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ORIGINAL INVESTIGATIONS

Surgery Does Not Improve Survival in Patients With Isolated Severe Tricuspid Regurgitation

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ABSTRACT

BACKGROUND Patients with isolated tricuspid regurgitation (TR) in the absence of left-sided valvular dysfunction are often managed nonoperatively.

OBJECTIVES The purpose of this study was to assess the impact of surgery for isolated TR, comparing survival for isolated severe TR patients who underwent surgery with those who did not.

METHODS A longitudinal echocardiography database was used to perform a retrospective analysis of 3,276 adult patients with isolated severe TR from November 2001 to March 2016. All-cause mortality for patients who underwent surgery versus those who did not was analyzed in the entire cohort and in a propensity-matched sample. To assess the possibility of immortal time bias, the analysis was performed considering time from diagnosis to surgery as a time-dependent covariate.

RESULTS Of 3,276 patients with isolated severe TR, 171 (5%) underwent tricuspid valve surgery, including 143 (84%) repairs and 28 (16%) replacements. The remaining 3,105 (95%) patients were medically managed. When considering surgery as a time-dependent covariate in a propensity-matched sample, there was no difference in overall survival between patients who received medical versus surgical therapy (hazard ratio: 1.34; 95% confidence interval: 0.78 to 2.30; $p = 0.288$). In the subgroup that underwent surgery, there was no difference in survival between tricuspid repair versus replacement (hazard ratio: 1.53; 95% confidence interval: 0.74 to 3.17; $p = 0.254$).

CONCLUSIONS In patients with isolated severe TR, surgery is not associated with improved long-term survival compared to medical management alone after accounting for immortal time bias. (J Am Coll Cardiol 2019;74:715–25)
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Moderate-to-severe tricuspid regurgitation (TR) affects >1.6 million people in the United States and is generally associated with a poor prognosis (1). Most patients with significant TR have concomitant left-sided heart disease and heart failure. Historically, these patients often were treated with medical therapy targeting the underlying disease processes and diuretic agents

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

TR = tricuspid regurgitation

to address volume overload (2). It is generally unclear if these therapies alter prognosis or improve symptoms, especially in patients with primary valve disease (3). Current American College of Cardiology/American Heart Association guidelines now recommend tricuspid valve surgery for patients with severe, symptomatic TR, especially those with annular dilation and right heart failure. However, this is associated with a weak (Class C) level of evidence and is only recommended in patients undergoing concomitant left-sided valve surgery (4). As a result, only about 500 patients in the United States undergo surgery for isolated tricuspid regurgitation each year (4).

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Whereas the clinical significance of TR is well established in patients with left-sided valvular heart disease, the effect of isolated TR was only recently described in 2004, when it was shown to be a significant predictor of mortality independent of the underlying degree of pulmonary hypertension or ventricular function (5). Recent studies have reported a growing population of adult patients without left-sided heart disease, pulmonary hypertension, or congenital abnormalities who are developing isolated severe TR (1). However, the role of surgery in these patients is unclear. Single-center studies have reported variable perioperative outcomes and long-term mortality rates following isolated tricuspid valve surgery (6), and there is a distinct lack of comparative outcomes for medically versus surgically treated patients. Furthermore, percutaneous techniques to repair or replace the tricuspid valve are in development (NCT02787408, NCT02339974, NCT02574650, NCT02981953, NCT02471807), potentially offering an opportunity to improve right ventricular function at lower procedural risk (7).

In the setting of these important issues, we aim to assess the effect of tricuspid valve surgery for isolated TR on mortality. In this analysis, we compared propensity-matched samples of patients who underwent surgery versus those who did not. Furthermore, we compared overall survival between patients who underwent a tricuspid valve repair versus replacement.

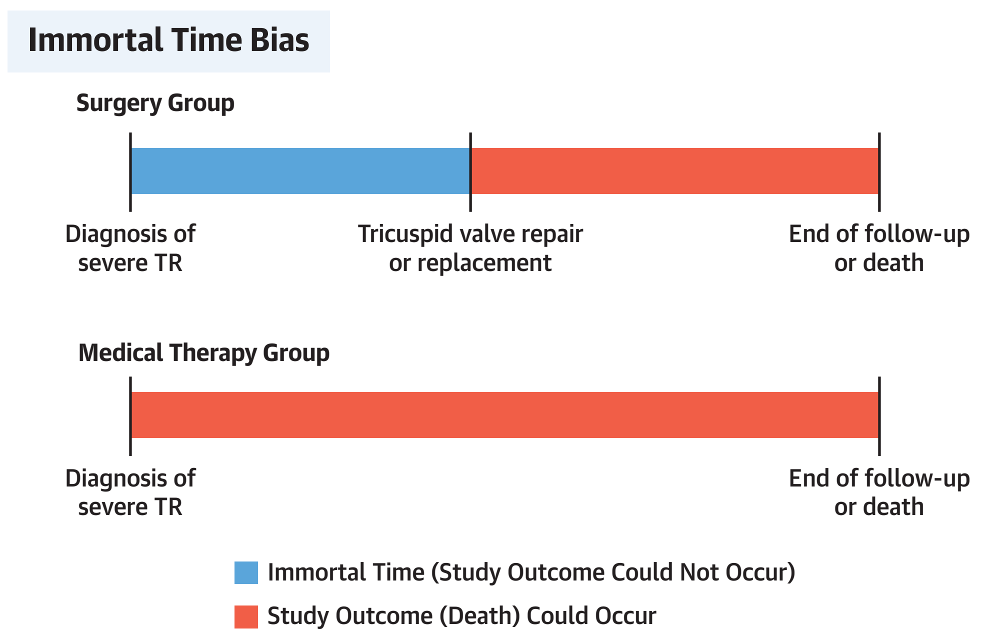
METHODS

STUDY SAMPLE. Using an institutional, longitudinal echocardiography database at the Massachusetts General Hospital, a retrospective cohort analysis was performed on all adult patients who underwent an echocardiogram at our institution between November 2001 and March 2016 and who were found to have isolated severe TR. Severe TR was defined by comprehensive 2-dimensional and Doppler echocardiography in all patients and assessed by integrating a number of imaging and Doppler parameters such as leaflet morphology, central jet area, vena contracta width, hepatic vein systolic flow, and the density and shape of the continuous wave Doppler velocity profile as outlined in the guidelines of the American Society of Echocardiography (8). Patients with significant left-sided valvular heart disease or severe pulmonic stenosis or insufficiency were excluded. Significant left-sided valvular dysfunction was defined as moderate or severe insufficiency or stenosis of the mitral or aortic valves. The first echocardiographic diagnosis of isolated severe TR defined each patient's entry point into the study and was considered time zero for all time-to-event analyses. All patients were followed per routine clinical practice with clinical examination and transthoracic echocardiography at the discretion of their care providers. The decision to undergo surgical intervention or medical management was made on an individual basis by the patient's cardiologist and cardiac surgeon. Institutional review board approval at Partners Healthcare was obtained for completion of this study.

STUDY DESIGN AND DEFINITIONS. The primary exposure was medical versus surgical management of isolated severe TR. All operations involving intervention on the tricuspid valve were included and consisted of tricuspid valve repair ($n = 143$) and tricuspid valve replacement ($n = 28$). The decision to perform repair versus replacement was determined by the patient's care providers based on pre-operative clinical characteristics, echocardiographic parameters, and intraoperative findings. The primary outcome was all-cause mortality. Survival was defined as the time from the date of first echocardiographic diagnosis of severe TR to the date of death. Death was determined by querying the Social Security Death Index and was deemed complete as of April 25, 2018. For patients recorded as deceased but without a date of death, an estimated date of death was imputed as halfway between the date of last known follow-up at our institution and April 25, 2018. Secondary outcomes included the degree of residual TR after repair versus replacement techniques in the surgery group.

Demographic and clinical characteristics of all patients were collected from the Partners Research Data Repository including the patient's age, sex, race, and history of hypertension, diabetes mellitus, congestive heart failure, coronary artery disease, chronic kidney disease (defined as an estimated glomerular filtration rate <60 ml/min), and chronic obstructive

FIGURE 1 Graphical Depiction of Immortal Time Bias



Immortal time bias is created by the span of time in observational studies when the outcome could not have occurred due to how the exposure was defined. In this case, this was the time from diagnosis of severe tricuspid regurgitation (TR) to surgery. The subject necessarily had to survive until surgery to be classified as having surgery in this analysis.

pulmonary disease. Echocardiographic parameters included left ventricular ejection fraction and estimated echocardiographic right ventricular systolic pressure.

STATISTICAL ANALYSIS. All data are presented as n (%) for categorical variables and mean ± SD for normally distributed continuous variables or median (interquartile range [IQR]) for non-normally distributed continuous variables. Between-group differences were analyzed using a Student's *t*-test or Mann-Whitney *U* test for continuous variables and a chi-square or Fisher exact test for categorical variables. A propensity-matched sample was generated for patients who underwent medical versus surgical management. Propensity matching was performed based on 1-to-1 nearest neighbor matching with a greedy matching algorithm and a caliper width of 0.5. All covariates were used to assign the propensity score except right ventricular systolic pressure, as there was a significant amount of missing data in this variable. To test the validity of this approach, a sensitivity analysis was conducted including right ventricular systolic pressure in the propensity model to ensure it did not dramatically alter the results. An additional sensitivity analysis was considered in which the covariate pattern in the surgical patient was assessed at the time of surgery as opposed to the time of diagnosis. This was performed to verify that matched pairs had comparable prognoses at the time of surgery in the surgical patient. The covariate balance after matching was assessed by the standardized bias (difference in means or proportions divided by the standard error). A covariate was considered well balanced if the standardized bias (SB) was <0.10.

To address variables that confound the relationship between treatment decision and death, a Cox proportional hazards model was constructed to identify independent risk factors for mortality. All covariates were included in the final model and the propensity score was incorporated using inverse probability weighting to calculate the propensity-adjusted hazard ratio. The proportional hazards assumption was checked by testing the Schoenfeld residuals for the global model as well as all included covariates and was not violated. To account for the potential of immortal time bias, the analysis was performed considering time from diagnosis of severe TR to surgery, which was incorporated as a time-dependent covariate in an extended Cox model comparing medical versus surgical management. Immortal time bias is defined as the span of time in

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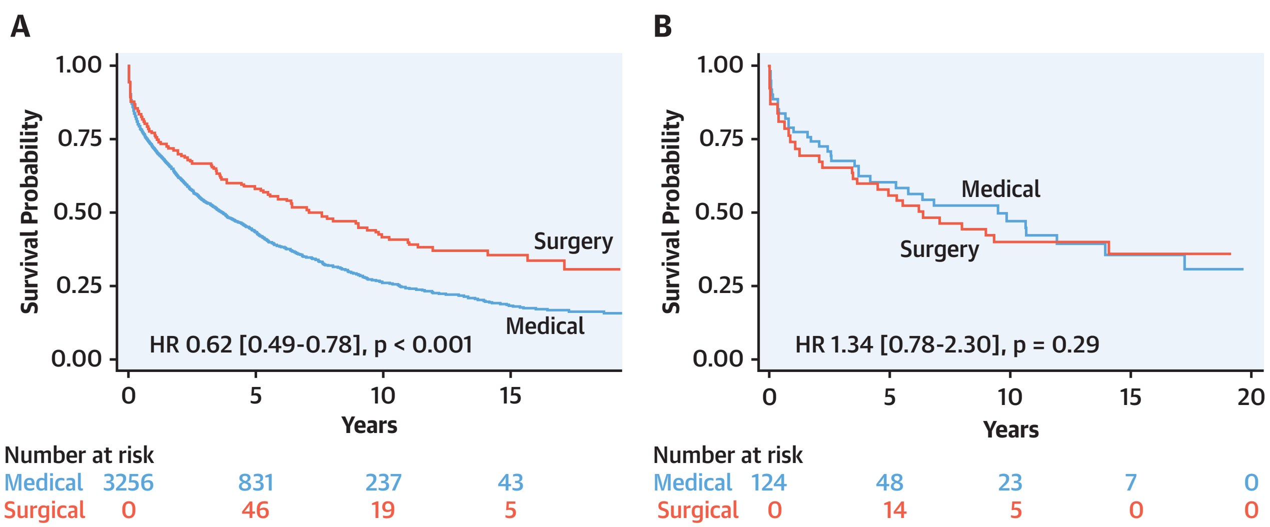
FIGURE 2 **Cumulative Survival Adjusting for Time From Diagnosis to Surgery**



Overall survival of **(A)** the entire cohort and **(B)** a propensity-matched sample of patients adjusting for time from diagnosis of severe tricuspid regurgitation (TR) to surgery as a time-dependent covariate. Hazard ratio (HR) is for surgery relative to medical management. Curves generated using an extended Kaplan-Meier estimator, which allows the cohorts to vary with time depending on the covariate pattern (surgery vs. no surgery.) The time of origin is the first echocardiographic diagnosis of severe TR for all patients; however, each curve does not correspond to a fixed cohort of patients, as surgical patients are allowed to contribute risk to the medical group before the time of surgery.

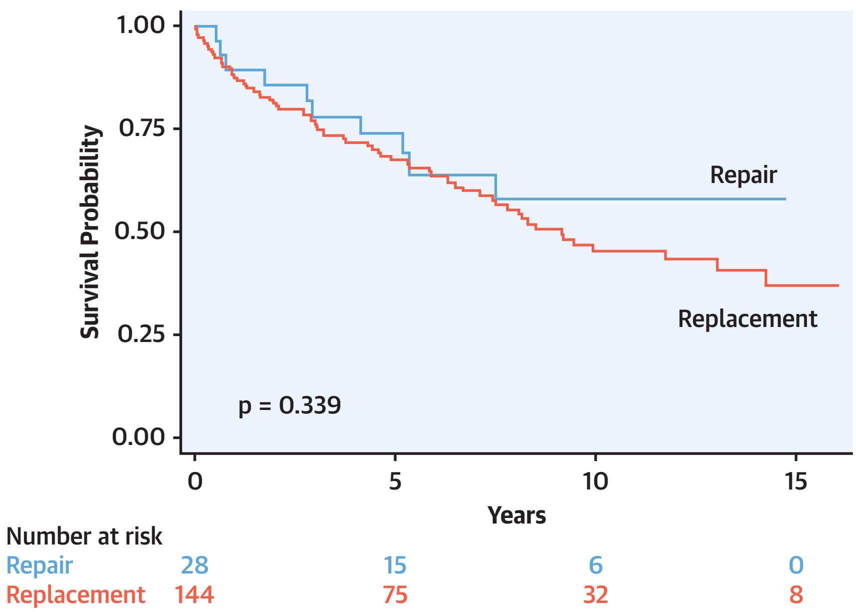
observational studies when the outcome could not have occurred due to how the exposure was defined (9) (**Figure 1**). In this case, this was the time from diagnosis of severe TR to surgery. To graphically illustrate the association between surgical treatment as a time-dependent covariate and mortality, an extended Kaplan-Meier estimator was used (**Figure 2**) (10). In this method, the time-zero for both medical and surgical patients is the time of first echocardiographic diagnosis of severe TR. The extended Kaplan-Meier estimator then updates the cohorts at each event time, such that the sizes of the risk sets can change during the course of study depending on the covariate pattern (surgery vs. no surgery) at each time point. In this case, a surgical patient is allowed to contribute risk to the medical group before the time of their surgery when they are receiving medical management alone. In this case, the curves generated by the extended Kaplan-Meier method do not represent fixed cohorts of patients, as patients can contribute to different curves at different time points during follow-up. The propensity-matched comparison with surgery as a time-dependent covariate was considered the primary analysis given the concern for immortal time bias. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). To assess the possibility that our results could be affected by selection bias related to care outside this health care system and to account for the possibility that patients had moderate-to-severe TR for a period of time before being referred to our center, we repeated the analysis in a "loyalty cohort" previously validated to represent patients receiving most of their care at our institution (11).

A pre-specified subgroup analysis was also performed on all patients undergoing surgery comparing overall survival for those who received a tricuspid repair versus replacement. The year of operation, presented in 5-year time intervals, was included as a time varying covariate in this analysis to account for era-specific differences in surgical techniques and perioperative management. Overall survival was compared using standard Kaplan-Meier (**Figure 3**) and Cox proportional hazards models. All analyses were completed using SAS version 9.4 (SAS Institute, Cary, North Carolina) and STATA version 13.1 (STATACorp, College Station, Texas). A p value <0.05 was considered statistically significant.

RESULTS

PATIENT DEMOGRAPHICS AND UNADJUSTED RESULTS. Of 3,276 patients identified with isolated severe TR, 171 (5%) underwent tricuspid valve surgery and the remaining 3,105 (95%) were medically managed. Of the patients who underwent surgery,

FIGURE 3 **Cumulative Survival of Surgical Subgroup**



Overall survival for patients who received surgery comparing tricuspid valve repair versus replacement.

143 (84%) had a tricuspid valve repair and 28 (16%) had a tricuspid valve replacement. Compared with patients who were medically managed, patients who underwent surgery were younger (age 73 years vs. 61 years; SB = 1.36), less likely to have coronary artery disease (31% vs. 16%; SB = 0.65), heart failure (83% vs. 72%; SB = 0.46), diabetes (4% vs. 1%; SB = 0.17), or chronic kidney disease (39% vs. 20%; SB = 0.41), and had a higher ejection fraction (52% vs. 57%; SB = 0.26) (**Table 1**). With respect to concurrent coronary artery disease, of the 171 patients who underwent TV surgery, 3 (2%) had a history of prior coronary artery bypass grafting (CABG) and 29 (17%) had concurrent CABG at the time of tricuspid valve intervention. Of the 3,105 patients who were medically managed, 122 (4%) had a history of prior CABG and 15 (<1%) underwent isolated CABG after the time of severe TR diagnosis. Median follow-up time for all patients was 2.6 years (IQR: 0.6 to 5.3 years).

PROPENSITY-MATCHED COMPARISON. From this cohort, a propensity-matched sample of 62 pairs (representing 124 unique patients) was generated (**Table 1**). The etiologies of severe TR in this sample included functional in 73 (59%), degenerative in 8 (6%), acquired due to endocarditis, rheumatic heart disease, or carcinoid in 25 (20%), pacemaker induced in 5 (4%), and congenital in 13 (11%). Patients who underwent surgery were more likely to have acquired (32% vs. 8%; SB = 0.77) and congenital (18% vs. 3%; SB = 0.53) disease, and were less likely to have functional disease (39% vs. 79%; SB = 0.31) compared with patients who underwent medical management. Patients were otherwise well matched in terms of age (SB = 0.05), sex (SB ≤0.01), comorbidities, and left ventricular function (SB = 0.08). Of the 40 patients in the medical group and 39 patients in the surgical group with heart failure, 24 (39%) and 17 (27%) had right heart failure, respectively, and 11 (17%) had biventricular failure in both groups. Echocardiographic evidence of right ventricular dilation was present in 47 (76%) versus 48 (77%) patients in the medical and surgical groups, respectively (SB = 0.04). The indication for surgery was severe TR in all cases.

PROPENSITY-MATCHED COMPARISON ACCOUNTING FOR IMMORTAL TIME. The median time from diagnosis of severe TR to surgery was 2.9 months (IQR: 0.5 to 15.7 months) in the entire cohort and 3.7 months (IQR: 0.5 to 25.7 months) in the propensity-matched sample. Overall survival when adjusting for time from diagnosis to surgery as a time-dependent covariate is presented in **Figure 2**. In the unadjusted comparison of the entire cohort (**Figure 2A**), patients who underwent surgery had an apparent survival benefit (HR: 0.62; 95% CI: 0.49 to 0.78; p < 0.001); however, when applied to the propensity-matched sample

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TABLE 1 Baseline Characteristics of the Entire Cohort and Propensity-Matched Sample

	Entire Cohort			Propensity-Matched Sample		
	Medical (n = 3,105)	Surgical (n = 171)	SB*	Medical (n = 62)	Surgical (n = 62)	SB*
Clinical						
Age, yrs	73.0 ± 15.5	61.0 ± 16.2	1.36	51.0 ± 18.8	52.0 ± 16.0	0.05
Female	1,681 (54)	93 (54)	0.08	31 (30)	31 (50)	<0.01
Race	–	–	0.19	–	–	0.10
White	2,561 (83)	137 (80)	–	49 (79)	48 (77)	–
Black	162 (5)	8 (5)	–	6 (10)	3 (5)	–
Hispanic	103 (3)	4 (2)	–	0 (0)	1 (2)	–
Asian	73 (2)	5 (3)	–	1 (1)	2 (3)	–
Other/unknown	206 (7)	17 (10)	–	6 (10)	8 (13)	–
Hypertension	2,355 (76)	89 (52)	0.73	27 (44)	26 (42)	0.10
Diabetes mellitus	117 (4)	2 (1)	0.17	2 (3)	2 (3)	0.03
Coronary artery disease	948 (31)	28 (16)	0.65	5 (8)	4 (6)	<0.01
Heart failure	2,578 (83)	123 (72)	0.46	40 (64)	39 (63)	0.04
Chronic kidney disease	1,218 (39)	34 (20)	0.41	15 (24)	13 (21)	0.07
COPD	871 (28)	28 (16)	0.17	14 (23)	13 (21)	<0.01
Echocardiographic						
LVEF, %	52 ± 19.6	57 ± 18.7	0.26	57 ± 19.2	57 ± 19.7	0.08
RVSP, mm Hg	54 ± 19.9	53 ± 22.7	0.47	52 ± 22.2	45 ± 21.2	0.37

Values are mean ± SD or n (%). *Standardized bias (SB) assesses the balance of a measured covariate between comparison groups in a propensity-matched analysis. A covariate is considered well-balanced if the standardized bias is <0.10.
COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure.

(Figure 2B), there was no significant difference in overall survival for patients who were medically managed compared with patients who underwent surgery. On multivariable Cox regression modeling (Table 2), surgical intervention demonstrated no significant difference in survival compared with medical management alone (HR: 1.34; 95% CI: 0.78 to 2.30; p = 0.288).

SENSITIVITY ANALYSES. A sensitivity analysis including right ventricular systolic pressure in the propensity-matched analysis generated 54 propensity-matched pairs for comparison (Online Tables 1 and 2). Consistent with the primary analysis, surgical intervention showed no difference in survival compared with medical management alone (HR: 0.71; 95% CI: 0.38 to 1.30; p = 0.270).

A second sensitivity analysis considering a "loyalty cohort" of patients who are likely to receive the majority of their care at our institution generated 855 patients, of which 38 (4%) underwent surgery and 817 (96%) were medically managed. In this sample, the median time from diagnosis of severe TR to surgery was significantly longer at 13.5 months (IQR: 4.2 to 31.7 months) (compared with 2.9 months in the total sample) and the median follow-up time was 3.2 years (IQR: 1.5 to 5.9). Demographic and clinical characteristics of the loyalty cohort as well as a propensity-matched loyalty sample consisting of 30 total patients (15 surgery, 15 medical) are presented in Online Table 3. In the unmatched comparison of the entire loyalty cohort adjusting for time from diagnosis to surgery as a time-dependent covariate, surgery had an apparent survival benefit compared with medical therapy alone (HR: 0.55; 95% CI: 0.33 to 0.91; p = 0.02). However, when comparing medical with surgical management in a propensity-matched loyalty cohort adjusting for time from diagnosis to surgery, there was no significant difference in overall survival (HR: 1.77; 95% CI: 0.58 to 5.41; p = 0.31). This was limited by a relatively small sample size; however,

TABLE 2 Multivariable Predictors of Mortality in Propensity-Matched Sample Adjusting for Time From Diagnosis to Surgery as a Time-Dependent Covariate

Risk Factors	HR	95% CI	p Value
Management			
Medical	Ref.		
Surgical	1.34	0.78–2.30	0.288
Age, yrs	1.01	0.99–1.03	0.156
Female	0.62	0.35–1.09	0.099
Hypertension	0.91	0.51–1.62	0.749
Coronary artery disease	1.06	0.41–2.73	0.901
Heart failure	2.54	1.32–4.88	0.005
Chronic kidney disease	1.38	0.75–2.55	0.299
COPD	1.62	0.91–2.89	0.104

CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio.

the results are consistent with the analysis in the total sample (Online Figure 1).

A final sensitivity analysis considering the covariate pattern in the surgical group at the time of surgery generated an additional 62 matched pairs for comparison (Online Table 4). Despite a slightly higher burden of comorbid disease in both groups, there was no significant difference in overall survival comparing medical with surgical management after adjusting for surgery as a time-dependent covariate (HR: 1.30; 95% CI: 0.75 to 2.26; $p = 0.343$) (Online Table 5).

REPAIR VERSUS REPLACEMENT. In the subgroup of patients who underwent tricuspid valve surgery, there was no statistically significant difference in operative mortality (8% vs. 4%; $p = 0.379$) or long-term unadjusted survival between those who underwent a tricuspid valve repair versus replacement (**Figure 3**) ($p = 0.339$). This association remained nonsignificant on adjusted multivariable analysis (HR: 1.53; 95% CI: 0.74 to 3.17; $p = 0.254$) (**Table 3**). Risk factors associated with an increased risk of mortality after surgery included advanced age (HR: 1.04; 95% CI: 1.02 to 1.06; $p < 0.001$) and a history of heart failure (HR: 2.86; 95% CI: 1.46 to 5.62; $p = 0.002$) at the time of initial presentation. The year of operation had no effect on overall survival in this sample (HR for years 2012 to 2016 relative to 2001 to 2006: 0.46; 95% CI: 0.18 to 1.14; $p = 0.087$). Of note, the number of patients with mild to moderate residual TR immediately after tricuspid valve repair was 29 (20%) compared with 1 (3%) after replacement ($p = 0.03$). Overall survival was not statistically significant for patients with mild to moderate residual TR immediately after repair/replacement compared with those without post-operative TR ($p = 0.45$).

TABLE 3 Multivariable Predictors of Mortality in Surgical Subgroup

Risk Factors	HR	95% CI	p Value
TV intervention			
Repair	Ref.		
Replacement	1.53	0.74–3.17	0.254
Age, yrs	1.04	1.02–1.06	<0.001
Female	0.77	0.47–1.26	0.298
Year of operation			
2001–2006	Ref.		
2007–2011	0.49	0.24–1.00	0.064
2012–2016	0.46	0.18–1.14	0.087
Hypertension	0.72	0.44–1.17	0.182
Coronary artery disease	0.80	0.44–1.46	0.472
Heart failure	2.86	1.46–5.62	0.002
Chronic kidney disease	1.32	0.76–2.28	0.329
COPD	1.42	0.80–2.51	0.234
LVEF, %	1.00	0.98–1.01	0.521

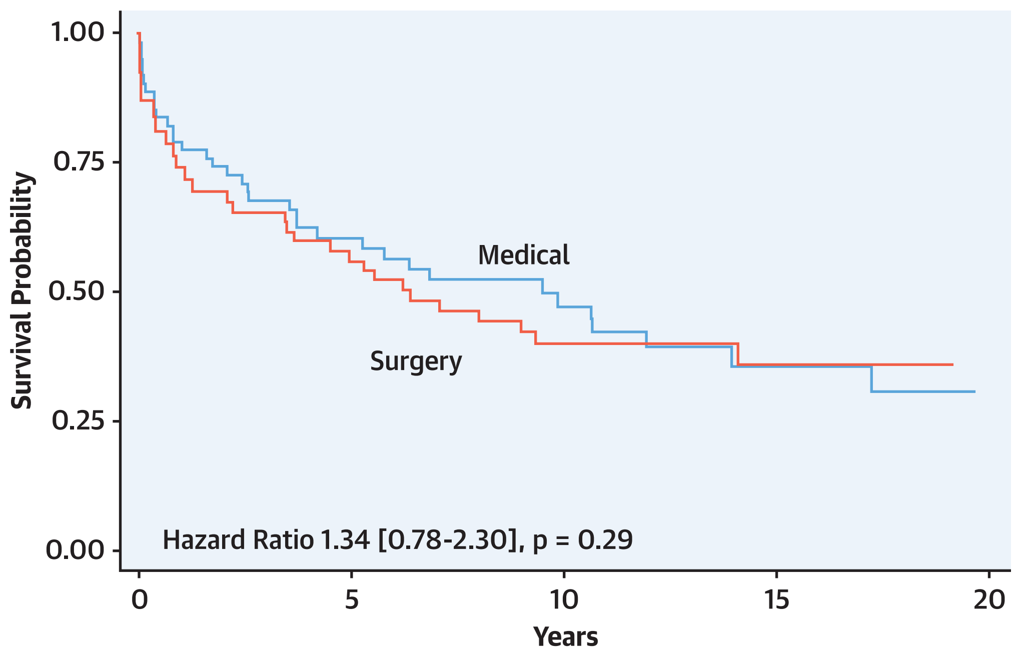
LVEF = left ventricular ejection fraction; other abbreviations as in **Table 2**.

DISCUSSION

In this study, we found no difference in long-term survival regardless of whether patients with isolated severe TR underwent surgery or medical therapy alone after accounting for immortal time bias (**Central Illustration**). Furthermore, in the surgical group, tricuspid valve repair versus replacement was not associated with a survival difference. To our knowledge, this is the largest analysis of clinical outcomes for surgery for isolated severe TR compared with patients who do not undergo surgery. These results are important because they suggest that forthcoming randomized controlled trials with novel percutaneous techniques to address severe TR may not demonstrate differences in mortality. However, catheter-based therapies provide the important opportunity to rethink and optimally define the appropriate timing of intervention in patients with tricuspid regurgitation, which may affect overall survival or symptomatic quality of life. Surgical mortality may be adversely affected by the practice of delaying operative intervention—up to 8 years in our population—thereby allowing for the development of right heart failure and end-organ damage. For the aortic and mitral valves, the timing of surgical referral is based on an integration of symptoms, disease severity, and markers of LV dysfunction (1). A similar approach is needed for patients with isolated tricuspid disease and may affect overall survival.

In addition to informing clinical decision-making, this work demonstrates critical concepts for the analysis of cardiovascular procedures and surgery with observational data. Even in the propensity-matched sample, which adjusts for measured differences in patient characteristics, surgery was associated with a two-thirds reduction in mortality. Although analyses are commonly performed this way, this type of analysis does not account for the fact that patients in the surgical group do not have surgery immediately after diagnosis. As such, the finding in the propensity-matched analysis is likely related to immortal time bias. In this case, this "immortal time" was the time from diagnosis of severe TR to surgery. The subject necessarily had to survive until surgery to be classified as having surgery in this analysis. In an unadjusted analysis, the time spent awaiting surgical

CENTRAL ILLUSTRATION Surgery Versus Medical Therapy for Severe Tricuspid Regurgitation



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Cumulative survival in propensity-matched sample of patients with isolated severe tricuspid regurgitation adjusting for time from diagnosis to surgery as a time-dependent covariate. Curves generated using an extended Kaplan-Meier estimator, which allows the cohorts to vary with time depending on the covariate pattern (surgery vs. no surgery). The time of origin is the first echocardiographic diagnosis of severe tricuspid regurgitation for all patients; however, each curve does not correspond to a fixed cohort of patients, as surgical patients are allowed to contribute risk to the medical group before the time of surgery.

intervention is erroneously attributed to surgical intervention, thereby offering an apparent survival advantage to the surgery group. Ultimately, adjusting for time from diagnosis to surgery changed our conclusion in the propensity-matched analysis from a significant surgical benefit to no difference between groups. This bias has been demonstrated in other areas of cardiac surgery (12-14). Various analytic techniques including time-dependent models or landmark analyses have been previously described to account for this immortal bias (15), and should be employed in appropriate analytic settings.

Clinically, our findings extend previous analyses focused on the long-term outcomes associated with TR. In a large Veterans Affairs cohort study of 5,223 patients, severe TR was associated with a 36.1% 1-year mortality risk (5). When adjusting for age, pulmonary hypertension, and left ventricular ejection fraction, severe TR was still found to be an independent risk factor for mortality, with an HR of 1.31 (95% CI: 1.05 to 1.66) compared with patients without TR. In another series, limited to patients with isolated TR, severe TR was associated with worse long-term survival (HR: 1.78; 95% CI: 1.10 to 2.82) even when adjusting for significant cardiopulmonary comorbidities (16). In our study, similar to these previous analyses, we demonstrate a 31% (IQR: 30% to 33%) and 63% (IQR: 61% to 65%) 1- and 5-year mortality rate for the entire cohort of patients who underwent medical management alone. Here, we have also demonstrated that surgery does not appear to modify that increased risk of mortality.

In isolated surgical series, long-term mortality rates associated with severe TR are similarly high. Perioperative mortality rates range from 2% to 20% and 1-year post-operative mortality rates range from 17% to 24% (3,17,18-24). These rates are considerably higher than contemporary operative mortality rates after isolated mitral valve repair (range 1.4% to 2.6%), mitral valve replacement (3.8%), and aortic valve replacement (2.2%) in the United States (25-27). Given the lack of data available to inform the appropriate timing of surgery for patients with isolated severe TR, this mortality difference is likely partially explained by the practice of delayed operative intervention, thereby allowing for the development of significant end-organ failure including right ventricular dysfunction, cirrhosis, and renal failure. In our study, we found heart failure to be a significant independent predictor of mortality after surgical intervention. In the surgical cohort, 72% had evidence of heart failure at the time of diagnosis, and yet, >25% of patients waited for >1 year before receiving a surgical referral. In fact, an inverse relationship exists between duration of TR and outcomes (28), and factors associated with late presentation, such as heart failure, exerted a greater effect on overall mortality than the addition of concomitant other valvular procedures. They argued that this supported a more aggressive and earlier indication for tricuspid valve surgery (28), similar to left-sided valvular lesions for which guidelines support surgical referral before severe heart failure symptoms or left ventricular dysfunction.

Our work here fills a critical gap: there had been a distinct lack of comparative data directly comparing medical versus surgical intervention. To date, only 1 study has compared long-term survival in patients with isolated TR treated with medical therapy versus surgery (29). In this analysis, 45 propensity-matched pairs were compared. Although there was a trend toward improved survival in the surgical group, this did not reach statistical significance (HR: 0.29; 95% CI: 0.08 to 1.10; $p = 0.07$). Although those results did not reach statistical significance with a smaller sample size, the magnitude of the HR is similar to the HR in our study without the time-dependent covariate. As such, our results likely differ because our analysis accounts for the possibility of immortal time bias.

Multiple studies have been conducted comparing the outcomes of tricuspid valve repair versus replacement, and the findings are mixed. In patients with extreme annular dilation, leaflet abnormalities, or previously failed TV repair, TV replacement may be required (30). However, operative mortality is often reported to be higher for TV replacement compared with repair. For example, Zack et al. (21) compared in-hospital mortality rates for >5,000 patients receiving an isolated tricuspid valve repair or replacement and found that adjusted in-hospital mortality was significantly increased for tricuspid valve replacement compared with repair (odds ratio: 1.91; 95% CI: 1.18 to 3.09; $p = 0.009$) (21). These series, however, may be confounded by a greater number of comorbidities in patients undergoing replacement and the inclusion of complex multivalvular operations in patients with concurrent left-sided valvular pathology and advanced heart failure. In contrast, Moraca et al. (22) performed a propensity-matched analysis of 68 pairs of patients (approximately one-half of whom underwent isolated tricuspid valve surgery), and found no difference in operative or long-term mortality between those who received a repair versus a replacement (22). This suggests that when comorbidities are balanced, operative mortality may be similar between repair and replacement. Consistent with these findings, we also report no difference in overall survival based on the type of surgical intervention. However, given the relatively small sample size pertaining to this secondary analysis, we are not able to reach firm conclusions on this secondary analytic aim.

STUDY LIMITATIONS. First, as a single-center study, the external validity of our results is uncertain. Given the granular data including echocardiographic parameters used in this analysis, a multicenter study for this question is likely to be very challenging. Second, given the retrospective nature of the study, the authors were unable to standardize medical regimens for severe TR, and therefore, the medically managed group represents a heterogenous sample of individually targeted medical therapies based on patient and provider preferences. Third, the timing of surgical referral was not uniform and varied from 1 day to 8 years at the extremes of our study. This is likely reflective of significant treatment selection or indication bias, which affects the timing and selection of patients for surgical therapy. Unfortunately, current guidelines do not provide any data about the indications for surgery or the optimal timing of intervention in patients with isolated severe tricuspid regurgitation, which results in substantial and unavoidable clinical heterogeneity that is difficult to define retrospectively and is likely influenced by individual patient characteristics and provider preferences. Despite statistical methods to address this issue, such as propensity matching and adjusting for immortal time bias, we acknowledge the possibility of residual treatment selection/indication bias that cannot be completely eliminated outside of a randomized controlled clinical trial. Surgical mortality, in this case, may be adversely affected by delaying operative intervention, especially when right ventricular dysfunction or end-organ damage develop. The unmatched surgical sample was, on average, younger and had less comorbid disease than patients who were medically managed. Although we

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attempted to rigorously control for this with propensity matching, we acknowledge the possibility of residual confounding and cannot entirely exclude treatment selection bias. Fourth, as a single-center study, we cannot exclude selection bias related to care received outside of our system. Reassuringly, the sensitivity analysis in a loyalty cohort confirmed the main conclusions and support the finding that there is no difference in survival for patients who receive medical versus surgical management. Finally, while the severity of TR reported in our study conformed to accepted guidelines (8), future analyses may benefit from considering a recently proposed modification for quantifying severe TR (31), which subdivides severe TR into severe, massive, and torrential TR to determine if this more specific quantification will provide additional insight, particularly if these criteria are included in future guidelines.

CONCLUSIONS

In patients with isolated severe tricuspid regurgitation, there is no difference in long-term survival for patients who undergo surgical intervention compared with medical management alone. These results emphasize the importance of accounting for immortal time bias in observational research and suggest that forthcoming randomized controlled trials of novel percutaneous therapies for severe TR should focus on the optimal timing of intervention in patients with tricuspid regurgitation with respect to overall survival and quality of life.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with isolated severe TR, valve replacement/and repair do not improve long-term survival compared with medical management, after accounting for immortal time bias.

COMPETENCY IN PRACTICE-BASED LEARNING: This study emphasizes the importance of accounting for immortal time bias in assessing the efficacy of surgical procedures using longitudinal observational data.

REFERENCES

1. Fender EA, Zack CJ, Nishimura RA. Isolated tricuspid regurgitation: Outcomes and therapeutic interventions. Heart 2018;104:798–806.

2. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II. Circulation 2008;117:1717–31.

3. Kundi H, Popma JJ, Cohen DJ, et al. Prevalence and outcomes of isolated tricuspid valve surgery among Medicare beneficiaries. Am J Cardiol 2019;123:132–8.

4. Alqahtani F, Berzingi CO, Aljohani S, Hijazi M, Al-Hallak A, Alkhouli M. Contemporary trends in the use and outcomes of surgical treatment of tricuspid regurgitation. J Am Heart Assoc 2017;6:e007597.

5. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405–9.

6. Kim JB, Jung SH, Choo SJ, Chung CH, Lee JW. Surgical outcomes of severe tricuspid regurgitation: Predictors of adverse clinical outcomes. Heart 2013;99:181–7.

7. Rodés-Cabau J, Hahn RT, Latib A, et al. Transcatheter therapies for treating tricuspid regurgitation. J Am Coll Cardiol 2016;67:1829–45.

8. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation. J Am Soc Echocardiogr 2017;30:303–71.

9. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol 2008;167:492–9.

10. Snapinn SM, Jiang Q, Iglewicz B. Illustrating the impact of a time-varying covariate with an Extended Kaplan-Meier estimator. Am Stat 2005;59:301–7.

11. Atlas SJ, Grant RW, Chang Y, Ferris TG BM. Patient loyalty within a primary care practice network: a population-based approach to quality assessment and improvement efforts. J Gen Intern Med 2005;20 Suppl 1:25–296.

12. Mantel N, Byar DP. Evaluation of response-time data involving transient states: an illustration using heart-transplant data. J Am Stat Assoc 1974;69:81–6.

13. Clark DA, Stinson EB, Griepp RB, Schroeder JS, Shumway NE, Harrison DC. Cardiac transplantation in man. VI. Prognosis of patients selected for cardiac transplantation. Ann Intern Med 1971;75:15–21.

14. Deville C, Fontan F, Chevalier JM, Madonna F, Ebner A, Besse P. Surgery of post-infarction ventricular septal defect: risk factors for hospital death and long-term results. Eur J Cardiothorac Surg 1991;5:167–74; discussion 175.

15. Dafni U. Landmark analysis at the 25-year landmark point. Circ Cardiovasc Qual Outcomes 2011;4:363–71.

16. Topilsky Y, Nkomo VT, Vatury O, et al. Clinical outcome of isolated tricuspid regurgitation. J Am Coll Cardiol Img 2014;7:1185–94.

17. Ejiofor JI, Neely RC, Yammine M, et al. Surgical outcomes of isolated tricuspid valve procedures: repair versus replacement. Ann Cardiothorac Surg 2017;6:214–22.

18. Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. J Thorac Cardiovasc Surg 2012;143:1043–9.

19. Chang B-C, Song S-W, Lee S, Yoo K-J, Kang M-S, Chung N. Eight-year outcomes of tricuspid annuloplasty using autologous pericardial strip for functional tricuspid regurgitation. Ann Thorac Surg 2008;86:1485–92; discussion 1493.

20. Bouleti C, Juliard J-M, Himbert D, et al. Tricuspid valve and percutaneous approach: No longer the forgotten valve! Arch Cardiovasc Dis 2016;109:55–66.

21. Zack CJ, Fender EA, Chandrashekar P, et al. National trends and outcomes in isolated tricuspid valve surgery. J Am Coll Cardiol 2017;70:2953–60.

22. Moraca RJ, Moon MR, Lawton JS, et al. Outcomes of tricuspid valve repair and replacement: a propensity analysis. Ann Thorac Surg 2009;87:83–9.

23. Kim Y-J, Kwon D-A, Kim H-K, et al. Determinants of surgical outcome in patients with isolated tricuspid regurgitation. Circulation 2009; 120:1672–8.

24. Farag M, Arif R, Sabashnikov A, et al. Repair or replacement for isolated tricuspid valve pathology? insights from a surgical analysis on long-term survival. Med Sci Monit 2017;23: 1017–25.

25. Kaneko T, Vassileva CM, Englum B, et al. Contemporary outcomes of repeat aortic valve replacement: a benchmark for transcatheter valve-in-valve procedures. Ann Thorac Surg 2015; 100:1298–304; discussion 1304.

26. Badhwar V, Peterson ED, Jacobs JP, et al. Longitudinal outcome of isolated mitral repair in older patients: results from 14,604 procedures performed from 1991 to 2007. Ann Thorac Surg 2012;94:1870–7; discussion 1877–9.

27. Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2009;87: 1431–7; discussion 1437–9.

28. Kilic A, Saha-Chaudhuri P, Rankin JS, Conte JV. Trends and outcomes of tricuspid valve surgery in North America: an analysis of more than 50,000 patients from the Society of Thoracic Surgeons database. Ann Thorac Surg 2013;96:1546–52.

29. Lee J-W, Song J-M, Park JP, Lee JW, Kang D-H, Song J-K. Long-term prognosis of isolated significant tricuspid regurgitation. Circ J 2010;74:375–80.

30. Mangoni AA, DiSalvo TG, Vlahakes GJ, Polanczyk CA, Fifer MA. Outcome following isolated tricuspid valve replacement. Eur J Cardiothorac Surg 2001;19:68–73.

31. Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. Eur Hear J Cardiovasc Imaging 2017;18:1342–3.

KEY WORDS immortal time bias, isolated severe tricuspid regurgitation, survival analysis

APPENDIX For supplemental tables and a figure, please see the online version of this paper.