Impact of Tricuspid Regurgitation in Patients With Heart Failure and Mitral Valve Disease from a Nationwide Cohort Study

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Concomitant heart failure (HF) and mitral valve disease (MVD) portend significant morbidity and mortality. Although associated Tricuspid regurgitation (TR) is a common occurrence in this scenario, it is not well known whether there are additional prognostic implications. We sought to assess whether coexistent TR is associated with higher readmission rates or increased mortality in patients with HF and MVD. We identified 1,520,871 encounters with a primary diagnosis of HF in the 2013 to 2014 Nationwide Readmission Database. We excluded patients without MVD, patients <18 years old, those with rheumatic heart disease and infective endocarditis. We also excluded patients who were discharged in December, hospital transfers, and cases where follow-up or outcomes were missing. Logistic regression was used to evaluate the association between baseline characteristics (including the presence of tricuspid valve disease), mortality as well as 30-day readmission rates. A total of 221,127 admissions with HF and MVD were identified. Median age was 79 years (IQR, 67 to 87), 55% were female, 2.7% died during hospitalization, and the 30-day readmission rate was 20.3%. Nearly 1/3 had concomitant TR (n = 78,356, 35%). The presence of TR was neither associated with elevated risk of mortality (hazard ratio 0.98, 95% confidence interval 0.93 to 1.04) nor 30-day readmission rate (odds ratio 1.01, 95% confidence interval 0.98 to 1.03). HF accounted for 33% of 30-day readmissions, while combined cardiac causes accounted for 54%. In conclusion concomitant TR in patients with HF and MVD was not associated with worse short-term outcomes in terms of inpatient hospital mortality and 30-day readmission rates. **(Am J Cardiol 2019;124:926−931)**

Heart failure (HF) is a leading cause of hospitalization and readmissions,[1,2] with 1/5 of those hospitalized for HF being readmitted within 30 days.[3] It is also associated with significant mortality.[4−6] Coexistent mitral valve disease (MVD), when encountered in patients with HF, is associated with increased morbidity and mortality.[7,8] When both HF and MVD are present, it is not uncommon to have associated tricuspid regurgitation (TR) secondary to pulmonary artery pressure elevation and right ventricular remodeling or primary tricuspid valve disease (TVD) with adverse long-term outcomes.[9−11] However as the short-term prognostic implications are not well determined, we sought to study the impact of concomitant TR on short-term readmission rates and mortality in patients with HF and MVD.

Methods

This was an observational cohort study consisting of patients admitted with HF and concomitant MVD from the Nationwide Readmission Database (NRD) registry for the years 2013 to 2014. The NRD is sponsored by the Agency for Healthcare Research and Quality, and is part of the Healthcare Cost and Utilization Project. It provides discharge data from 22 states, accounting for 51.2% of the total United States (US) resident population and 49.3% of all hospitalizations, with the national estimates being produced by using the provided sampling weights.[12] As these data are deidentified and publicly available, the need for informed consent and institutional review board approval was waived.

The principal diagnosis of HF admission was identified by utilizing Agency for Healthcare Research and Quality clinical classification software[13] diagnosis category 108. This included HF, nonhypertensive, with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes 398.91, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9,[14] as well as other ICD-9 codes that indicate HF (402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93).[15] Patients who had systolic HF (ICD-9 428.2) and combined systolic and diastolic HF (ICD-9 428.4) were labeled as HF with

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reduced ejection fraction (HFrEF), while patients with diastolic HF (ICD-9 428.3) were labeled as HF with preserved ejection fraction (HFpEF). MVD was also identified using ICD-9 (Supplementary Table). We identified the index HF admission and readmissions within 30 days, which was labeled as all-cause readmissions.

The study included patients admitted with a primary diagnosis of HF, along with an associated diagnosis of MVD. We excluded patients <18 years old, same-day readmissions, patients with missing data, patients with infective endocarditis and patients with rheumatic heart disease. Patients who were admitted in December were excluded when assessed for 30-day readmissions, as each year's sample of NRD is unique and linked from January to December of the same year only, and it would be unknown if December admissions would be readmitted in January of the following year. Similarly we excluded patients admitted from October to December and from July to December when we assessed the 90-day and 120-day readmissions, respectively. Patient demographics and length of stay (LOS) were obtained from the database. Comorbidities were identified using ICD-9 codes, clinical classification software codes, and/or Elixhauser comorbidity variables, when appropriate (Supplementary Table). We identified the all-cause 30-day readmission by ICD-9 codes assigned for primary diagnosis of the readmission. LOS values were categorized into groups (0 to 2 day, 3 to 5, and ≥6 days).

Continuous variables were described as medians and interquartile ranges, and categorical variables were described as percentages. We used the Mann-Whitney test to compare continuous variables, and the chi-square test and Fisher's exact test to compare categorical variables, whenever appropriate. Further, we used bivariable and multivariable logistic regression analyses to evaluate the association between patient characteristics and mortality and all-cause readmissions. Variables with $p < 0.2$ in bivariable analysis were considered eligible to enter the multivariable model. Associations were expressed as hazard ratios (HRs) for mortality and odds ratios (ORs) for the readmission rates, with their 95% confidence intervals (CIs). A $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 25.0 (IBM Corp, Armonk, New York).

Results

A total of 1,520,871 index HF admissions were recorded in the NRD from 2013 to 2014. After exclusions, a total of 221,127 encounters were included of which 35% (n = 78,356) had concomitant MVD with TVD. (Figure 1) The median patient age was 79 years (interquartile ranges 67 to 87), 55% were females, more than half of patients had HFrEF (54.6%), 30.9% had HFpEF, and 14.5% had unreported subclass. Rest of the characteristics of patients included in the index HF admit cohort along with comparison between those with isolated MVD and those with concomitant TVD are presented in Table 1. Patients with TVD had similar LOS [median of 4 (3 to 7) compared with 4 days (3 to 6) in patients with MVD alone]. There was no significant difference in the cost of index admission (median of $25 844 [$15 073 to 46 593], vs $25 577 [$14 881 to 46 320] in HF patients with MVD alone, p = 0.172].

The overall inpatient mortality rate was 2.7% (n = 5,883). There was no difference in mortality between patients with concomitant TR compared with HF with MVD only (HR 0.89, 95% CI 0.93 to 1.04). Inpatient mortality was also lower in patients with HFpEF (HR 0.76, 95% CI 0.71−0.81) versus those with HFrEF, and in those with LOS of 3 to 5 (HR 0.63, 95% CI 0.58 to 0.68) compared with 0 to 2 days. Additional factors associated with inpatient mortality are presented in Table 2.

In patients who survived their hospitalization, the overall 30-day readmission rate was 20.3% (n = 43,786). HF was the single most common cause of 30-day readmission (33%), while combined cardiac causes accounted for 54% (mainly HF 33%, valvular heart disease 5.1%, arrhythmia/conduction disease 5%). Further breakdown of the overall causes of readmissions are represented in Figure 2. By logistic regression analysis, 30-day readmission rates were similar in patients

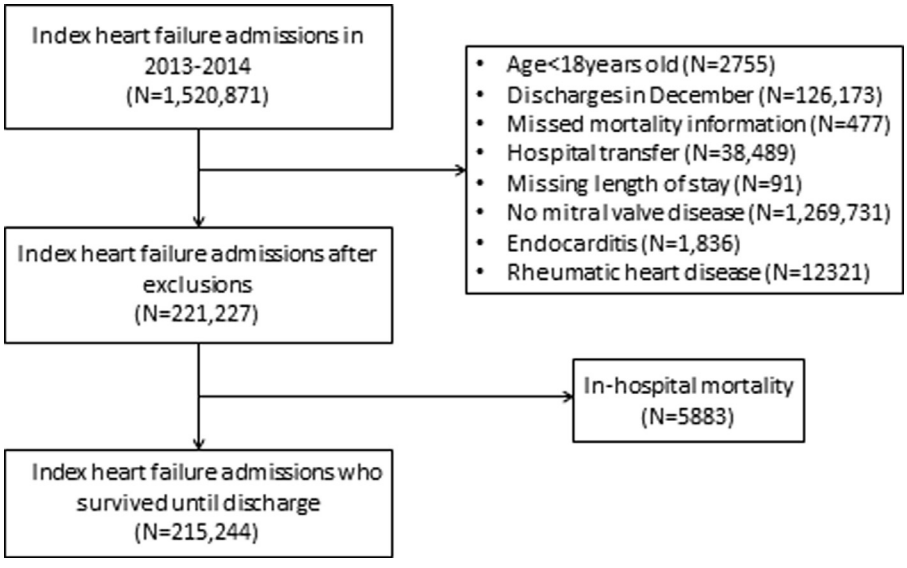

Figure 1. Flow diagram of the screened and enrolled population.

Table 1
Characteristics of index heart failure admissions

Variable	Total (n = 221,127)	Concomitant TVD with MVD (n = 78,356) (35.4%)	Isolated MVD with no TVD (n = 142,772) (64.6%)	p
Age (years), median (IQR)	79 (67-87)	80 (67-87)	79 (67-86)	<0.001
Women	121,690 (55%)	43,535 (55.6%)	78,155 (54.7%)	<0.001
HF subtype				
• HFrEF	120,832 (54.6%)	43,212 (55.1%)	77,620 (54.4%)	<0.001
• HFpEF	68,290 (30.9%)	23,906 (30.5%)	44,384 (31.1%)	<0.001
• Undetermined/missing	32,006 (14.5%)	11,238 (14.3%)	20,768 (14.5%)	0.001
Hypertension	154,730 (70%)	54,118 (69.1%)	100,612 (70.5%)	<0.001
Diabetes mellitus	80,047 (36.2%)	27,722 (35.4%)	52,325 (36.6%)	<0.001
Hyperlipidemia	112,227 (50.8%)	38,716 (49.4%)	73,511 (51.5%)	<0.001
Coronary atherosclerosis	124,287 (56.2%)	42,429 (54.1%)	81,858 (57.3%)	<0.001
Peripheral vascular disease	30,856 (14%)	10,825 (13.8%)	20,031 (14%)	0.163
Pulmonary hypertension	85,030 (38.5%)	39,818 (50.8%)	45,212 (31.7%)	<0.001
Pericardial disease	3,979 (1.8%)	1,924 (2.5%)	2,055 (1.4%)	<0.001
Arrhythmia and conducting disorder	155,736 (70.4%)	58,643 (74.8%)	97,093 (68%)	<0.001
Anemia	76,129 (34.4%)	28,350 (36.2%)	47,779 (33.5%)	<0.001
Hypothyroidism	42,905 (19.4%)	15,798 (20.2%)	27,107 (19%)	<0.001
Renal disease	93,533 (42.3%)	34,882 (44.5%)	58,651 (41.1%)	<0.001
Chronic liver disease	6,415 (2.9%)	2,842 (3.6%)	3,573 (2.5%)	<0.001
Cancer and lymphoma	8,346 (3.8%)	2,965 (3.8%)	5,381 (3.8%)	0.859
LOS (days), median (IQR)	4 (3-6)	4 (3-7)	4 (3-6)	<0.001
Length of stay (days)				
• 0-2	49,424 (22.4%)	15,651 (20%)	33,773 (23.7%)	<0.001
• 3-5	98,869 (44.7%)	34,912 (44.6%)	63,957 (44.8%)	<0.001
• ≥6	72,834 (32.9%)	27,792 (35.5%)	45,042 (31.5%)	<0.001
Total charges ($), median (IQR)	25 669 (14 947-46 438)	25 844 (15 073-46 593)	25 577 (14 881-46 320)	0.172

HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; IQR = interquartile range; LOS = length of stay; MVD = mitral valve disease; TVD = tricuspid valve disease.

with isolated MVD versus those with combined TR plus MVD (OR 1.01, 95% CI 0.98 to 1.03). Characteristics of all the risk factors associated with the 30-day readmissions are presented in Table 3. At 90 days, patients with combined TR and MVD had slightly lower readmission rates compared with patients with isolated MVD (OR 0.975, 95% CI 0.96 to 0.99), however the difference did not seem significant at 120 days (OR 0.98, CI 0.96 to 1.01).

Discussion

The main finding of our study was that in patients with HF and MVD the presence of concomitant TR was not associated with adverse short-term outcomes, specifically inpatient all-cause mortality, longer LOS in hospital, or up to 120-day all-cause readmissions.

Our analysis of 221,127 patients shows about 1/3 of subjects have concomitant TR along with HF and MVD. This set of patients had higher incidence of pulmonary hypertension, HFrEF, renal disease, and associated arrhythmias, but this did not translate into worse short-term outcomes. Older age was an independent risk factor associated with increased mortality, but similar 30-day readmissions, irrespective of presence of TR. HFpEF patients were associated with lower mortality but had similar 30-day readmissions. Patients with associated PVD, arrhythmias, anemia, chronic liver disease, or renal disease had higher inpatient mortality. But patients with associated diabetes, CAD, PVD, pericardial disease, chronic renal, or liver disease had more frequent readmissions.

TVD consists of both TS and TR, which is much more common. Approximately 80% of TR cases are functional in nature and related to tricuspid annular dilation and leaflet tethering due to pressure and/or volume overload. The prevalence of functional TR in patients who underwent echocardiography is reported to be as high as 65% to 85%, with significant TR (Grade >2/4) being present in about 1.2% to 15.6% of these patients.[16–18] Moreover, the incidence of TR is expected to continue to increase as the incidence of left ventricular dysfunction increases.[19]

TVD, which mainly consists of TR in the developed world, has been associated with increased adverse outcomes over the long-term. In a study of 5,223 In veterans in the US Veteran's Health Administration system who were followed for 4 years, the 1-year survival of severe TR patients was only 64%, (compared with 92% without TR or 90% with mild TR).[20] These poor outcomes were independent of age, biventricular systolic function, PH, right ventricular size, and inferior vena cava dilatation. In another study of 813 medically managed patients with moderate or severe, isolated TR, the 5-year survival was only 74% independent of patient age.[21] TR has also been independently associated with reduced long-term survival in patients with ischemic or idiopathic left ventricular systolic dysfunction, with or without clinical HF,[22] and in patients with only functional MR. Agricola et al reported that the presence of TR, even in functional MR patients, increased the HF episodes (HR 1.4, 95% CI 1.1 to 2.1, p = 0.01) and decreased the survival free of all-cause mortality (HR 1.6, 95% CI 1.2 to 2.1, p = 0.01).[23]

Table 2
Bivariable and multivariable association with in-hospital mortality

Variable	Bivariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Age−10(years)	1.364 (1.332-1.397)	<0.001	1.374 (1.336-1.412)	<0.001
Women	0.975 (0.926-1.027)	0.342	–	
TVD	0.981 (0.929-1.036)	0.487	–	
HF subtype				
• HFrEF	Reference		Reference	
• HFpEF	0.863 (0.812-0.917)	<0.001	0.756 (0.709-0.806)	<0.001
Hypertension	0.655 (0.621-0.691)	<0.001	0.645 (0.607-0.685)	<0.001
Diabetes mellitus	0.842 (0.796-0.889)	<0.001	0.901 (0.846-0.961)	0.001
Hyperlipidemia	0.690 (0.655-0.727)	<0.001	0.673 (0.633-0.715)	<0.001
Coronary atherosclerosis	1.083 (1.027-1.141)	0.003	1.008 (0.948-1.072)	0.807
Peripheral vascular disease	1.255 (1.170-1.345)	<0.001	1.139 (1.053-1.233)	0.001
Pulmonary hypertension	1.154 (1.095-1.216)	<0.001	1.065 (1.004-1.129)	0.037
Pericardial disease	1.086 (0.900-1.310)	0.388	-	
Arrhythmia and conducting disorder	1.599 (1.501-1.703)	<0.001	1.298 (1.209-1.395)	<0.001
Anemia	1.300 (1.233-1.370)	<0.001	1.133 (1.066-1.204)	<0.001
Hypothyroidism	1.073 (1.007-1.144)	0.031	0.924 (0.859-0.993)	0.031
Renal disease	1.686 (1.600-1.776)	<0.001	1.580 (1.487-1.680)	<0.001
Chronic liver disease	1.321 (1.153-1.515)	<0.001	1.512 (1.301-1.757)	<0.001
Cancer and lymphoma	1.422 (1.265-1.598)	<0.001	1.215 (1.062-1.391)	0.005
Length of stay (days)				
• 0-2	Reference		Reference	
• 3-5	0.614 (0.571-0.661)	<0.001	0.628 (0.576-0.683)	<0.001
• ≥6	1.492 (1.397-1.593)	<0.001	1.441 (1.333-1.559)	<0.001

CI = confidence interval; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HR = hazard ratio; TVD = tricuspid valve disease.

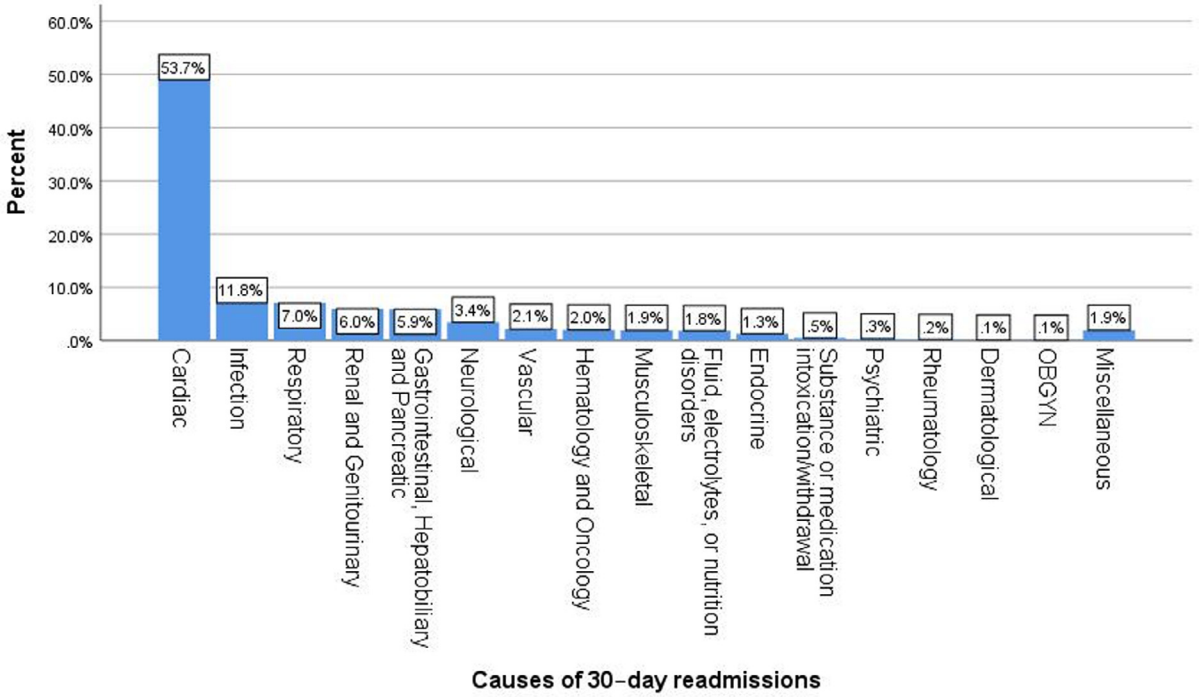

Figure 2. Causes of 30-day readmissions.

TR seems to have worse outcomes whether associated with MVD or not. Although isolated TR has been shown to likely lead to decreased survival if left untreated,[21] concomitant TV repair during left valve surgery has been shown to reduce mortality.[24,25] A meta-analysis of 15 studies with a total of 2,840 patients showed that TR repair at the time of left-sided valve surgery was associated with a significantly lower risk of cardiac-related mortality (OR 0.38; 95% CI: 0.25 to 0.58; p <0.001), with a trend toward a lower risk of all-cause mortality (OR 0.57; 95% CI: 0.32 to 1.05; p = 0.07) at a mean weighted follow-up of 6 years.[26] It has also been shown that concomitant TV repair in patients

Table 3
Bivariable and multivariable association with 30-day readmissions

Variable	Bivariable OR (95% CI)	p	Multivariable OR (95% CI)	p
Age-10 (years)	0.999 (0.992-1.007)	0.823	–	
Women	0.990 (0.970-1.011)	0.360	–	
TVD	1.005 (0.983-1.027)	0.657	–	
HF subtype				
• HFrEF	Reference		Reference	
• HFpEF	1.019 (0.995-1.044)	0.114	1.010 (0.986-1.035)	0.405
Hypertension	0.990 (0.967-1.013)	0.382	–	
Diabetes mellitus	1.190 (1.164-1.215)	<0.001	1.118 (1.092-1.146)	<0.001
Hyperlipidemia	1.031 (1.010-1.053)	0.004	0.980 (0.957-1.003)	0.091
Coronary atherosclerosis	1.163 (1.139-1.188)	<0.001	1.108 (1.081-1.135)	<0.001
Peripheral vascular disease	1.219 (1.184-1.255)	<0.001	1.130 (1.095-1.167)	<0.001
Pulmonary hypertension	1.080 (1.057-1.104)	<0.001	1.024 (1.000-1.048)	0.050
Pericardial disease	1.143 (1.060-1.234)	0.001	1.161 (1.069-1.261)	<0.001
Arrhythmia and conducting disorder	1.047 (1.023-1.071)	<0.001	1.056 (1.029-1.083)	<0.001
Anemia	1.336 (1.307-1.365)	<0.001	1.205 (1.176-1.235)	<0.001
Hypothyroidism	1.009 (0.982-1.036)	0.525	–	
Renal disease	1.384 (1.356-1.414)	<0.001	1.227 (1.198-1.257)	<0.001
Chronic liver disease	1.234 (1.163-1.310)	<0.001	1.192 (1.117-1.272)	<0.001
Cancer and lymphoma	1.284 (1.219-1.353)	<0.001	1.248 (1.179-1.321)	<0.001
Disposition				
• Discharged home with self-care	Reference		Reference	
• Discharge to extended care facility	1.320 (1.285-1.357)	<0.001	1.153 (1.117-1.189)	<0.001
• Home health care	1.227 (1.197-1.258)	<0.001	1.135 (1.104-1.167)	<0.001
• Against medical advice	1.858 (1.657-2.082)	<0.001	1.912 (1.678-2.179)	<0.001
• Discharge alive, destination unknown	1.260 (1.150-1.381)		1.158 (1.043-1.286)	0.006
Length of stay (days)				
• 0-2	Reference		References	
• 3-5	1.141 (1.109-1.174)	<0.001	1.092 (1.058-1.128)	<0.001
• ≥6	1.505 (1.462-1.550)	<0.001	1.325 (1.280-1.371)	<0.001

CI = confidence interval; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; OR = odd ratio; TVD = tricuspid valve disease.

undergoing MV surgery with moderate functional TR does not lead to increased perioperative complication rates, but may have long-term benefit.[27,28]

In our study, TVD was not associated with worse short-term outcomes, specifically inpatient mortality or 30-day readmission. This may be because the majority of these patients probably have functional, volume related TR which is a reflection of associated HF and MVD, improving when the latter are treated appropriately. Diuretic therapy has been the main stay of acute treatment for HF to relieve the congestion and reduce preload.[19,29] This can lead to improvement in right sided hemodynamics with resultant regression of the severity of TR.[30]

Our study is unique in that it includes real-world outcomes nationwide. However, it has some limitations: We were unable to determine the proportion of patients with TVD who had TS as opposed to TR, though this is a rare occurrence in the US, relatively. Hence we use the terms TVD and TR interchangeably. In addition, data on the severity of TR are missing. Previous studies have shown that the severity of TR is inversely proportional to overall survival and outcomes in HF patients.[9,31] The duration of TR also seems to impact long-term outcomes, whether it is isolated TR or concomitant with MVD.[32,33] Also, data on concomitant right ventricular dysfunction was unavailable. Moreover, details on severity of MVD were missing though concomitant TVD is most commonly assumed to be functional TR in these cases. Finally, this study has limitations inherent to using an administrative database such as the NRD, reliance on using ICD−9 codes to identify primary or secondary diagnoses, and absence of primary patient level data. TVD is likely to be under-reported. Moreover, the NRD tracks patients admitted within the same state and does not track deaths that occurred outside of the hospital or emergency department. However, many of these limitations are balanced by the large and nationally represented patient group in this study.

In conclusion, concomitant TVD in patients with HF and MVD is not associated with worse short-term outcomes including in hospital mortality and 30-day readmission rates. Further studies are needed to assess its long-term impact, especially in this era of developing transcatheter treatment options for TR.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.070.

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