Despite a greater prevalence of previous tobacco use and major depressive disorder, patients with a history of malignancy had TAVI safely with a low in-hospital all-cause mortality. However, patients with a malignancy history had a greater cost of hospitalization and more frequent implantation of pacemaker devices. Inclusion of cancer stage and duration of remission during risk assessment, as well as the incorporation of oncology/cardio-oncology, psychology, and psychiatry services in the heart team may be beneficial.

Author Contributions

Jelani K. Grant: Conceptualization, Methodology, Software, Writing- Original draft preparation, Writing- Reviewing and Editing. Louis Vincent: Methodology, Software, Writing- Reviewing and Editing. **Bertrand Ebner:** Methodology, Software, Writing- Reviewing and Editing. **Jennifer Maning:** Methodology, Software, Writing- Reviewing and Editing. **Harjit Singh:** Writing- Original draft preparation. **Odunayo Olorunfemi:** Writing- Reviewing and Editing, Supervision. **Neal I. Olarte:** Writing- Reviewing and Editing, Supervision. **Rosario Colombo:** Writing- Reviewing and Editing, Supervision. **Gilberto Lopes:** Writing- Reviewing and Editing, Supervision. **Joao Braghiroli:** Writing- Reviewing and Editing, Supervision.

Disclosures

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