Impact of tricuspid regurgitation on postoperative outcomes after non-cardiac surgeries

Parth Parikh, Kinjal Banerjee, Ambreen Ali, Anil Anumandla, Aditi Patel, Yash Jobanputra, Venu Menon, Brian Griffin, E Murat Tuzcu, Samir Kapadia

ABSTRACT

Objective Tricuspid regurgitation (TR) severity has known adverse implications, its impact on patients undergoing non-cardiac surgery (NCS) remains unclear. We sought to determine the impact of TR on patient outcomes after NCS.

Methods We performed a retrospective cohort study in patients undergoing NCS. Outcomes in patients with moderate or severe TR were compared with no/trivial TR after adjusting for baseline characteristics and revised cardiac risk index (RCRI). The primary outcome was defined as 30-day mortality and heart failure (HF), while the secondary outcome was long-term mortality.

Results Of the 7064 patients included, 312 and 80 patients had moderate and severe TR, respectively. Thirty-day mortality was higher in moderate TR (adjusted OR 2.44, 95% CI 1.25 to 4.76) and severe TR (OR 2.85, 95% CI 1.04 to 7.79) compared with no/trivial TR. There was no difference in 30-day HF in patients with moderate TR (OR 1.48, 95% CI 0.90 to 2.44) or severe TR (OR 1.42, 95% CI 0.60 to 3.39). The adjusted HR for long-term mortality in moderate TR was 1.55 (95% CI 1.31 to 1.82) and 1.87 (95% CI 1.40 to 2.50) for severe TR compared with no/trivial TR.

Conclusion Increasing TR severity has higher postoperative 30-day mortality in patients undergoing NCS, independent of RCRI risk factors, ejection fraction or mitral regurgitation. Severity of TR should be considered in risk stratification for patients undergoing NCS.

INTRODUCTION

Non-cardiac surgery (NCS) has been associated with postoperative morbidity and mortality. Risk scores and guidelines are used to risk-stratify and guide the management of patients undergoing NCS to help decrease adverse cardiac events post-surgically. Previous studies have assessed postoperative outcomes in patients with mitral regurgitation (MR) and aortic stenosis after undergoing NCSs. Left sided valvular disorders have been shown to increase the risk of postoperative adverse events. Findings of these reports have been reflected in the ACC/AHA guidelines for perioperative risk evaluation and management for patients undergoing NCS.

Tricuspid valve has been referred to by some as the ‘ignored valve’. It was previously believed that reversing any left sided valvular abnormality would reverse the tricuspid regurgitation (TR) as well. However, recent studies have shown that moderate to severe grades of TR have poor prognostic implications in terms of long-term survival. Additionally, patients with severe grades of TR and heart failure (HF) with reduced ejection fraction have been shown to have poor outcomes as well. Given the high prevalence (approximately US$1.6 million in the USA) of moderate to severe TR, a significant number would be expected to undergo NCS. However, there is a lack of information regarding the impact of TR in patients undergoing NCS. This becomes even more important as we are now entering a time where percutaneous...
interventions are being performed for TR.\textsuperscript{11} Our objective was to evaluate the impact of moderate and severe TR on outcome of patients after NCS.

\section*{METHODS}

\subsection*{Study design}

We performed a retrospective study at a tertiary care centre in the USA in patients undergoing NCS.

\subsection*{Patient and public involvement}

The research question was generated based on review of published literature which showed poor outcomes in terms of long-term survival for patients with varying severity of TR and the lack of literature in patients undergoing a NCS in this population. Although, patients were not directly involved in the research project, our study is a retrospective observational study using data which has already been collected for clinical decision making which was utilised in better understanding the outcomes of the patients who underwent a NCS.

\subsection*{Patient population}

All adult patients who underwent a NCS at our institute from 2000 to 2016 were considered for inclusion. The patient cohort was selected from our Internal Medicine Preoperative Assessment and Consultation clinic where they presented for preoperative risk stratification and optimisation.

Patients were included in the study if they were \textgeq 18 years in age, seen for preoperative assessment in an outpatient setting and subsequently underwent a NCS with an echocardiogram at our institute within 90 days prior to the surgery. We excluded patients undergoing an emergent surgery who did not receive outpatient preoperative assessment, echocardiography was technically difficult, echocardiography did not report the grade of TR or the patient was lost to follow-up within 30 days of surgery.

\subsection*{Data collection}

Data were collected from electronic medical records. Data collected included baseline demographics, clinical characteristics, details of surgery, echocardiographic parameters and clinical outcomes. Variables used to calculate the revised cardiac risk index (RCRI) score, namely history of ischaemic heart disease (IHD)/coronary artery disease (CAD), history of HF, diabetes mellitus requiring insulin, preoperative creatinine and risk of surgery were also collected. History of IHD was defined as a history of myocardial infarction, history of a positive exercise test, current chest pain due to myocardial ischaemia, use of nitrate therapy or ECG with pathological Q waves. Congestive HF was defined as pulmonary oedema, bilateral rales or S3 gallop, paroxysmal nocturnal dyspnoea and chest X-ray showing pulmonary vascular redistribution. History of cerebrovascular disease included prior transient ischaemic attack or stroke. A creatinine \textgeq 2mg/dL obtained preoperatively as per the RCRI score indicated renal insufficiency. We used to last date the patient was seen in our hospital system while calculating our median follow-up time. All missing data were collected through review of electronic medical charts.

\subsection*{Echocardiographic evaluation}

All patients had undergone a two-dimensional echocardiography with Doppler colour-flow mapping within 90 days prior to surgery. The proximal isovelocity surface area, vena contracta width, ratio of regurgitant jet area to right atrial area on colour Doppler, flow of hepatic vein and colour-wave jet density were used to evaluate grade of TR when available. TR jet velocity and right ventricle (RV) systolic pressure was calculated using the simplified Bernoulli equation. The sum of the tricuspid jet gradient and the estimated right atrial pressure was used to calculate the estimated pulmonary artery systolic pressure (PASP).\textsuperscript{12,13} The results for each echocardiogram variable were assigned by the interpreting echocardiography staff on the combination of these multiple data points. No further corrections were made to the echocardiography results following the initial interpretation, which was obtained from the echocardiography database. Echocardiographic details of the methods utilised at our institute have been published previously.\textsuperscript{14–17}

\subsection*{Outcomes}

The primary outcome was 30-day all-cause mortality and HF. Postoperatively, HF was defined as pulmonary oedema, bilateral rales or S3 gallop, paroxysmal nocturnal dyspnoea and chest X-ray showing pulmonary vascular redistribution. Secondary outcomes included long-term mortality. Short-term and long-term mortality data were obtained using multiple resources like electronic medical record review, Social Security Death Index and Ohio Death Index.

\subsection*{Statistical analysis}

Continuous variables were expressed as mean\pm SD and compared with the Student’s t-test or expressed as median with IQR as appropriate. Categorical variables were expressed as number (percentage) and compared with the $\chi^2$ test. HF and mortality at 30 days were analysed as with a multivariable logistic regression model, since only patients having 30-day follow-up were included. Covariates included in the model were TR severity, age, gender, ejection fraction, MR and components of the RCRI score. For long-term mortality, a Cox regression model with similar covariates was used to account for censoring and lost to follow-up.

A subgroup analysis was performed including only patients with a reported estimation of RVSP. Covariates used for the subgroup analysis were TR severity, age, gender, PASP, RV dysfunction and RV enlargement. Multivariate regression models were used to evaluate predictors for the primary and secondary outcomes in patients with TR. Kaplan-Meier survival analysis was performed for long-term outcomes. Missing data were supplemented from manual review of electronic medical charts.
records and imaging where needed. All significance tests were conducted using a two-tailed p value of 0.05. All analyses were done on Stata V.14.

RESULTS

Patient characteristics
Of the 7285 patients who fulfilled the inclusion criteria, 221 were excluded (figure 1). Of the 7064 patients who constituted the study group, 5144 (72%) had no/trivial TR, 1528 (21%) had mild TR, 312 (4%) had moderate TR and 80 (1%) had severe TR. Table 1 shows the baseline characteristics and RCRI variables of patients based on TR grade. Online supplementary figure 1 shows the type of NCS which was performed in the cohort of 7064 patients.

Primary outcomes

30-day mortality
The primary outcome of 30-day mortality was observed in 107 (1.51%) patients. Mortality was higher in moderate TR compared with no/trivial TR (4.17% vs 1.13%, p<0.001) and severe TR compared with no/trivial TR (6.25% vs 1.13%, p<0.001). After multivariate adjustment, the 30-day mortality was higher in moderate TR (OR of 2.44; 95% CI 1.25 to 4.76) as well as severe TR (OR 2.85; 95% CI 1.04 to 7.79) (figure 2A). For univariate analysis, see online supplementary table 1.

30-day HF
Thirty-day HF was observed in 293 (4.14%) patients. It was higher for moderate TR compared with no/trivial TR (6.73% vs 3.75%, p=0.008). A similar trend was also observed for severe TR, but it failed to reach statistical significance (7.5% vs 3.75 %, p=0.08). After multivariate adjustment, there was no difference in 30-day HF for moderate TR (p=0.127) and severe TR (p=0.427) (figure 2B). For univariate analysis, see online supplementary table 2. Patients with moderate and severe TR had more HF compared with patients with no/trivial TR (adjusted OR 1.60; 95% CI 1.00 to 2.56, p=0.051).
Impact of PASP and ventricular function

In a subgroup of 4289 patients with TR jet velocity, patients with moderate/severe TR and elevated PASP had higher mortality compared with patients with ≤mild TR and normal PASP (p<0.001). In addition, patients with moderate/severe TR and normal PASP also had higher mortality compared with patients with ≤mild TR and normal PASP (p<0.009) (figure 3A). On multivariate analysis, the factors associated with an increased 30-day mortality were elevated PASP (OR 1.88; 95% CI 1.12 to 3.16; p=0.017) and RV dysfunction (OR 4.47; 95% CI 1.74 to 11.48; p=0.002), see online supplementary table 3.

Long-term mortality

The median follow-up time was 49.9 months (IQR 19.5–91.6). Long-term mortality was higher in patients with severe TR (HR 1.87; 95% CI 1.40 to 2.50) and moderate
TR (HR 1.55; 95% CI 1.31 to 1.82) when compared with no/trivial TR on multivariate analysis (table 3). Survival up to 5 years is shown in figure 3B.

Predictors of outcomes in patients with TR
For 30-day mortality, history of IHD (OR 2.81; 95% CI 1.44 to 5.49) and elevated risk of surgery (OR 3.43; 95% CI 1.59 to 7.38) were significant predictors in the postoperative period after NCS. Diabetes mellitus requiring insulin (OR 2.68; 95% CI 1.46 to 4.92), elevated risk of surgery (OR 2.42; 95% CI 1.33 to 4.40), moderate or severe MR (OR 1.70; 95% CI 1.03 to 2.82) and history of IHD (OR 1.72; 95% CI 1.10 to 2.69) were predictors of HF at 30 days after NCS (figure 4).

Table 2 Comparing various echocardiographic parameters of patients with moderate and severe tricuspid regurgitation in patients with and without 30-day mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>No outcome (n=374)</th>
<th>Outcome (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (%)</td>
<td>Number (%)</td>
<td></td>
</tr>
<tr>
<td>PASP &gt;40 mm Hg</td>
<td>282 (75.4)</td>
<td>16 (88.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>RV dysfunction</td>
<td>39 (10.43)</td>
<td>7 (38.89)</td>
<td>0.0002</td>
</tr>
<tr>
<td>RV enlargement</td>
<td>67 (17.91)</td>
<td>6 (33.33)</td>
<td>0.1</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>65 (17.38)</td>
<td>7 (38.89)</td>
<td>0.02</td>
</tr>
<tr>
<td>Mod/Sev MR</td>
<td>96 (25.67)</td>
<td>5 (27.78)</td>
<td>0.8</td>
</tr>
</tbody>
</table>
| LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; RV, right ventricle.

DISCUSSION
The aim of our study was to determine the impact of TR on postoperative outcomes in patients undergoing NCS. Our study demonstrated that there was an increased 30-day mortality and long-term mortality in patients with moderate and severe TR when compared with patients with no/trivial TR after undergoing a NCS. In a subgroup of patients who had a measurable TR jet velocity for determining the RVSP, those with an elevated PASP and higher grade of TR had the highest mortality.

In 1977, Goldman et al published an index for cardiac risk in patients undergoing NCS. Subsequently, studies have focused on left sided valvular lesions such as aortic stenosis and MR, which have showed an increasing adverse outcome with NCSs. The tricuspid valve did not receive as much attention, possibly because it was thought to be reversible after correction of the secondary cardiac pathology and mechanical treatments were not as well developed. The grade of TR shows the advanced state of cardiac disease most often reflecting left sided valvular disease. In patients with left sided valvular disease, the elevated left atrial pressure is reflected through an elevated pulmonary artery pressure which in turn causes RV dilation and worsening of secondary TR. However, it does not follow a similar course in reverse. Recent studies have shown that in patients with significant TR, even after correction of left sided valvular abnormalities, TR may not be corrected and continues to have poor prognosis. This has in turn led to a growing interest in the tricuspid valve recently. There is recommendation to consider tricuspid valve repair in patients with significant TR who are undergoing left sided valve surgery. In addition to severity of TR, RV dysfunction...
Table 3 Univariate and multivariate analysis of long-term mortality compared with no/trivial TR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI) P value</th>
<th>Multivariate HR (95% CI) P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild TR</td>
<td>1.34 (1.21 to 1.47) &lt;0.001</td>
<td>1.07 (0.96 to 1.18) 0.213</td>
</tr>
<tr>
<td>Moderate TR</td>
<td>2.27 (1.94 to 2.65) &lt;0.001</td>
<td>1.55 (1.31 to 1.82) &lt;0.001</td>
</tr>
<tr>
<td>Severe TR</td>
<td>3.10 (2.34 to 4.11) &lt;0.001</td>
<td>1.87 (1.40 to 2.30) &lt;0.001</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>2.66 (2.46 to 2.88) &lt;0.001</td>
<td>2.45 (2.25 to 2.66) &lt;0.001</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.43 (1.32 to 1.54) &lt;0.001</td>
<td>1.28 (1.18 to 1.39) &lt;0.001</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>1.75 (1.57 to 1.94) &lt;0.001</td>
<td>1.28 (1.13 to 1.43) &lt;0.001</td>
</tr>
<tr>
<td>History of IHD</td>
<td>1.41 (1.29 to 1.54) &lt;0.001</td>
<td>1.01 (0.92 to 1.11) 0.859</td>
</tr>
<tr>
<td>History of CVA</td>
<td>1.29 (1.12 to 1.47) &lt;0.001</td>
<td>1.10 (0.95 to 1.26) 0.194</td>
</tr>
<tr>
<td>Creatinine &gt;2 mg/dL</td>
<td>2.12 (1.82 to 2.47) &lt;0.001</td>
<td>1.84 (1.57 to 2.15) &lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus requiring Insulin</td>
<td>1.42 (1.22 to 1.64) &lt;0.001</td>
<td>1.43 (1.23 to 1.66) &lt;0.001</td>
</tr>
<tr>
<td>Elevated risk of surgery</td>
<td>1.60 (1.41 to 1.82) &lt;0.001</td>
<td>1.45 (1.27 to 1.64) &lt;0.001</td>
</tr>
<tr>
<td>LVEF &lt;50%</td>
<td>1.96 (1.74 to 2.21) &lt;0.001</td>
<td>1.34 (1.18 to 1.54) &lt;0.001</td>
</tr>
<tr>
<td>&gt;Moderate MR</td>
<td>2.25 (1.95 to 2.59) &lt;0.001</td>
<td>1.45 (1.25 to 1.69) &lt;0.001</td>
</tr>
</tbody>
</table>

CVA, cerebrovascular accident; IHD, ischaemic heart disease; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation.

and elevated PASP have been shown to have poor prognostic implications on long-term survival. Nath et al showed that TR was an independent predictor of mortality irrespective of PASP and RV function. They demonstrated a HR of 1.31 in patients with moderate or higher TR irrespective of their PASP. Another study by Topilsky et al showed that isolated severe TR was associated with higher mortality and cardiac events with an adjusted HR of 1.78 (95% CI 1.10 to 2.82). Lindman et al, while using the inoperable cohort of PARTNER II in their study, demonstrated that patients with moderate or severe TR and right heart enlargement had a higher odds of mortality at 1 year. There is a gap in the literature, with lack of focus on the postoperative outcomes of patients with TR after undergoing NCS.

Our study demonstrated that 5% of our cohort had moderate or higher TR of which 1% was severe TR. The prevalence of severe TR in our study was higher when compared with the national prevalence which is estimated to be 1.6 million (around 0.5%) in the USA. However, studies have shown the prevalence of clinically significant TR to increase with increasing age which would be in line with our findings. Our study demonstrated a significant adverse outcome in patients with moderate and severe TR, especially in terms of short-term and long-term mortality following a NCS. The RCRI score has been shown to distinguish between patients with high and low risk of encountering adverse cardiac events after NCS.

In our analysis, even after adjusting for individual indices of RCRI, MR and LV dysfunction to moderate and severe TR was shown to be associated with increased 30-day mortality. In terms of 30-day HF, we found that patients with moderate or severe TR did have a trend towards higher 30-day HF but did not reach statistical significance when compared with no/trivial TR in adjusted analysis. This may be attributed to fewer events in moderate and severe TR individually. When we grouped patients with
predictors for 30-day HF compared with no/trivial TR. As secondary TR is thought to go hand-in-hand with RV dilatation, RV dysfunction and elevated PASP, we performed a subgroup analysis in patients with a TR jet on echocardiography. We found that RV dysfunction and elevated PASP were associated with a higher mortality in these patients. Furthermore, patients who had moderate or higher TR along with a PASP >40 mm Hg had the highest mortality. While patients who had either moderate TR or higher TR, or PASP >40 mm Hg alone still had higher mortality compared with patients who had lesser than moderate degree of TR and a PASP <40 mm Hg. This shows that along with TR, the PASP as well as RV function do play a role in terms of poor outcomes for the patients following a NCS. We found that a prior history of IHD and an elevated risk of surgery were significant predictors of mortality at 30 days following the NCS. In terms of predictors for non-30-day HF, moderate or severe MR, history of IHD, insulin dependent diabetes mellitus and an elevated risk of surgery were significant predictors.

The current ACC (American College of Cardiology)/AHA (American Heart Association) guidelines on perioperative evaluation and care for patients undergoing NCSs provides recommendations on management of patients undergoing NCSs with valvular abnormalities. However, there has not been a focus on TR due to a lack of evidence. Our study provides evidence that there is an increased mortality in patients with moderate or severe TR after undergoing a NCS, and the severity of TR should be taken into consideration when risk stratifying these patients prior to undergoing NCSs. Optimization of volume status before and during surgery may be warranted based on the clinical situation. Although, the predictors for 30-day mortality and HF are largely non-modifiable (prior history of IHD, elevated risk of surgery, moderate/severe MR, insulin dependent diabetes mellitus), closer preoperative and postoperative monitoring of patients with these risk factors may be necessary. With the emergence of transcatheter therapies for TR as an option, identification of the disease burden and the impact on outcomes is important, making it a treatable risk factor. It still remains to be seen whether any intervention in this group of patients, who suffer from higher grades of TR, can change outcome while undergoing a NCS.

LIMITATIONS
This retrospective study is limited by the inherent biases of non-randomised observational studies. The study may not be representative of the general population as it is performed at a tertiary care referral centre. We were not able to check for interobserver variability for the echocardiographic variables. However, all echocardiograms are read and interpreted by cardiologists as per the previously published methods. Pulmonary artery pressure quantification was based on presence of an adequate TR envelope. We did not look at any events which may have occurred between the time of the echocardiography being done and the NCS. However, since we excluded patients who were undergoing emergent surgeries, a significant event would have led to the NCS not being performed. We have reported cardiac and all-cause mortality in our primary and secondary outcomes.

CONCLUSIONS
Increasing TR severity has an adverse postoperative outcome in terms of mortality in patients undergoing NCS. There was increased mortality independent of the RCRI risk factors, LVEF or MR. Patients with an elevated PASP and moderate or severe TR had the highest mortality. Appropriate risk stratification of these patients may be beneficial prior to undergoing a NCS.

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