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Morbidity and Mortality Outcomes of Patients requiring Isolated Tricuspid Valve Surgery

Harvey; Outcomes following Isolated Tricuspid Valve Surgery

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Patient and Public involvement: Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

Ethical approval: The study protocol was approved by the New South Wales Population and Health Services Research Ethics Committee, reference number: 2013/09/479. The Ethics Committees granted a waiver of the usual requirement for the consent of the individual to the use of their health information. All patient data were de-identified and analysed anonymously.

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Transparency: The senior author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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ABSTRACT

Objectives: The aim of the study was to evaluate mortality and morbidity outcomes following open-heart isolated tricuspid valve surgery (TVSx) with medium-long term follow up.

Design: Retrospective cohort study.

Setting: New South Wales (NSW) public and private hospital admissions between 1-Jan-2002 and 30-Jun-2018

Participants: A total of 537 patients underwent open isolated-TVSx during the study period.

Primary and Secondary outcome measures: Primary outcome was all-cause mortality tracked from the death registry to 31-Dec-2018. Secondary morbidity outcomes including admission for congestive cardiac failure (CCF), new atrial fibrillation (AF), infective endocarditis (IE), pulmonary embolism (PE), and insertion of a permanent pacemaker (PPM) or implantable-cardioverter-defibrillator (ICD), were tracked from the Admitted Patient Data Collection (APDC) data base. Independent mortality associations were determined using the Cox regression method.

Results: A total of 537 patients underwent open isolated-TVSx (46% male): median age (interquartile-range) was 63.5yo (43.9-73.8yo) with median length-of-stay 16days (10-31days). Main cardiovascular comorbidities were AF (54%) and CCF (42%); 67% had rheumatic TV. In-hospital and total mortality were 7.4% and 39.3% respectively (mean follow-up: 4.8yrs). Cause-specific deaths were evenly split between cardiovascular and noncardiovascular causes. Predictors of mortality included a history of congestive cardiac failure (hazard ratio [HR]=1.78, 95% confidence interval [CI]=1.33-2.38, p<0.001) and chronic pulmonary disease (HR=2.66, 95%CI=1.63-4.33, p<0.001). In-hospital PPM rate

was 10.0%. At 180days, 53 (9.9%) patients were admitted for CCF, 25 (10.1%) had new AF, 7 (1.5%) had new IE, and <1% had PE, post-discharge PPM or ICD insertion.

Conclusion: Open isolated-TVSx carries significant mortality risk, with decompensated CCF and new AF the most common morbidities encountered post-surgery. This report forms a benchmark to compare outcomes with newer percutaneous tricuspid interventions.

Key Words: Outcomes, tricuspid valve surgery, isolated cardiac valve surgery

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A relatively large cohort of patients for an infrequently performed set of procedures.
- Study cohort was derived from a statewide unselected population from all public and private healthcare facilities that performed cardiothoracic surgery
- The use of a death registry with cause-specific data analysis adds detail to all-cause mortality figures.
- Comprises a heterogeneous group of procedures: TVSx annuloplasty, repair, replacement.
- Dataset lacks granular details such as echocardiographic data (e.g., RV size and function) or aetiology of TV dysfunction

INTRODUCTION

The burden of tricuspid valve (TV) disease is expected to increase with the increasing age of the Australian population. The prevalence of moderate or severe TV regurgitation of any cause in developed countries is 4.0% in those over the age of 75, and 1.1% in those 65-74 (1). The prevalence of tricuspid valve stenosis, rare in developed countries, is not known.

The presence of tricuspid regurgitation (TR) is an independent predictor of increased mortality, both by itself (isolated functional TR) and for secondary aetiologies including left-sided valvular disease, heart failure, arrhythmogenic right ventricular cardiomyopathy, and pulmonary arterial hypertension (2-10).

TV surgery (TVSx) is largely performed in combination with other cardiac procedures, most frequently left-sided valve surgery (11). Society guidelines have consistently recommended isolated TVSx for patients with severe primary TR as their sole valvular lesion (12, 13). More recently the 2020 American Heart Association (AHA) and 2021 European Society of Cardiology (ESC) Valvular Heart Disease guidelines have recommended TVSx for select patients with severe secondary TR regardless of the presence of an indication for concurrent left-sided valve surgery or a history of prior left-sided valve surgery (14, 15).

Isolated open-heart TVSx (open-TVSx) has traditionally been associated with high mortality rates. Reported in-hospital mortality rates have varied over time from 8.8-19.0% in small (n<500) older studies (16, 17), to 8.8-9.7% in larger studies (n=1364 in Alqahtani et al, and n=5005 in Zack et al) over the last twenty years (11, 18), to as low as 3.2% in a recent single-

centre study (n=95) involving carefully selected patients (19). However longer-term morbidity outcomes, including re-admission for heart failure, permanent pacemaker (PPM) requirement, pulmonary embolism (PE) or new-onset atrial fibrillation (AF), are not well-described. Moreover, while an association between TVSx and PE has not been described, worsening TR has been numerically (although not statistically) associated with pulmonary embolism, TR may result from chronic thromboembolic disease, and PE is a plausible complication of TVSx given the association between left-sided valvular intervention and stroke (20-22).

The primary aim of this study was to determine the incidence and temporal trends of open-heart isolated-TVSx in an Australian statewide cohort and examine their mortality outcomes. The secondary aim was to characterize morbidity events after isolated-TVSx.

METHODS

Study population

The Centre for Health Record Linkage (CHeReL), established in 2006, holds one of the largest data linkage systems in Australia containing high-quality linked health data of residents in the state of New South Wales (NSW) (23). From its Admission-Patient-Data-Collection (APDC) database, which includes ≥97% of all healthcare facilities in the state, we identified consecutive admissions that involved open-heart surgery (excluding percutaneous approach) for tricuspid valve pathology (see Supplementary Table 1 for relevant ACHI procedure codes) either as primary or secondary procedures coded under the Australian Classification of Health Interventions (ACHI) coding system between 1-July-2001 and 31-December-2018. Our research group has published detailed outcomes studies using data obtained from the APDC database (24-29).

Data sources

Variables obtained from the APDC database for each hospital admission that involved TVSx include admission date, age, gender, country of birth, admission referral source, length of admission, and in-hospital mortality.

The primary and all secondary diagnoses (potentially up to 50 secondary diagnoses) associated with each admission were retrieved from the APDC database. Each diagnosis was

coded in the APDC database according to the International Classification of Diseases, Tenth Revision Australian Modification (ICD-10AM). For this study, we pre-specified the indication for cardiac valve surgery during admission as either for endocarditis (as primary or secondary diagnosis) or as non-endocarditis valve surgery, and if concomitant coronary artery bypass graft (CABG) surgery was performed in the same admission (see Supplementary Table 1 for relevant ICD-10AM and ACHI codes). In addition, whether rheumatic tricuspid valve was documented during admission was recorded. Additional comorbidities extracted for this study include ischemic heart disease, prior percutaneous coronary interventions [PCI] and/or CABG surgery, CCF, stroke, peripheral vascular disease, prosthetic heart valve, and AF), primary or secondary pulmonary hypertension, cardiac risk factors (including hypertension, hyperlipidaemia, diabetes and current/ex-smoker), malignancy, chronic pulmonary disease, neurodegenerative disease, chronic kidney disease and history of intravenous drug use (IVDU). In addition, the overall comorbid status of each patient was quantified using the Charlson comorbidity index (CCI) (30). A value of 0 indicates no comorbidity, while higher values represent an increasing burden of comorbid illnesses.

Study outcomes

The primary outcome of the study was all-cause and cause-specific death rates, tracked from the statewide death registry also held by CHeReL. For mortality analysis, cases were limited to only NSW state residents to minimize incomplete tracking. The end-of-study date was set at 31-December-2018. All death certificates were reviewed to ascertain cause-specific death

rates. Each death was coded independently by two reviewers (AN and VC) according to general principles set by the World Health Organization (31). Reviewers were blinded to patient's background comorbid illnesses during coding. Disparities were resolved by consensus. Cause-specific mortality were based on prior published classifications (26). In brief, cardiovascular cause was defined as death due to acute myocardial infarction, CCF, stroke, cardiac-related causes (when more than one cardiac cause of death was recorded), or PE. Noncardiovascular causes included death due to sepsis, malignancy, other noncardiovascular causes, or undefined. Patients with multiple potential causes of death on their death certificates were classified as "undefined" and labelled as noncardiovascular death for the purposes of the present study.

Secondary outcomes of the study were tracked from the APDC database using linkage method to determine morbidity events during follow-up post-surgery. These include first re-admission for CCF, development of new AF or infective endocarditis, PE, and the need for a PPM or implantable-cardioverter-defibrillator (ICD) implantation.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Approval was granted by the NSW Population and Health Services Research Ethics Committee, reference number: 2013/09/479. The Ethics Committees granted a waiver of the usual requirement for the consent of the individual to the use of their health information. All patient data were de-identified and analysed anonymously.

Statistical analysis

To determine the incidence and temporal trend on case-volumes of isolated open-TVSx statewide during the study period, all admissions between 1-January-2002 and 31-December-2018 were included. For the rest of the analyses, the study cohort was limited to NSW state residents and confined to the index admission between 1-January-2002 and 30-June-2018, enabling a minimum of six months follow-up. Thus, for those who had repeat TVSx during the study period (recurring patients), only their initial admission was included. End-of-study follow-up was prespecified at 31-December-2018.

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data given in absolute numbers and percentages. Linear regression was used to determine trends in TVSx caseload per-annum over the study period, excluding 2018 to minimize ascertainment bias as the APDC database receives six-monthly updates. To identify predictors of mortality post open-TVSx, Cox proportional hazard regression method was used. Univariables considered include age (dichotomized by mean age), gender, admission referral source, year-groups of surgery (stratified into 2002-2005, 2006-2009, 2010-2013, 2014-2018), indication for surgery (infective endocarditis), rheumatic tricuspid valve status, types of open-TVSx, concomitant CABG, other cardiovascular and noncardiovascular comorbidities. Univariables with $p<0.05$ were included in the multivariable Cox regression analysis, except for age and gender which were included irrespective of significance. The proportional hazards assumption was checked with log-minus-log plots.

All analyses were performed using SPSS v25.0 (IBM, USA) and Stata 16.1. A two-tailed probability value <0.05 was considered statistically significant. No sponsors had a role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

RESULTS

Temporal trend of TV cases

There were 575 cases of open isolated-TVSx in the calendar years of 2002 to 2018, averaging 34 ± 14 cases per-annum (Supplementary Figure 1). There was a significant increase in case numbers by an average of 2.73 cases per-annum over the study period (95% CI 1.95-3.50, p<0.001) (Figure 1). The bulk of TVS cases were TV annuloplasty (n=272) and replacement (n=245), with case volume for both surgeries increasing during the study period (Supplementary Figures 2-3). A smaller number of non-annuloplasty TV repairs (n=85) and valvotomies (n=5) were performed. While there were significant increases in TV repair caseloads during the study period, TV valvotomy caseloads were so small as to preclude trend analysis (Supplementary Figures 4-5).

Baseline demographic and surgical characteristics of study cohort

The study cohort's median age was 63.5yo (43.9-73.8yo) and was 46.4% male. (Table 1). A total of 14.3% of patients had concomitant CABG, and endocarditis was the indication for TVSx in 10.4% of patients. A rheumatic tricuspid valve was documented in 66.5% of patients.

Table 1. Study cohort demographic and surgical characteristics.

Parameters	Isolated TVSx (N=537)
Demographics	
Age, years	58.2 ± 20.1
Median (IQR)	63.5 (43.9 – 73.8)
Males	249 (46.4)
Country of birth	
Australia plus territories / New Zealand	379 (70.6)
Europe	77 (14.3)
Asia	33 (6.1)
Other	48 (8.9%)
Co-morbidities	
Cardiovascular disease *	454 (84.5)
Ischemic heart disease	104 (19.4)
Prior PCI / CABG	31 (5.8)
Congestive cardiac failure	200 (37.2)
Stroke	11 (2.0)
Peripheral vascular disease	25 (4.7)
Prosthetic heart valve	59 (11.0)
Atrial fibrillation/flutter	289 (53.8)
Cardiac risk factors *	323 (60.1)
Hypertension	138 (25.7)
Hyperlipidaemia	16 (3.0)
Diabetes	82 (15.3)
Current/ex-smoker	198 (36.9)
Primary PHT	11 (2.0)
Secondary PHT	74 (13.8)
Malignancy	10 (1.9)
Chronic pulmonary disease	31 (5.8)
Neurodegenerative disease *	3 (0.6)
Chronic kidney disease	73 (13.6)
IVDU history	54 (10.1)
Charlson comorbidity index score †	1.4 ± 1.9
Median (IQR)	1 (0 - 2)
Surgical characteristics	
Indication for valve surgery	
Endocarditis	56 (10.4)
Non-endocarditis	481 (89.6)
Rheumatic tricuspid valve	357 (66.5)
Concomitant CABG ‡	77 (14.3)
Types of TVSx §	
Annuloplasty	262 (48.8)
Replacement	217 (40.4)
Repair	83 (15.5)
Open valvotomy	5 (0.9)

Others	15 (2.8)
Length of hospital stay, days	24.4 ± 23.5
Median (IQR)	16 (10 – 31)

Plus-minus values represent mean ± standard deviation; all others represent numbers of patients with values in brackets representing percentages, or otherwise stated.
CABG, coronary artery bypass graft; IVDU, intravenous drug use; PCI, percutaneous coronary interventions; PHT, pulmonary hypertension; TVSx, tricuspid valve surgery.

* Cardiovascular disease includes history of ischemic heart disease (include PCI and/or CABG), stroke, congestive cardiac failure, peripheral vascular disease, prosthetic heart valve and/or atrial fibrillation/flutter. Cardiac risk factors include history of hypertension, hyperlipidaemia, diabetes and/or smoking (current/previous). Neurodegenerative disease includes dementia, central nervous systemic atrophies, Parkinson's disease, basal ganglia degeneration, and/or nervous systemic degenerative diseases.

† Conditions included in the Charlson comorbidity index include myocardial infarction, congestive cardiac failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease (mild vs. moderate to severe), diabetes (with or without organ damage), hemiplegia, moderate to severe renal disease, any tumour (within last 5 years), lymphoma, leukemia, metastatic solid tumour and acquired immunodeficiency syndrome.

‡ Concomitant CABG performed during same admission for cardiac valve surgery.

§ More than one type of TV surgery might be performed on a patient during the same admission.

AF was the most common cardiovascular comorbidity (58.3%), followed by CCF (37.2%) and ischemic heart disease (19.4%). A history of smoking (36.9%), hypertension (25.7%), and diabetes (15.3%) was common. Of the noncardiovascular comorbidities, secondary pulmonary hypertension (13.8%) and chronic kidney disease (13.6%) were the most common. Concomitant malignancy was rare, comprising 1.9% of the cohort. 10.1% had a documented history of IVDU. The median Charlson comorbidity index was 1 (interquartile range [IQR] 0-2). The median length of stay was 16 days (IQR 10-31 days).

All-cause and cause-specific mortality

A total of 211 (39.3%) patients died during a mean follow-up of 4.82 ± 3.94 years (Table 2). In-hospital mortality rate was 7.4%, with 62 (11.5%) patients dying within 180-days post open isolated-TVSx. A cardiovascular cause of death occurred in 45% of in-hospital deaths,

and in 52% of post-discharge deaths (Table 3). Of the cardiovascular causes of death, heart failure was the most frequent cause, representing 10.0% (n=4) of in-hospital deaths and 25.2% (n=43) of post-discharge deaths. Sepsis was the most identified noncardiovascular cause of death, documented in 7 (17.5%) in-hospital deaths and 37 (21.6%) post-discharge deaths.

Table 2. Morbidity and mortality outcomes following isolated TVSx.

Cumulative incidence, no. (%)	30-days	180-days	2-years	End-of-study†
Congestive cardiac failure	11 (2.0)	53 (9.9)	109 (20.2)	157 (29.2)
Atrial fibrillation *	10 (4.0)	25 (10.1)	40 (16.1)	68 (27.4)
Infective endocarditis *	4 (0.9)	7 (1.5)	10 (2.1)	26 (5.6)
Pulmonary embolism	1 (0.2)	2 (0.4)	5 (0.9)	7 (1.3)
Permanent pacemaker	2 (0.4)	3 (0.6)	20 (3.7)	40 (7.5)
Implantable cardioverter defibrillator	1 (0.2)	3 (0.6)	4 (0.8)	13 (2.4)
All-cause death	18 (3.4)	62 (11.5)	108 (20.1)	211 (39.3)

* Atrial fibrillation (AF) and infective endocarditis (IE) incidences were based on patients without baseline AF (n=248) or IE (n=466) during isolated tricuspid valve surgery (TVSx) admission.
† End-of-study was 31-December-2018.

Table 3. Cause-specific death outcomes.

Categories	In-hospital (N=40) No. (%) *	Post-discharge (N=171) No. (%) *
Cardiovascular causes	**18 (45.0)**	**89 (52.0)**
Acute myocardial infarction	0 (0)	6 (3.5)
Heart failure	7 (17.5)	43 (25.2)
Stroke	4 (10.0)	15 (8.8)
Pulmonary embolism	0 (0)	2 (1.17)
Cardiac-related †	7 (17.5)	23 (13.5)
Noncardiovascular causes	**22 (55.0)**	**82 (48.0)**
Sepsis	7 (17.5)	37 (21.6)
Malignancy	1 (2.5)	15 (8.8)
Other	7 (17.5)	17 (10.0)
Undefined	7 (17.5)	13 (7.6)

* No. (%) represents total number of deaths from each specific cause and value in brackets represents the percentage out of total deaths.
† Cardiac-related cause of death is coded when more than one cardiac cause of death is recorded on the death certificate.

Morbidity outcomes

Table 2 shows the cumulative incidence of the study's pre-specified morbidity events after isolated-TVSx. The development of new AF (in those without a prior history of AF at index isolated-TVSx) and admissions for CCF were the most frequent morbidities documented during follow-up: the cumulative incidence of AF at 180-days and by end-of-study were 10.1% and 27.4% of patients respectively, while 53 (9.9%) patients had an admission for CCF within the first 180-days following isolated-TVSx, reaching 29.2% by end-of-study follow-up. Across the study period the rate of PE admission was low at 1.3%. 10.0% of patients had PPM implanted during their index isolated-TVSx admission. A further 40 (7.5%) and 13 (2.4%) patients required PPM and ICD implantations by end-of-study follow-up respectively.

Independent predictors for all-cause mortality

Independent predictors for all-cause mortality following open isolated-TVSx were age ≥59 years, a background history of CCF, chronic pulmonary disease, and malignancy (Table 4). Malignancy was the strongest predictor of mortality (adjusted hazard ratio [aHR]=3.49, 95% confidence interval [CI]=1.73-7.07; p<0001), followed by a history of chronic pulmonary disease (aHR=2.21, 95%CI=1.36-3.59; p<0.001). Neither gender, indication for surgery, rheumatic TV status, types of TVSx performed, concomitant CABG, history of ischemic heart disease, stroke, diabetes, pulmonary hypertension, chronic kidney disease, smoking status or history of IVDU were associated with the primary outcome (Supplementary Tables 2 and 3).

Table 4. Independent predictors for all-cause mortality.

Multivariable analysis *	Parameters	aHR (95% CI)	p value
All-cause death during follow-up (4.82 ± 3.94 years)	Age ≥59 years (mean age)	1.76 (1.26 – 2.47)	0.001
	Congestive cardiac failure	1.78 (1.33 – 2.38)	<0.001
	Chronic pulmonary disease	2.21 (1.36 – 3.59)	<0.001
	Malignancy	3.49 (1.73 – 7.07)	<0.001

Plus-minus value represents mean ± standard deviation.
CI, confidence interval; aHR, adjusted hazard ratio.
* **Multivariable Cox regression method was used to identify independent predictors for all-cause mortality. Only significant independent predictors are shown in the above table (see Supplementary Table 3 for complete multivariable analysis results).**

DISCUSSION

The present study examined the caseload and outcomes of open isolated-TVSx over a 17-year period in an unselected Australian statewide population. The main findings were: 1) open isolated-TVSx case volumes have increased significantly over the study period; 2) high post-operative mortality rates in the short and intermediate-term comparable to those in international studies; 3) heart failure and sepsis were the most common specific causes of death in both in-hospital and post-discharge follow-up; 4) new AF and admissions for CCF were the two most common morbidities encountered post-surgery; and, 5) age ≥59 years and history of CCF, chronic pulmonary disease and malignancy were associated with increased mortality risk.

TVSx caseloads

Alqahtani et al demonstrated a significant increase in the caseload of both open isolated-TV repairs and replacements in the United States (US) between 2003 and 2014 using the Nationwide Inpatient Sample (NIS) (11). While the NIS captured about 20% of US admissions during this period, our study showed similarly increasing caseload findings in a statewide population where ≥97% of hospital admissions are captured, with the state of NSW approximating 32% of Australia's overall population. While the increase in caseload was significant, the procedure is still relatively rare as shown in our study, with open isolated-TVSx cases representing only 1.8% of total open-heart cardiac valve surgery. We postulate the increased caseload reflects the growth and ageing of the NSW population over this timeframe.

Prior studies mostly limited to in-hospital outcomes

Existing literature has been mostly limited to in-hospital outcomes after open isolated-TVSx. There are two larger US-based studies examining in-hospital mortality and morbidity in addition to several smaller studies (11, 32). Our study showed an in-hospital mortality (7.4%) that is lower than the 8.8-9.7% reported in recent studies using similar administrative datasets (11, 18), but higher than the 3.4% rate reported in a recent single-centre study based on carefully selected patients (19). In-hospital PPM implantation rates (10.0%) in our study were also at the lower end of reported figures, which range from 9.5-24.4% (11, 19, 32).

Cause-specific deaths following open isolated-TVSx

This study is the first of its scale to examine cause-specific mortality after isolated TVSx. The two leading causes of death both in-hospital and post-discharge were sepsis and CCF. Fatal decompensated CCF may reflect unsuccessful attempted medical and/or surgical management of severe TV regurgitation with associated heart failure – indeed a history of CCF predicted a near 70% increased mortality risk in our multivariable analysis. On the other hand, the large proportion of deaths by sepsis are likely driven by the baseline comorbidities in our population. This is supported by our study's demonstration of strong independent associations between increased mortality and the presence of malignancy, older age and chronic pulmonary disease. While more conservative case selection may reduce mortality

rates, the goal of surgery in these unwell patients may have been to improve quality of life (a parameter not directly measured in this administrative dataset) rather than longevity.

Morbidity following open isolated-TVSx

Morbidity after TVSx may provide a surrogate for quality of life, and providing data surrounding long-term morbidity forms an important aspect of informed consent prior to surgery. These data also form a benchmark against which to compare newer percutaneous interventions. In the present study, the main morbidities encountered post-discharge were re-admission for decompensated CCF (9.9%) and new AF (10.1%), although low rates of admissions for IE, PE, PPM and ICD insertions (all <1% except for IE at 1.5%) were also observed within the first 180-days. Two smaller studies have examined medium-long term morbidity outcomes following open isolated-TVSx. Dreyfus et al described a 38% incidence of heart failure hospitalisation at 5-years post-discharge in a French cohort of 466 patients who underwent isolated-TVSx (33). Wong et al described a much lower rate of 13.8% heart failure hospitalisation post-discharge during a mean follow-up of 4.9 years in a younger Taiwanese cohort (n=333) compared to 29.2% of patients in our study with a similar mean follow-up duration (34). While Dreyfus et al did not report on rates of post-discharge PPM insertion, Wong et al observed a 5.2% incidence of post-discharge PPM insertion by end-of-study, compared to 7.6% in our study. Notably, these and other studies have not reported on rates of PE, ICD insertion, or de novo infective endocarditis post-discharge. Reassuringly, these events appear to be low.

Pathomechanistic reasons for high mortality and morbidity associated with open-heart isolated-TVSx

There are two main hypotheses which attempt to explain why open isolated-TVSx has consistently been associated with high in-hospital mortality and morbidity rates, despite not being considered technically more difficult than left sided-valvular surgery. The first is that patients are referred late for surgery, by which time the consequences of severe TR are, at best, partly remediable by surgery (e.g., right ventricular (RV) dilation and/or dysfunction, cardiac cirrhosis) (32, 33). Furthermore, patients with impaired RV size and/or function may not tolerate the increased afterload created by surgical correction of TR, and consequently further decompensate. Supporting this hypothesis, Hamandi et al (19) reported a dramatically lower in-hospital mortality of 3.2%, highlighting early referral as a defining feature of their single-centre 95 patient cohort study. However, in-hospital mortality in their cohort was still higher than that reported for left-sided valve surgery in the literature (11, 16-18). The second hypothesis is that severe TR patients form a more comorbid cohort of patients, whose comorbidities often exacerbate the severity of their TR. (e.g. pulmonary disease). Indeed, our study showed chronic pulmonary disease to be associated with a 2.7-fold increased risk of death post-surgery.

Comparison with percutaneous tricuspid valve interventions

There is presently little published data on outcomes following isolated TV intervention, and no long-term data. Published international registry data (n=312) has reported a 30-day all-

cause mortality rate of 3.6% following percutaneous TV intervention, varying depending on the technique used from 2.8% with MitraClip to 7.6% with Cardioband (mean age 76.6yo) (35). More recently, the TRILUMINATE trial (n=85), an international, prospective, single arm study examining safety and efficacy of the TriClip edge-to-edge repair system, reported a 1-year all-cause mortality rate of 7.1% (36). Mean ages for patients in both above trials were greater than 75 years of age. While comparison between isolated-TVSx and percutaneous interventions is currently limited by their different cohorts with respect to age, comorbidities, and indication, our data forms an important benchmark against which to compare emerging data on mid-long term outcomes following percutaneous TV intervention.

Strengths and limitations

This study's strengths lie in the large cohort of patients who underwent open isolated-TVSx, a relatively rare procedure compared to other cardiac valve surgery. In addition, our study cohort was derived from a statewide unselected population and included patients from all public and private healthcare facilities that performed cardiothoracic surgery, thus reflecting real-world clinical practice. Our long study period also allows for longitudinal trend analysis of medium to long-term outcomes including identifying important clinical predictors of mortality. The use of a death registry with cause-specific data analysis adds important detail to all-cause mortality figures.

However, this study is limited by its retrospective study design, which limits the imputation of causal links in our multivariable analysis. There was also no propensity-matched control

group that did not undergo surgery against which to compare outcomes post TVSx. Additionally, this is an observational study reflecting current practise on isolated TVSx which includes a heterogeneous group of procedures (e.g. annuloplasty, repair, replacement) with less clear evidence on the best approach compared to aortic or mitral valve procedures. Furthermore, our administrative data lacks important granular details such as echocardiographic data (e.g. RV size and function), functional class, medication usage, exact aetiology of TV disease, or indication for surgery (longevity vs quality of life). This speaks to the need for a national registry of tricuspid valve surgeries with such granular detail, especially with the development of newer TV interventions.

CONCLUSION

Open isolated-TVSx carries a significant risk of post-operative mortality, with admission for decompensated CCF and new AF the most common morbidities encountered post-surgery. Independent predictors of mortality include age ≥59yo and comorbidities including history of cardiac failure, chronic pulmonary disease and malignancy. This study forms a benchmark against which to compare outcomes with newer percutaneous TV interventions.

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REFERENCES

1. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. JACC: Cardiovascular Imaging. 2019;12(3):433-42.

2. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. Journal of the American College of Cardiology. 2004;43(3):405-9.

3. Ruel M, Rubens FD, Masters RG, Pipe AL, Bédard P, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. The Journal of thoracic and cardiovascular surgery. 2004;128(2):278-83.

4. Hahn RT, Asch F, Weissman NJ, Grayburn P, Kar S, Lim S, et al. Impact of tricuspid regurgitation on clinical outcomes: the COAPT trial. Journal of the American College of Cardiology. 2020;76(11):1305-14.

5. Mehr M, Karam N, Taramasso M, Ouarrak T, Schneider S, Lurz P, et al. Combined tricuspid and mitral versus isolated mitral valve repair for severe MR and TR: an analysis from the TriValve and TRAMI registries. Cardiovascular Interventions. 2020;13(5):543-50.

6. McCarthy FH, Vemulapalli S, Li Z, Thourani V, Matsouaka RA, Desai ND, et al. Association of tricuspid regurgitation with transcatheter aortic valve replacement outcomes: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. The Annals of Thoracic Surgery. 2018;105(4):1121-8.

7. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. Circulation. 2019;140(3):196-206.

8. Chen L, Larsen CM, Le RJ, Connolly HM, Pislaru SV, Murphy JG, et al. The prognostic significance of tricuspid valve regurgitation in pulmonary arterial hypertension. The Clinical Respiratory Journal. 2018;12(4):1572-80.

9. Pinamonti B, Dragos AM, Pyxaras SA, Merlo M, Pivetta A, Barbati G, et al. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry. European heart journal. 2011;32(9):1105-13.

10. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, et al. Clinical outcome of isolated tricuspid regurgitation. JACC: Cardiovascular Imaging. 2014;7(12):1185-94.

11. 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. Journal of the American Heart Association. 2017;6(12):e007597.

12. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;63(22):2438-88.

13. Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Journal of Cardio-Thoracic Surgery. 2017;52(4):616-64.

14. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin III JP, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart

Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2021;77(4):450-500.

15. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European heart journal. 2022;43(7):561-632.

16. Staab ME, Nishimura RA, Dearani JA. Isolated tricuspid valve surgery for severe tricuspid regurgitation following prior left heart valve surgery: analysis of outcome in 34 patients. Journal of Heart Valve Disease. 1999;8(5):567-74.

17. Do QB, Pellerin M, Carrier M, Cartier R, Hebert Y, Page P, et al. Clinical outcome after isolated tricuspid valve replacement: 20-year experience. The Canadian journal of cardiology. 2000;16(4):489-93.

18. Zack CJ, Fender EA, Chandrashekar P, Reddy YN, Bennett CE, Stulak JM, et al. National trends and outcomes in isolated tricuspid valve surgery. Journal of the American College of Cardiology. 2017;70(24):2953-60.

19. Hamandi M, Smith RL, Ryan WH, Grayburn PA, Vasudevan A, George TJ, et al. Outcomes of isolated tricuspid valve surgery have improved in the modern era. The Annals of thoracic surgery. 2019;108(1):11-5.

20. Chorin E, Rozenbaum Z, Topilsky Y, Konigstein M, Ziv-Baran T, Richert E, et al. Tricuspid regurgitation and long-term clinical outcomes. European Heart Journal-Cardiovascular Imaging. 2020;21(2):157-65.

21. Russo A, Grigioni F, Avierinos J-F, Freeman WK, Suri R, Michelena H, et al. Thromboembolic complications after surgical correction of mitral regurgitation: incidence, predictors, and clinical implications. Journal of the American College of Cardiology. 2008;51(12):1203-11.

22. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. The Lancet. 2016;387(10034):2218-25.

23. Centre for Health Record Linkage (CHeReL).Available at http://www.cherel.org.au.

24. Lee A-H, Ng ACC, Yong ASC, Hyun K, Brieger D, Kritharides L, et al. Outcomes of 1,098 patients following transcatheter aortic valve implantation: a statewide population-linkage cohort study. Heart, Lung and Circulation. 2021;30(8):1213-20.

25. Cheng Y-Y, Brieger D, Bannon P, Chow V, Kritharides L, Ng ACC. Outcomes Following Triple Cardiac Valve Surgery Over 17-years: A Multicentre Population-Linkage Study. Heart, Lung and Circulation. 2022.

26. Ng AC, Chung T, Yong AS, Wong HS, Chow V, Celermajer DS, et al. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. Circ Cardiovasc Qual Outcomes. 2011;4(1):122-8.

27. Ng ACC, Lau JK, Chow V, Adikari D, Brieger D, Kritharides L. Outcomes of 4838 patients requiring temporary transvenous cardiac pacing: a statewide cohort study. International Journal of Cardiology. 2018;271:98-104.

28. Brieger DB, Ng AC, Chow V, D'Souza M, Hyun K, Bannon PG, et al. Falling hospital and postdischarge mortality following CABG in New South Wales from 2000 to 2013. Open Heart. 2019;6(1):e000959.

29. Cheng Y-Y, Chow V, Brieger D, Yan TD, Kritharides L, Ng ACC. Outcomes of 16,436 patients requiring isolated aortic valve surgery: A statewide cohort study. International Journal of Cardiology. 2021;326:55-61.

30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

31. National Center for Health Statistics. Instructions for Classifying the Underlying Cause-of-Death, ICD-10. 2008:1-259. http://www.cdc.gov/nchs/about/major/dvs/im.htm Accessed June 10, 2009.

32. Kawsara A, Alqahtani F, Nkomo VT, Eleid MF, Pislaru SV, Rihal CS, et al. Determinants of morbidity and mortality associated with isolated tricuspid valve surgery. Journal of the American Heart Association. 2021;10(2):e018417.

33. Dreyfus J, Flagiello M, Bazire B, Eggenspieler F, Viau F, Riant E, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. European Heart Journal. 2020;41(45):4304-17.

34. Wong WK, Chen SW, Chou AH, Lee HA, Cheng YT, Tsai FC, et al. Late outcomes of valve repair versus replacement in isolated and concomitant tricuspid valve surgery: a nationwide cohort study. Journal of the American Heart Association. 2020;9(8):e015637.

35. Taramasso M, Alessandrini H, Latib A, Asami M, Attinger-Toller A, Biasco L, et al. Outcomes after current transcatheter tricuspid valve intervention: mid-term results from the international TriValve registry. JACC: Cardiovascular Interventions. 2019;12(2):155-65.

36. Lurz P, Stephan von Bardeleben R, Weber M, Sitges M, Sorajja P, Hausleiter J, et al. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. Journal of the American College of Cardiology. 2021;77(3):229-39.

Figure 1. Temporal trend of annual isolated tricuspid valve surgical volume during study period.

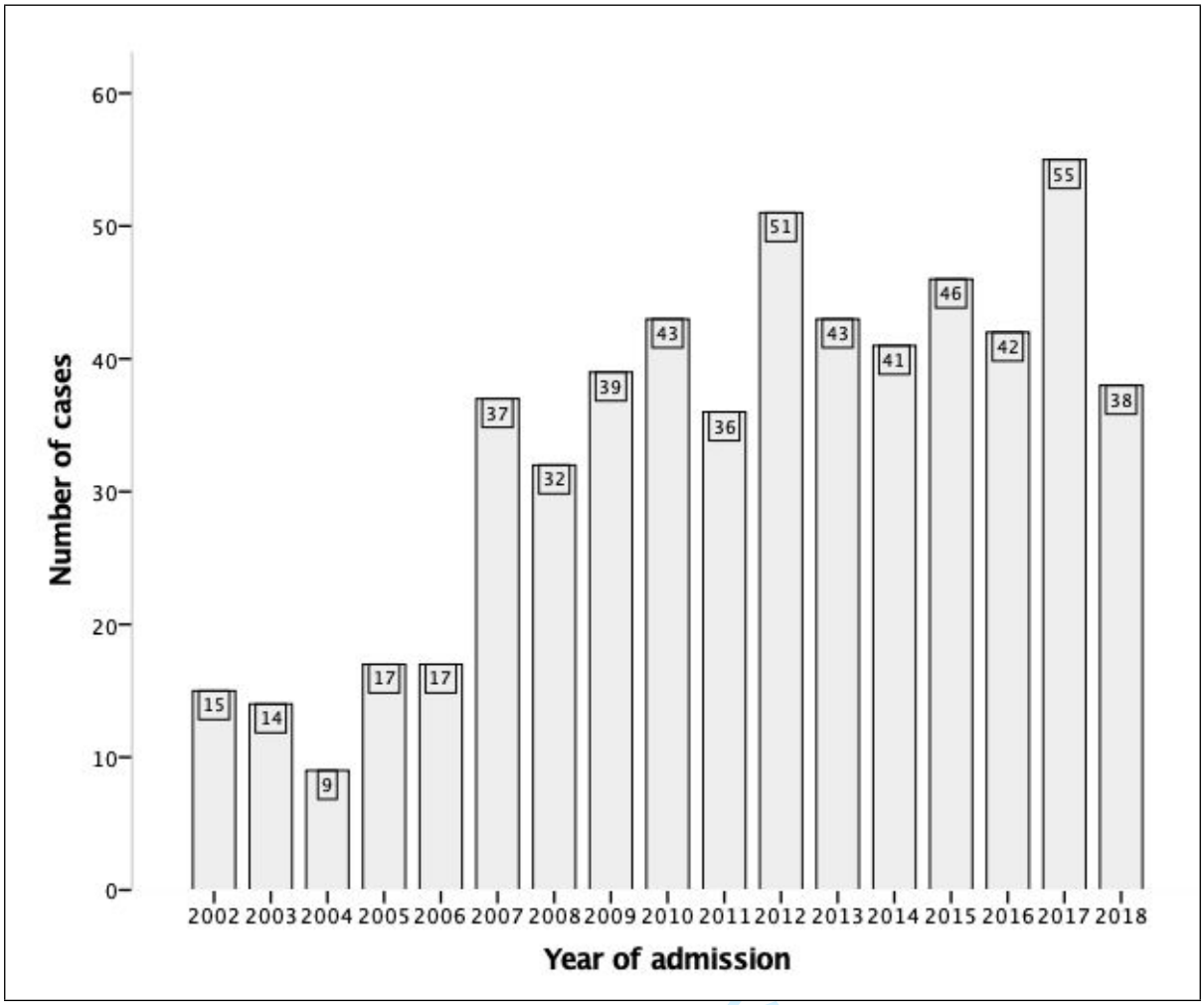

Figure Legend

Figure shows temporal trend of annual volume of isolated tricuspid valve surgery during study period (n=575), with a mean (±SD) of 34 ± 14 cases per-annum. Annual case volumes significantly increased over the study period with an average rise of 2.73 cases per year (95% CI 1.95-3.50, p<0.001).

SUPPLEMENTARY MATERIAL

Morbidity and Mortality Outcomes of Patients requiring Isolated Tricuspid Valve Surgery

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Table of Contents

Supplementary Table 1. Study comorbidities International Classification of Diseases Tenth Revision Australian Modification (ICD-10AM) codes and Australian Classification of Health Interventions (ACHI) procedural codes

No.	Comorbidity *	ICD-10AM codes
1	Endocarditis (indication for cardiac valve surgery)	I33, I38, I39
2	Atrial fibrillation/flutter	I48
3	Acute myocardial infarction	I21, I22, I23
4	Ischemic heart disease	I20, I21, I22, I23, I24, I25
5	Prior PCI / CABG	Z95.1, Z95.5
6	Congestive cardiac failure	I42, I43, I50, I11.0, I13.0, I13.2
7	Peripheral vascular disease	E09.5, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, E14.51, E14.52, I70, I71, I72, I73, I74, I77, I78, I79
8	Stroke	G45-45.9, G46-G46.8, I60, I61, I62, I63, I64
9	Prosthetic heart valve	Z95.2, Z95.3, Z95.4
10	Cardiovascular disease (defined as morbidities item nos. 2, 4-9)	I48, I20-I25, Z95.1, Z95.5, I42, I43, I50, I11.0, I13.0, I13.2, I70, I71, I72, I73, I74, I77, I78, I79, E09.5, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, E14.51, E14.52, G45-45.9, G46-G46.8, I60-I62, I63-I64, Z95.2, Z95.3, Z95.4
11	Hypertension	I10, I11, I12, I13, I15
12	Hyperlipidaemia	E78
13	Diabetes	E09, E10, E11, E13, E14, Z92.22
14	Current/ex-smoker	F17, Z72.0, Z86.43
15	Cardiac risk factors (defined as morbidities item nos. 11-14)	I10, I11, I12, I13, I15, E78, E09, E10, E11, E13, E14, Z92.22, Z72.0, F17, Z86.43
16	Systemic connective tissue disease	M30, M31, M32, M33, M34, M35, M36
17	Chronic pulmonary disease (include asthma, chronic airways limitation, interstitial lung disease, cystic fibrosis with pulmonary manifestation)	E84.0, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J70, J82, J84, J99
18	Malignancy	C00-C96, D00-D09
19	Chronic kidney disease	N18, N19
20	Dementia	F00, F01, F02, F03
21	Neurodegenerative diseases (defined as dementia, central nervous systemic atrophies, Parkinson's disease, basal ganglia degeneration and/or nervous systemic degenerative diseases)	F00, F01, F02, F03, G10-G14, G20, G23, G30, G31
22	Peptic ulcer disease	K25, K26, K27, K28
23	Liver disease – mild	K70.0, K70.1, K70.2, K70.9, K71.0, K71.1, K71.2, K71.3, K71.4, K71.5, K71.6, K71.8, K71.9, K73, K75, K76, K77
24	Liver disease – moderate-severe	I82.0, K70.3, K70.4, K71.7, K72, K74
25	Chronic kidney disease – moderate-severe	N18.3, N18.4, N18.5
26	Diabetes with organ damage	E09.21, E09.29, E09.31, E09.32, E09.40, E09.42, E09.51, E09.52, E09.71, E09.72, E09.8, E10.21, E10.22, E10.29, E10.31, E10.32, E10.33, E10.34, E10.35, E10.36, E10.39, E10.40, E10.41, E10.42, E10.43, E10.49, E10.51, E10.52, E10.53, E10.61, E10.62, E10.63, E10.69, E10.71, E10.73, E10.8,

		E11.21, E11.22, E11.29, E11.31, E11.32, E11.33, E11.34, E11.35, E11.36, E11.39, E11.40, E11.41, E11.42, E11.43, E11.49, E11.51, E11.52, E11.53, E11.61, E11.62, E11.63, E11.69, E11.71, E11.72, E11.73, E11.8, E13.21, E13.22, E13.29, E13.31, E13.32, E13.33, E13.34, E13.35, E13.36, E13.39, E13.40, E13.41, E13.42, E13.43, E13.49, E13.51, E13.52, E13.53, E13.61, E13.62, E13.63, E13.69, E13.71, E13.72, E13.73, E13.8, E14.21, E14.22, E14.29, E14.31, E14.32, E14.33, E14.34, E14.35, E14.36, E14.39, E14.40, E14.41, E14.42, E14.43, E14.49, E14.51, E14.52, E14.53, E14.61, E14.62, E14.63, E14.69, E14.71, E14.72, E14.73, E14.8
27	Lymphoma	C81, C82, C83, C84, C85, C86, C88
28	Leukemia	C90, C91, C92, C93, C94, C95, C96
29	Metastatic solid tumour	C76, C77, C78, C79, C80
30	Hemiplegia	G81, G82
31	Acquired Immune Deficiency Syndrome (AIDS)	B20, B21, B22, B23, B24
32	Any tumor/malignancy excluding lymphoma and/or leukemia	C00-C80, D00-D09
33	Primary pulmonary hypertension	I27.0
34	Secondary pulmonary hypertension	I27.2
35	Intravenous drug use (IVDU) history	F11, F11.0, F11.1, F11.2, F11.3, F11.4, F11.5, F11.6, F11.7, F11.8, F11.9, F15.0, F15.00, F15.01, F15.02, F15.09, F15.1, F15.10, F15.11, F15.12, F15.19, F15.2, F15.20, F15.21, F15.22, F15.29, F15.3, F15.30, F15.31, F15.32, F15.39, F15.4, F15.40, F15.41, F15.42, F15.49, F15.5, F15.50, F15.51, F15.52, F15.59, F15.6, F15.60, F15.61, F15.62, F15.69, F15.7, F15.70, F15.71, F15.72, F15.79, F15.8, F15.80, F15.81, F15.82, F15.89, F15.9, F15.90, F15.91, F15.92, F15.99, T40.0, T40.1, T40.2, T40.3, T40.4, T40.6, T43.61
36	Rheumatic disease involving the tricuspid valve	I07, I07.0, I07.1, I07.2, I07.8, I07.9, I08.1, I08.2, I08.3

* To calculate the Charlson Comorbidity Index (CCI) score, without age adjustment, for individual patient during a particular admission of interest, use the following morbidity item numbers with their corresponding ICD-10AM codes to derive the patient's CCI score:

a) 1 score for each morbidity item – 3, 6, 7, 8, 13, 16, 17, 20, 22, 23
b) 2 score for each morbidity item – 25, 26, 27, 28, 30, 32
c) 3 score for morbidity item – 24
d) 6 score for morbidity item – 29, 31

No.	ACHI procedures	ACHI procedural codes
1	Coronary angiography (cardiac catheterization with or without angioplasty or stenting)	38200-00, 38203-00, 38206-00, 38215-00, 38218-00, 38218-01, 38218-02, 38300-00, 38303-00, 38306-00, 38306-01, 38306-02
2	Transoesophageal echocardiogram	55118-00
3	CABG (Coronary artery bypass graft)	38456-19, 38497-00, 38497-01, 38497-02, 38497-03, 38497-04, 39497-05, 38497-06, 38497-07, 38500-00, 38500-01, 38500-02, 38500-03, 38500-04, 38500-05, 38503-00,

		38503-01, 38503-02, 38503-03, 38503-04, 38503-05, 38637-00, 38653-08, 90201-00, 90201-01, 90201-02, 90201-03
4	Lone tricuspid valve surgery (Only single valve surgery in single admission) (exclude percutaneous approach)	38456-11, 38456-17, 38475-01, 38477-01, 38480-02, 38481-02, 38488-04, 38488-05, 38489-03, 38653-06
5	Combined aortic, mitral, tricuspid and pulmonary valves surgery (All four valves surgery in single admission) (exclude percutaneous approach)	38456-01, 38456-10, 38456-11, 38456-15, 38456-16, 38456-17, 38456-18, 38475-00, 38475-01, 38475-02, 38477-00, 38477-01, 38477-02, 38480-00, 38480-01, 38480-02, 38481-00, 38481-01, 38481-02, 38483-00, 38485-00, 38485-01, 38487-00, 38488-00, 38488-01, 38488-02, 38488-03, 38488-04, 38488-05, 38488-06, 38488-07, 38489-00, 38489-01, 38489-02, 38489-03, 38489-04, 38489-05, 38653-04, 38653-05, 38653-06, 38653-07
6	Combined aortic, mitral and tricuspid valves only surgery (All three valves surgery in single admission) (exclude percutaneous approach)	38456-10, 38456-11, 38456-15, 38456-16, 38456-17, 38475-00, 38475-01, 38475-02, 38477-00, 38477-01, 38477-02, 38480-00, 38480-01, 38480-02, 38481-00, 38481-01, 38481-02, 38483-00, 38485-00, 38485-01, 38487-00, 38488-00, 38488-01, 38488-02, 38488-03, 38488-04, 38488-05, 38489-00, 38489-01, 38489-02, 38489-03, 38653-04, 38653-05, 38653-06
7	Combined aortic, tricuspid and pulmonary valves only surgery (All three valves surgery in single admission) (exclude percutaneous approach)	38456-01, 38456-10, 38456-11, 38456-15, 38456-17, 38456-18, 38475-01, 38475-02, 38477-01, 38477-02, 38480-00, 38480-02, 38481-00, 38481-02, 38483-00, 38488-00, 38488-01, 38488-04, 38488-05, 38488-06, 38488-07, 38489-00, 38489-01, 38489-03, 38489-04, 38489-05, 38653-04, 38653-06, 38653-07
8	Combined mitral, tricuspid and pulmonary valves only surgery (All three valves surgery in single admission) (exclude percutaneous approach)	38456-01, 38456-11, 38456-16, 38456-17, 38456-18, 38475-00, 38475-01, 38477-00, 38477-01, 38480-01, 38480-02, 38481-01, 38481-02, 38485-00, 38485-01, 38487-00, 38488-02, 38488-03, 38488-04, 38488-05, 38488-06, 38488-07, 38489-02, 38489-03, 38489-04, 38489-05, 38653-05, 38653-06, 38653-07
9	Combined aortic and tricuspid valves only surgery (All two valves surgery in single admission) (exclude percutaneous approach)	38456-10, 38456-11, 38456-15, 38456-17, 38475-01, 38475-02, 38477-01, 38477-02, 38480-00, 38480-02, 38481-00, 38481-02, 38483-00, 38488-00, 38488-01, 38488-04, 38488-05, 38489-00, 38489-01, 38489-03, 38653-04, 38653-06
10	Combined mitral and tricuspid valves only surgery (All two valves surgery in single admission) (exclude percutaneous approach)	38456-11, 38456-16, 38456-17, 38475-00, 38475-01, 38477-00, 38477-01, 38480-01, 38480-02, 38481-01, 38481-02, 38485-00, 38485-01, 38487-00, 38488-02, 38488-03, 38488-04, 38488-05, 38489-02, 38489-03, 38653-05, 38653-06

11	Combined tricuspid and pulmonary valves only surgery (All two valves surgery in single admission) (exclude percutaneous approach)	38456-01, 38456-11, 38456-17, 38456-18, 38475-01, 38477-01, 38480-02, 38481-02, 38488-04, 38488-05, 38488-06, 38488-07, 38489-03, 38489-04, 38489-05, 38653-06, 38653-07
12	Tricuspid valve surgery sub-category: • Tricuspid valve open valvotomy	38456-11
13	Tricuspid valve surgery sub-category: • Tricuspid valve repair	38480-02, 38481-02
14	Tricuspid valve surgery sub-category: • Tricuspid valve annuloplasty	38475-01, 38477-01
15	Tricuspid valve surgery sub-category: • Tricuspid valve replacement (exclude percutaneous approach)	38488-04, 38488-05, 38489-03
16	Tricuspid valve surgery sub-category: • Other intrathoracic procedures on tricuspid valve	38456-17, 38653-06

Supplementary Table 2. Univariable associations with all-cause mortality during study period

Univariable analysis	Parameters	HR (95% CI)	P value
All-cause death during study follow-up (4.82 ± 3.94 years)	Age ≥59 years *	2.16 (1.60-2.89)	<0.001
	Male	1.02 (0.78-1.34)	0.87
	Referral source	-	0.27
	Emergency Department	1.00 (reference)	-
	Physician-referred	0.70 (0.48-1.02)	0.06
	External hospital-referred	0.84 (0.54-1.32)	0.45
	Others	1.33 (0.41-4.34)	0.63
	Unknown	0.52 (0.12-2.16)	0.37
	Indication for valve surgery †	-	-
	Endocarditis	0.57 (0.33-0.96)	0.03
	Rheumatic tricuspid valve	1.32 (0.98-1.77)	0.07
	Types of TV surgery ‡		
	Annuloplasty	0.92 (0.70-1.21)	0.56
	Replacement	1.35 (1.03-1.77)	0.03
	Repair	0.50 (0.32-0.79)	0.003
	Open valvotomy	0.39 (0.06-2.80)	0.35
	Others	0.57 (0.24-1.39)	0.22
	Concomitant CABG §	1.63 (1.16-2.29)	0.005
	Ischemic heart disease	1.55 (1.14-2.12)	0.006
	Prior PCI / CABG	1.30 (0.77-2.20)	0.33
	Congestive cardiac failure	1.94 (1.48-2.54)	<0.001
	Stroke	2.79 (1.23-6.31)	0.01
	Peripheral vascular disease	1.67 (0.95-2.93)	0.07
	Prosthetic heart valve	1.11 (0.74-1.65)	0.61
	Atrial fibrillation/flutter	1.28 (0.98-1.69)	0.07
	Hypertension	1.15 (0.86-1.55)	0.35
	Hyperlipidaemia	1.29 (0.68-2.44)	0.43
	Diabetes	1.54 (1.08-2.19)	0.02
	Current/ex-smoker	0.96 (0.73-1.28)	0.80
	Primary PHT	1.03 (0.43-2.51)	0.94
	Secondary PHT	2.05 (1.45-2.88)	<0.001
	Malignancy	3.54 (1.81-6.91)	<0.001
	Chronic pulmonary disease	2.62 (1.64-4.18)	<0.001
	Neurodegenerative disease ‖	1.73 (0.43-6.97)	0.44
	Chronic kidney disease	1.78 (1.24-2.57)	0.002
	IVDU history	0.64 (0.39-1.07)	0.09
	CCI score – per 1-score #	1.25 (1.18-1.33)	<0.001
	CCI score ≥1	2.39 (1.79-3.20)	<0.001
	Year of surgery	-	0.87
	2002-2005	1.00 (reference)	-
	2006-2009	0.86 (0.56-1.31)	0.48
	2010-2013	0.90 (0.59-1.38)	0.63
	2014-2018	0.82 (0.51-1.35)	0.44

Plus-minus value represents mean ± standard deviation (SD).

CABG, coronary artery bypass graft; CCI, Charlson comorbidity index; CI, confidence interval; HR, hazards ratio; IVDU, intravenous drug use; NA, not applicable due to small sample size; PCI, percutaneous coronary interventions; PHT, pulmonary hypertension; TV, tricuspid valve.

* **Age was dichotomized based on mean age of study cohort.**

† **Indication for cardiac valve surgery was either for endocarditis or for non-endocarditis cardiac valvular pathology.**

‡ **More than one type of TV surgery might be performed on a patient during the same admission.**

§ **Concomitant CABG performed during same admission for cardiac valve surgery.**

‖ **Neurodegenerative disease includes dementia, central nervous systemic atrophies, Parkinson's disease, basal ganglia degeneration, and/or nervous systemic degenerative diseases.**

\# **Conditions included in the Charlson Comorbidity Index include myocardial infarction, congestive cardiac failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease (mild vs. moderate to severe), diabetes (with or without organ damage), hemiplegia, moderate to severe renal disease, any tumour (within last 5 years), lymphoma, leukemia, metastatic solid tumour and acquired immunodeficiency syndrome.**

Supplementary Table 3. Independent predictors for all-cause mortality during study period

Multivariable analysis *	Parameters	aHR (95% CI)	P value
All-cause death during study follow-up (4.82 ± 3.94 years)	Age ≥59 years (mean age)	1.76 (1.26-2.47)	0.001
	Male	1.01 (0.76-1.34)	0.96
	Indication for valve surgery †		
	Endocarditis	1.00 (0.56-1.77)	0.99
	Types of TV surgery ‡		
	Replacement	1.32 (0.98-1.79)	0.07
	Repair	0.78 (0.0.47-1.28)	0.33
	Concomitant CABG §	1.34 (0.86-2.08)	0.20
	Ischemic heart disease	1.14 (0.77-1.70)	0.51
	Congestive cardiac failure	1.78 (1.33-2.38)	<0.001
	Stroke	2.25 (0.96-5.26)	0.06
	Diabetes	1.12 (0.77-1.65)	0.55
	Secondary PHT	1.36 (0.95-1.95)	0.10
	Malignancy	3.49 (1.73-7.07)	<0.001
	Chronic pulmonary disease	2.21 (1.36-3.59)	<0.001
	Chronic kidney disease	1.26 (0.85-1.87)	0.25

Plus-minus value represents mean ± standard deviation (SD).
CABG, coronary artery bypass graft; CI, confidence interval; aHR, adjusted hazards ratio; PCI, percutaneous coronary interventions; PHT, pulmonary hypertension; TV, tricuspid valve.

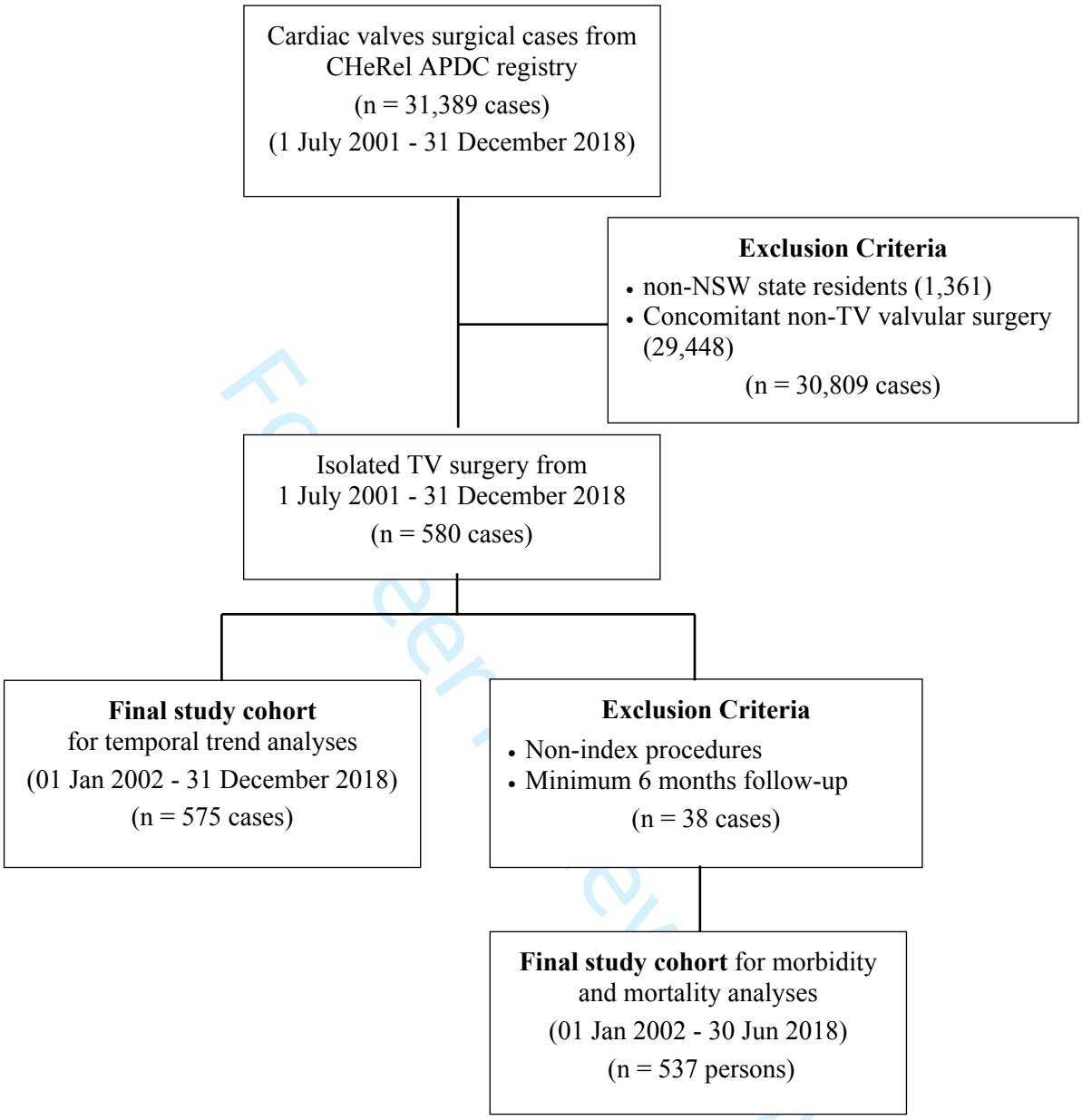
* Multivariable Cox regression method was used to identify independent predictors of all-cause mortality. Only univariables with P<0.05 were included in the multivariable analysis (see Supplementary Table 2 for univariable analysis results).

† Indication for cardiac valve surgery was either for endocarditis or non-endocarditis cardiac valvular pathology

‡ More than one type of TV surgery might be performed on a patient during the same admission.

§ Concomitant CABG performed during same admission for cardiac valve surgery.

Supplementary Figure 1. Study flow chart.



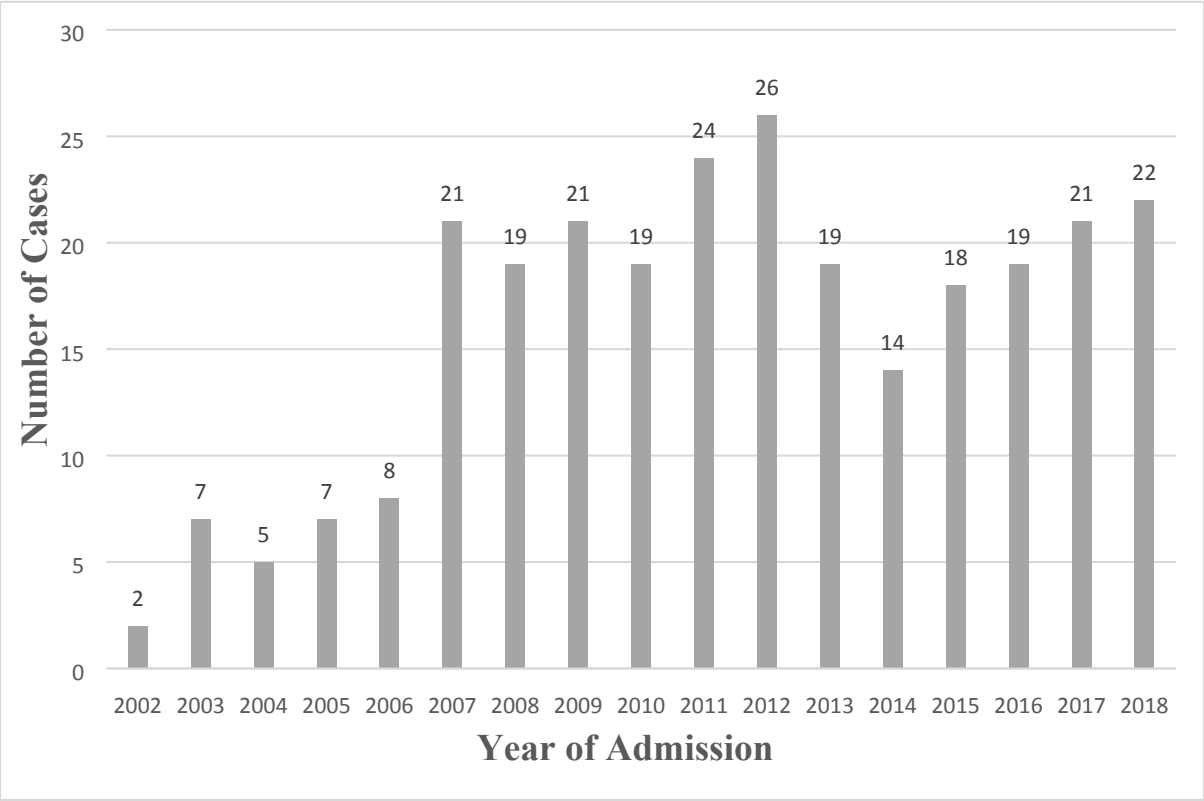
Legend

Flow chart shows the derivation of the study cohort.

APDC, Admitted Patient Data Collection; CHeReL, Centre for Health Record Linkage; NSW, New South Wales.

* Dataset containing all statewide admitted patients who underwent a broad range of cardiac procedures including coronary angiography, percutaneous coronary intervention, electrophysiology procedures and transesophageal echocardiography.

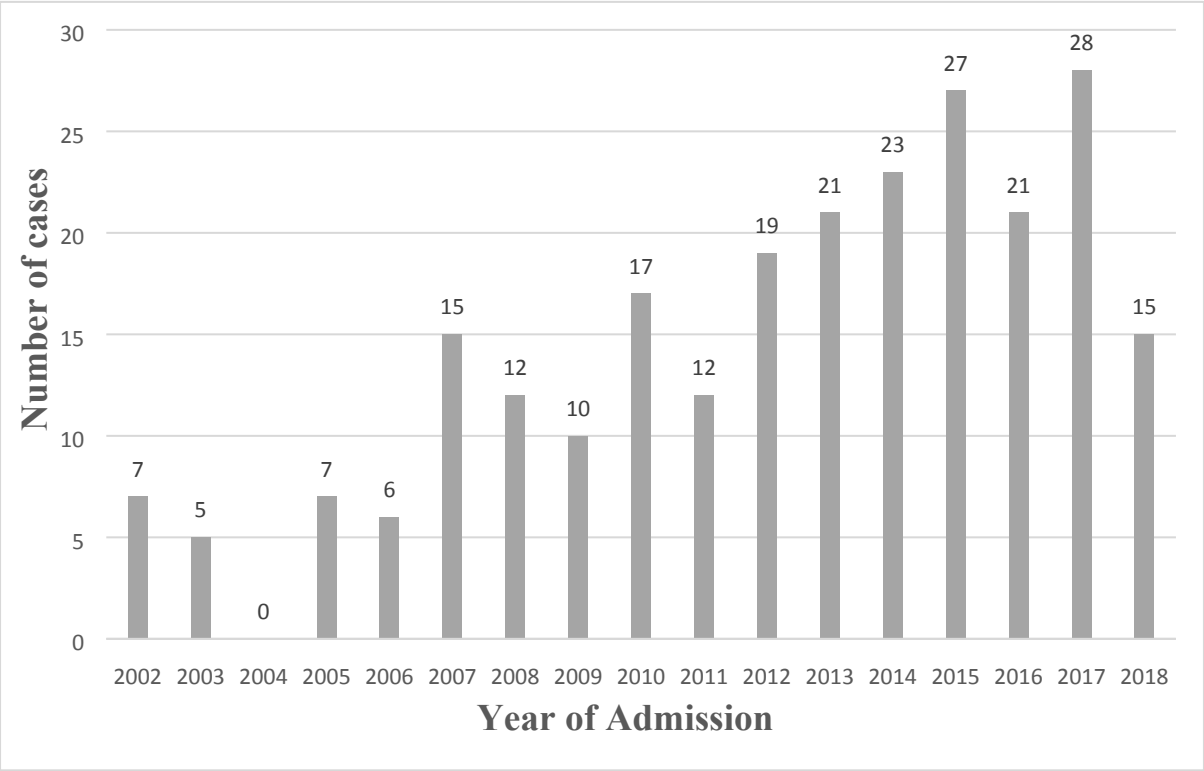
Supplementary Figure 2. Temporal trend of tricuspid valve annuloplasty during study period.



Legend

Figure shows temporal trend of tricuspid valve annuloplasty during study period (n=272), with a mean (±SD) of 16.0 ± 7.3 cases per annum. Tricuspid valve annuloplasty caseload increased significantly over the course of the study period by an average of 0.46 cases per year (95% CI 0.21-0.72, p=0.002).

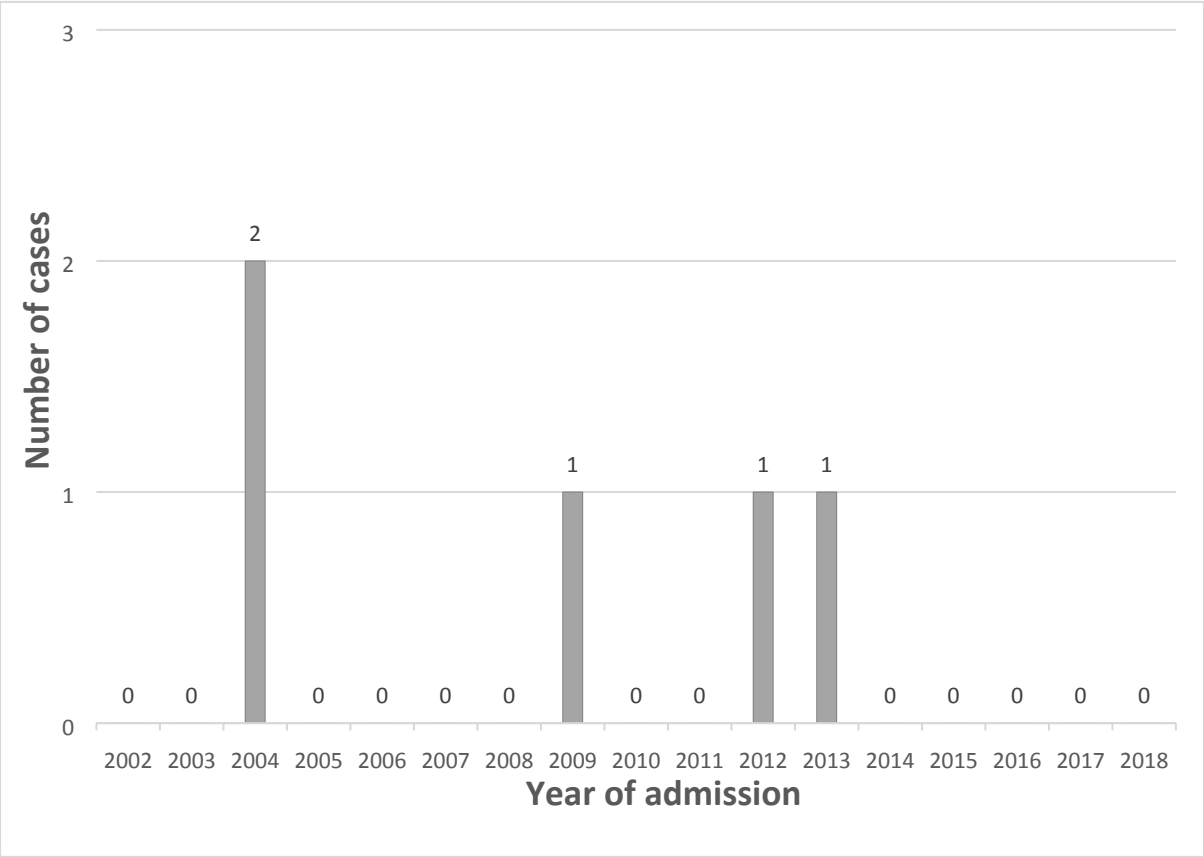
Supplementary Figure 3. Temporal trend of tricuspid valve replacement during study period.



Legend

Figure shows temporal trend of tricuspid valve replacement during study period (n=245), with a mean (±SD) of 14.4 ± 8.1 cases per annum. Tricuspid valve replacement caseload increased significantly over the study period by an average of 0.53 cases per year (95% CI 0.40-0.65, p<0.001).

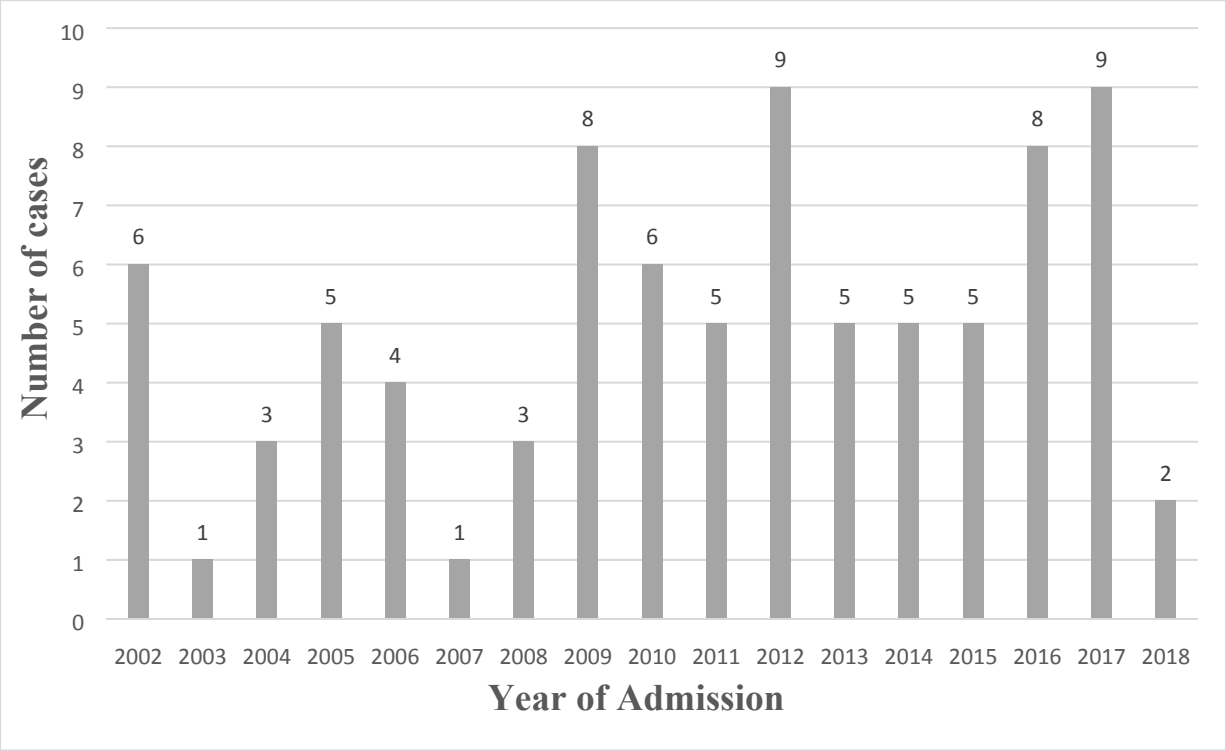
Supplementary Figure 4. Temporal trend of open tricuspid valvotomy during study period.



Legend

Figure shows temporal trend of open tricuspid valvotomy during study period (n=5), with a mean (±SD) of 0.3 ± 0.6 cases per annum. There was no significant change in annual caseload valvotomies over the course of the study period (p=0.64).

Supplementary Figure 5. Temporal trend of tricuspid valve repair during study period.



Legend

Figure shows temporal trend of tricuspid valve repair during study period (n=85), with a mean (±SD) of 5.0 ± 2.5 cases per annum. Tricuspid valve repairs increased significantly over the study period by an average of 1.13 cases per year (95% CI 0.24-2.02, p=0.02).

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	#3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	#4	Present key elements of study design early in the paper	8
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	8
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a (not a matched study)
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect	8-9

		modifiers. Give diagnostic criteria, if applicable	
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-9
Bias	#9	Describe any efforts to address potential sources of bias	9-10
Study size	#10	Explain how the study size was arrived at	8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	11-12
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	11-12
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	11-12
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a

Statistical methods	#12e	Describe any sensitivity analyses	n/a	
Results				
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.		13
Participants	#13b	Give reasons for non-participation at each stage	13	
Participants	#13c	Consider use of a flow diagram	13 (Figure 1)	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	13-15, Table 1	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a	

Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	15
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	13-17
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17-18
Main results	#16b	Report category boundaries when continuous variables were categorized	17-18
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17-18

Discussion			
Key results	#18	Summarise key results with reference to study objectives	19
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	23-24
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-23
Generalisability	#21	Discuss the generalisability (external validity) of the study results	22-23
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

BMJ Open

Morbidity and Mortality Outcomes of Patients requiring Isolated Tricuspid Valve Surgery: a Retrospective Cohort Study of 537 patients in New South Wales between 2002 and 2018

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Morbidity and Mortality Outcomes of Patients requiring Isolated Tricuspid Valve Surgery: a Retrospective Cohort Study of 537 patients in New South Wales between 2002 and 2018

Harvey; Outcomes following Isolated Tricuspid Valve Surgery

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Ethical approval: The study protocol was approved by the New South Wales Population and Health Services Research Ethics Committee, reference number: 2013/09/479. The Ethics Committees granted a waiver of the usual requirement for the consent of the individual to the

use of their health information. All patient data were de-identified and analysed anonymously.

Transparency: The senior author affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Word Count: 3732 words

ABSTRACT

Objectives: The aim of the study was to evaluate mortality and morbidity outcomes following open-heart isolated tricuspid valve surgery (TVSx) with medium-long term follow up.

Design: Retrospective cohort study.

Setting: New South Wales (NSW) public and private hospital admissions between 1-Jan-2002 and 30-Jun-2018

Participants: A total of 537 patients underwent open isolated-TVSx during the study period.

Primary and Secondary outcome measures: Primary outcome was all-cause mortality tracked from the death registry to 31-Dec-2018. Secondary morbidity outcomes including admission for congestive cardiac failure (CCF), new atrial fibrillation (AF), infective endocarditis (IE), pulmonary embolism (PE), and insertion of a permanent pacemaker (PPM) or implantable-cardioverter-defibrillator (ICD), were tracked from the Admitted Patient Data Collection (APDC) data base. Independent mortality associations were determined using the Cox regression method.

Results: A total of 537 patients underwent open isolated-TVSx (46% male): median age (interquartile-range) was 63.5yo (43.9-73.8yo) with median length-of-stay 16days (10-31days). Main cardiovascular comorbidities were AF (54%) and CCF (42%); 67% had rheumatic TV. In-hospital and total mortality were 7.4% and 39.3% respectively (mean follow-up: 4.8yrs). Cause-specific deaths were evenly split between cardiovascular and noncardiovascular causes. Predictors of mortality included a history of congestive cardiac failure (hazard ratio [HR]=1.78, 95% confidence interval [CI]=1.33-2.38, p<0.001) and chronic pulmonary disease (HR=2.66, 95%CI=1.63-4.33, p<0.001). In-hospital PPM rate

was 10.0%. At 180days, 53 (9.9%) patients were admitted for CCF, 25 (10.1%) had new AF, 7 (1.5%) had new IE, and <1% had PE, post-discharge PPM or ICD insertion.

Conclusion: Open isolated-TVSx carries significant mortality risk, with decompensated CCF and new AF the most common morbidities encountered post-surgery. This report forms a benchmark to compare outcomes with newer percutaneous tricuspid interventions.

Key Words: Outcomes, tricuspid valve surgery, isolated cardiac valve surgery

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A relatively large cohort of patients for an infrequently performed set of procedures.
- Study cohort was derived from a statewide unselected population from all public and private healthcare facilities that performed cardiothoracic surgery
- The use of a death registry with cause-specific data analysis adds detail to all-cause mortality figures.
- Comprises a heterogeneous group of procedures: TVSx annuloplasty, repair, replacement.
- Dataset lacks granular details such as echocardiographic data (e.g., RV size and function) or aetiology of TV dysfunction

INTRODUCTION

The burden of tricuspid valve (TV) disease is expected to increase with the increasing age of the Australian population. The prevalence of moderate or severe TV regurgitation of any cause in developed countries is 4.0% in those over the age of 75, and 1.1% in those 65-74 (1). The prevalence of tricuspid valve stenosis, rare in developed countries, is not known.

The presence of tricuspid regurgitation (TR) is an independent predictor of increased mortality, both by itself (isolated functional TR) and for secondary aetiologies including left-sided valvular disease, heart failure, arrhythmogenic right ventricular cardiomyopathy, and pulmonary arterial hypertension (2-10).

TV surgery (TVSx) is largely performed in combination with other cardiac procedures, most frequently left-sided valve surgery (11). Society guidelines have consistently recommended isolated TVSx for patients with severe primary TR as their sole valvular lesion (12, 13). More recently the 2020 American Heart Association (AHA) and 2021 European Society of Cardiology (ESC) Valvular Heart Disease guidelines have recommended TVSx for select patients with severe secondary TR regardless of the presence of an indication for concurrent left-sided valve surgery or a history of prior left-sided valve surgery (14, 15).

Isolated open-heart TVSx (open-TVSx) has traditionally been associated with high mortality rates. Reported in-hospital mortality rates have varied over time from 8.8-19.0% in small (n<500) older studies (16, 17), to 8.8-9.7% in larger studies (n=1364 in Alqahtani et al, and n=5005 in Zack et al) over the last twenty years (11, 18), to as low as 3.2% in a recent single-

centre study (n=95) involving carefully selected patients (19). However longer-term morbidity outcomes, including re-admission for heart failure, permanent pacemaker (PPM) requirement, pulmonary embolism (PE) or new-onset atrial fibrillation (AF), are not well-described. Moreover, while an association between TVSx and PE has not been described, worsening TR has been numerically (although not statistically) associated with pulmonary embolism, TR may result from chronic thromboembolic disease, and PE is a plausible complication of TVSx given the association between left-sided valvular intervention and stroke (20-22).

The primary aim of this study was to determine the incidence and temporal trends of open-heart isolated-TVSx in an Australian statewide cohort and examine their mortality outcomes. The secondary aim was to characterize morbidity events after isolated-TVSx.

METHODS

Study population

The Centre for Health Record Linkage (CHeReL), established in 2006, holds one of the largest data linkage systems in Australia containing high-quality linked health data of residents in the state of New South Wales (NSW) (23). From its Admission-Patient-Data-Collection (APDC) database, which includes ≥97% of all healthcare facilities in the state, we identified consecutive admissions that involved open-heart surgery (excluding percutaneous approach) for tricuspid valve pathology (see Supplementary Table 1 for relevant ACHI procedure codes) either as primary or secondary procedures coded under the Australian Classification of Health Interventions (ACHI) coding system between 1-July-2001 and 31-December-2018. Our research group has published detailed outcomes studies using data obtained from the APDC database (24-29).

Data sources

Variables obtained from the APDC database for each hospital admission that involved TVSx include admission date, age, gender, country of birth, admission referral source, length of admission, and in-hospital mortality.

The primary and all secondary diagnoses (potentially up to 50 secondary diagnoses) associated with each admission were retrieved from the APDC database. Each diagnosis was coded in the APDC database according to the International Classification of Diseases, Tenth

Revision Australian Modification (ICD-10AM). For this study, we pre-specified the indication for cardiac valve surgery during admission as either for endocarditis (as primary or secondary diagnosis) or as non-endocarditis valve surgery, and if concomitant coronary artery bypass graft (CABG) surgery was performed in the same admission (see Supplementary Table 1 for relevant ICD-10AM and ACHI codes). In addition, whether rheumatic tricuspid valve was documented during admission was recorded. Additional comorbidities extracted for this study include ischemic heart disease, prior percutaneous coronary interventions [PCI] and/or CABG surgery, CCF, stroke, peripheral vascular disease, prosthetic heart valve, and AF), primary or secondary pulmonary hypertension, cardiac risk factors (including hypertension, hyperlipidaemia, diabetes and current/ex-smoker), malignancy, chronic pulmonary disease, neurodegenerative disease, chronic kidney disease and history of intravenous drug use (IVDU). In addition, the overall comorbid status of each patient was quantified using the Charlson comorbidity index (CCI) (30). A value of 0 indicates no comorbidity, while higher values represent an increasing burden of comorbid illnesses. Conditions included in the CCI include age (1 point for every decade after 40), myocardial infarction, congestive cardiac failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease (mild vs. moderate to severe), diabetes (with or without organ damage), hemiplegia, moderate to severe renal disease, any tumour (within last 5 years), lymphoma, leukemia, metastatic solid tumour and acquired immunodeficiency syndrome.

Study outcomes

The primary outcome of the study was all-cause and cause-specific death rates, tracked from the statewide death registry also held by CHeReL. For mortality analysis, cases were limited to only NSW state residents to minimize incomplete tracking. The end-of-study date was set at 31-December-2018. All death certificates were reviewed to ascertain cause-specific death rates. Each death was coded independently by two reviewers (AN and VC) according to general principles set by the World Health Organization (31). Reviewers were blinded to patient's background comorbid illnesses during coding. Disparities were resolved by consensus. Cause-specific mortality were based on prior published classifications (26). In brief, cardiovascular cause was defined as death due to acute myocardial infarction, CCF, stroke, cardiac-related causes (when more than one cardiac cause of death was recorded), or PE. Noncardiovascular causes included death due to sepsis, malignancy, other noncardiovascular causes, or undefined. Patients with multiple potential causes of death on their death certificates were classified as "undefined" and labelled as noncardiovascular death for the purposes of the present study.

Secondary outcomes of the study were tracked from the APDC database using linkage method to determine morbidity events during follow-up post-surgery. These include first re-admission for CCF, development of new AF or infective endocarditis, PE, and the need for a PPM or implantable-cardioverter-defibrillator (ICD) implantation.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Approval was granted by the NSW Population and Health Services Research Ethics Committee, reference number: 2013/09/479. The Ethics Committees granted a waiver of the usual requirement for the consent of the individual to the use of their health information. All patient data were de-identified and analysed anonymously.

Statistical analysis

To determine the incidence and temporal trend on case-volumes of isolated open-TVSx statewide during the study period, all admissions between 1-January-2002 and 31-December-2018 were included. For the rest of the analyses, the study cohort was limited to NSW state residents and confined to the index admission between 1-January-2002 and 30-June-2018, enabling a minimum of six months follow-up. Thus, for those who had repeat TVSx during the study period (recurring patients), only their initial admission was included. End-of-study follow-up was prespecified at 31-December-2018.

All continuous variables are expressed as mean ± standard deviation (SD), unless otherwise stated, and categorical data given in absolute numbers and percentages. Linear regression was used to determine trends in TVSx caseload per-annum over the study period, excluding 2018 to minimize ascertainment bias as the APDC database receives six-monthly updates. To identify predictors of mortality post open-TVSx, Cox proportional hazard regression method was used. Univariables considered include age (dichotomized by mean age), gender, admission referral source, year-groups of surgery (stratified into 2002-2005, 2006-2009, 2010-2013, 2014-2018), indication for surgery (infective endocarditis), rheumatic tricuspid valve status, types of open-TVSx, concomitant CABG, other cardiovascular and noncardiovascular comorbidities. Univariables with $p<0.05$ were included in the multivariable Cox regression analysis, except for age and gender which were included irrespective of significance. The proportional hazards assumption was checked with log-minus-log plots.

All analyses were performed using SPSS v25.0 (IBM, USA) and Stata 16.1. A two-tailed probability value <0.05 was considered statistically significant. No sponsors had a role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Patient and Public involvement: Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research. Refer to the Methods section for further details.

RESULTS

Temporal trend of TV cases

There were 575 cases of open isolated-TVSx in the calendar years of 2002 to 2018, averaging 34 ± 14 cases per-annum (Supplementary Figure 1). There was a significant increase in case numbers by an average of 2.73 cases per-annum over the study period (95% CI 1.95-3.50, p<0.001) (Figure 1). The bulk of TVS cases were TV annuloplasty (n=272) and replacement (n=245), with case volume for both surgeries increasing during the study period (Supplementary Figures 2-3). A smaller number of non-annuloplasty TV repairs (n=85) and valvotomies (n=5) were performed. While there were significant increases in TV repair caseloads during the study period, TV valvotomy caseloads were so small as to preclude trend analysis (Supplementary Figures 4-5).

Baseline demographic and surgical characteristics of study cohort

The study cohort's median age was 63.5yo (43.9-73.8yo) and was 46.4% male. (Table 1). A total of 14.3% of patients had concomitant CABG, and endocarditis was the indication for TVSx in 10.4% of patients. A rheumatic tricuspid valve was documented in 66.5% of patients.

Table 1. Study cohort demographic and surgical characteristics.

Parameters	Isolated TVSx (N=537)
Demographics	
Age, years	58.2 ± 20.1
Median (IQR)	63.5 (43.9 – 73.8)
Males	249 (46.4)
Country of birth	
Australia plus territories / New Zealand	379 (70.6)
Europe	77 (14.3)
Asia	33 (6.1)
Other	48 (8.9%)
Co-morbidities	
Cardiovascular disease *	454 (84.5)
Ischemic heart disease	104 (19.4)
Prior PCI / CABG	31 (5.8)
Congestive cardiac failure	200 (37.2)
Stroke	11 (2.0)
Peripheral vascular disease	25 (4.7)
Prosthetic heart valve	59 (11.0)
Atrial fibrillation/flutter	289 (53.8)
Cardiac risk factors *	323 (60.1)
Hypertension	138 (25.7)
Hyperlipidaemia	16 (3.0)
Diabetes	82 (15.3)
Current/ex-smoker	198 (36.9)
Primary PHT	11 (2.0)
Secondary PHT	74 (13.8)
Malignancy	10 (1.9)
Chronic pulmonary disease	31 (5.8)
Neurodegenerative disease *	3 (0.6)
Chronic kidney disease	73 (13.6)
IVDU history	54 (10.1)
Charlson comorbidity index score †	1.4 ± 1.9
Median (IQR)	1 (0 - 2)
Surgical characteristics	
Indication for valve surgery	
Endocarditis	56 (10.4)
Non-endocarditis	481 (89.6)
Rheumatic tricuspid valve	357 (66.5)
Concomitant CABG ‡	77 (14.3)
Types of TVSx §	
Annuloplasty	262 (48.8)
Replacement	217 (40.4)
Repair	83 (15.5)
Open valvotomy	5 (0.9)

Others	15 (2.8)
Length of hospital stay, days	24.4 ± 23.5
Median (IQR)	16 (10 – 31)

Plus-minus values represent mean ± standard deviation; all others represent numbers of patients with values in brackets representing percentages, or otherwise stated.
CABG, coronary artery bypass graft; IVDU, intravenous drug use; PCI, percutaneous coronary interventions; PHT, pulmonary hypertension; TVSx, tricuspid valve surgery.

* Cardiovascular disease includes history of ischemic heart disease (include PCI and/or CABG), stroke, congestive cardiac failure, peripheral vascular disease, prosthetic heart valve and/or atrial fibrillation/flutter. Cardiac risk factors include history of hypertension, hyperlipidaemia, diabetes and/or smoking (current/previous). Neurodegenerative disease includes dementia, central nervous systemic atrophies, Parkinson's disease, basal ganglia degeneration, and/or nervous systemic degenerative diseases.

† Conditions included in the Charlson comorbidity index include myocardial infarction, congestive cardiac failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease (mild vs. moderate to severe), diabetes (with or without organ damage), hemiplegia, moderate to severe renal disease, any tumour (within last 5 years), lymphoma, leukemia, metastatic solid tumour and acquired immunodeficiency syndrome.

‡ Concomitant CABG performed during same admission for cardiac valve surgery.

§ More than one type of TV surgery might be performed on a patient during the same admission.

AF was the most common cardiovascular comorbidity (58.3%), followed by CCF (37.2%) and ischemic heart disease (19.4%). A history of smoking (36.9%), hypertension (25.7%), and diabetes (15.3%) was common. Of the noncardiovascular comorbidities, secondary pulmonary hypertension (13.8%) and chronic kidney disease (13.6%) were the most common. Concomitant malignancy was rare, comprising 1.9% of the cohort. 10.1% had a documented history of IVDU. The median Charlson comorbidity index was 1 (interquartile range [IQR] 0-2). The median length of stay was 16 days (IQR 10-31 days). Rheumatic TV disease was common in our cohort, representing 66.5% of our cohort.

All-cause and cause-specific mortality

A total of 211 (39.3%) patients died during a mean follow-up of 4.82 ± 3.94 years (Table 2). In-hospital mortality rate was 7.4%, with 62 (11.5%) patients dying within 180-days post

open isolated-TVSx. A cardiovascular cause of death occurred in 45% of in-hospital deaths, and in 52% of post-discharge deaths (Table 3). Of the cardiovascular causes of death, heart failure was the most frequent cause, representing 10.0% (n=4) of in-hospital deaths and 25.2% (n=43) of post-discharge deaths. Sepsis was the most identified noncardiovascular cause of death, documented in 7 (17.5%) in-hospital deaths and 37 (21.6%) post-discharge deaths.

Table 2. Morbidity and mortality outcomes following isolated TVSx.

Cumulative incidence, no. (%)	30-days	180-days	2-years	End-of-study†
Congestive cardiac failure	11 (2.0)	53 (9.9)	109 (20.2)	157 (29.2)
Atrial fibrillation *	10 (4.0)	25 (10.1)	40 (16.1)	68 (27.4)
Infective endocarditis *	4 (0.9)	7 (1.5)	10 (2.1)	26 (5.6)
Pulmonary embolism	1 (0.2)	2 (0.4)	5 (0.9)	7 (1.3)
Permanent pacemaker	2 (0.4)	3 (0.6)	20 (3.7)	40 (7.5)
Implantable cardioverter defibrillator	1 (0.2)	3 (0.6)	4 (0.8)	13 (2.4)
All-cause death	18 (3.4)	62 (11.5)	108 (20.1)	211 (39.3)

* Atrial fibrillation (AF) and infective endocarditis (IE) incidences were based on patients without baseline AF (n=248) or IE (n=466) during isolated tricuspid valve surgery (TVSx) admission.

† End-of-study was 31-December-2018.

Table 3. Cause-specific death outcomes.

Categories	In-hospital (N=40) No. (%) *	Post-discharge (N=171) No. (%) *
Cardiovascular causes	**18 (45.0)**	**89 (52.0)**
Acute myocardial infarction	0 (0)	6 (3.5)
Heart failure	7 (17.5)	43 (25.2)
Stroke	4 (10.0)	15 (8.8)
Pulmonary embolism	0 (0)	2 (1.17)
Cardiac-related †	7 (17.5)	23 (13.5)
Noncardiovascular causes	**22 (55.0)**	**82 (48.0)**
Sepsis	7 (17.5)	37 (21.6)
Malignancy	1 (2.5)	15 (8.8)
Other	7 (17.5)	17 (10.0)
Undefined	7 (17.5)	13 (7.6)

* No. (%) represents total number of deaths from each specific cause and value in brackets represents the percentage out of total deaths.

† Cardiac-related cause of death is coded when more than one cardiac cause of death is recorded on the death certificate.

Morbidity outcomes

Table 2 shows the cumulative incidence of the study's pre-specified morbidity events after isolated-TVSx. The development of new AF (in those without a prior history of AF at index isolated-TVSx) and admissions for CCF were the most frequent morbidities documented during follow-up: the cumulative incidence of AF at 180-days and by end-of-study were 10.1% and 27.4% of patients respectively, while 53 (9.9%) patients had an admission for CCF within the first 180-days following isolated-TVSx, reaching 29.2% by end-of-study follow-up. Across the study period the rate of PE admission was low at 1.3%. 10.0% of patients had PPM implanted during their index isolated-TVSx admission. A further 40 (7.5%) and 13 (2.4%) patients required PPM and ICD implantations by end-of-study follow-up respectively.

Independent predictors for all-cause mortality

Independent predictors for all-cause mortality following open isolated-TVSx were age ≥59 years, a background history of CCF, chronic pulmonary disease, and malignancy (Table 4). Malignancy was the strongest predictor of mortality (adjusted hazard ratio [aHR]=3.49, 95% confidence interval [CI]=1.73-7.07; p<0001), followed by a history of chronic pulmonary disease (aHR=2.21, 95%CI=1.36-3.59; p<0.001). Neither gender, indication for surgery, rheumatic TV status, , concomitant CABG, history of ischemic heart disease, stroke, diabetes, pulmonary hypertension, chronic kidney disease, smoking status or history of IVDU were associated with the primary outcome (Supplementary Tables 2 and 3). While

univariate analysis showed TV replacement was associated with increased mortality (HR=1.35, 95%CI =1.03-1.77; p=0.03) and TV repair was associated with reduced mortality (HR=0.50, 95%CI =0.32-0.79; p =0.003), type of TV surgery was not associated with the primary outcome in multivariate analysis (Supplementary Tables 2 and 3).

Table 4. Independent predictors for all-cause mortality.

Multivariable analysis *	Parameters	aHR (95% CI)	p value
All-cause death during follow-up (4.82 ± 3.94 years)	Age ≥59 years (mean age)	1.76 (1.26 – 2.47)	0.001
	Congestive cardiac failure	1.78 (1.33 – 2.38)	<0.001
	Chronic pulmonary disease	2.21 (1.36 – 3.59)	<0.001
	Malignancy	3.49 (1.73 – 7.07)	<0.001

Plus-minus value represents mean ± standard deviation.
CI, confidence interval; aHR, adjusted hazard ratio.

* **Multivariable Cox regression method was used to identify independent predictors for all-cause mortality. Only significant independent predictors are shown in the above table (see Supplementary Table 3 for complete multivariable analysis results).**

DISCUSSION

The present study examined the caseload and outcomes of open isolated-TVSx over a 17-year period in an unselected Australian statewide population. The main findings were: 1) open isolated-TVSx case volumes have increased significantly over the study period; 2) high post-operative mortality rates in the short and intermediate-term comparable to those in international studies; 3) heart failure and sepsis were the most common specific causes of death in both in-hospital and post-discharge follow-up; 4) new AF and admissions for CCF were the two most common morbidities encountered post-surgery; and, 5) age ≥59 years and history of CCF, chronic pulmonary disease and malignancy were associated with increased mortality risk.

TVSx caseloads

Alqahtani et al demonstrated a significant increase in the caseload of both open isolated-TV repairs and replacements in the United States (US) between 2003 and 2014 using the Nationwide Inpatient Sample (NIS) (11). While the NIS captured about 20% of US admissions during this period, our study showed similarly increasing caseload findings in a statewide population where ≥97% of hospital admissions are captured, with the state of NSW approximating 32% of Australia's overall population. While the increase in caseload was significant, the procedure is still relatively rare as shown in our study, with open isolated-TVSx cases representing only 1.8% of total open-heart cardiac valve surgery. We postulate the increased caseload reflects the growth and ageing of the NSW population over this timeframe.

Prior studies mostly limited to in-hospital outcomes

Existing literature has been mostly limited to in-hospital outcomes after open isolated-TVSx. There are two larger US-based studies examining in-hospital mortality and morbidity in addition to several smaller studies (11, 32). Our study showed an in-hospital mortality (7.4%) that is lower than the 8.8-9.7% reported in recent studies using similar administrative datasets (11, 18), but higher than the 3.4% rate reported in a recent single-centre study based on carefully selected patients (19). In-hospital PPM implantation rates (10.0%) in our study were also at the lower end of reported figures, which range from 9.5-24.4% (11, 19, 32).

Cause-specific deaths following open isolated-TVSx

This study is the first of its scale to examine cause-specific mortality after isolated TVSx. The two leading causes of death both in-hospital and post-discharge were sepsis and CCF. Fatal decompensated CCF may reflect unsuccessful attempted medical and/or surgical management of severe TV regurgitation with associated heart failure – indeed a history of CCF predicted a near 70% increased mortality risk in our multivariable analysis. On the other hand, the large proportion of deaths by sepsis are likely driven by the baseline comorbidities in our population. This is supported by our study's demonstration of strong independent associations between increased mortality and the presence of malignancy, older age and chronic pulmonary disease. While more conservative case selection may reduce mortality

rates, the goal of surgery in these unwell patients may have been to improve quality of life (a parameter not directly measured in this administrative dataset) rather than longevity.

Morbidity following open isolated-TVSx

Morbidity after TVSx may provide a surrogate for quality of life, and providing data surrounding long-term morbidity forms an important aspect of informed consent prior to surgery. These data also form a benchmark against which to compare newer percutaneous interventions. In the present study, the main morbidities encountered post-discharge were re-admission for decompensated CCF (9.9%) and new AF (10.1%), although low rates of admissions for IE, PE, PPM and ICD insertions (all <1% except for IE at 1.5%) were also observed within the first 180-days. Two smaller studies have examined medium-long term morbidity outcomes following open isolated-TVSx. Dreyfus et al described a 38% incidence of heart failure hospitalisation at 5-years post-discharge in a French cohort of 466 patients who underwent isolated-TVSx (33). Wong et al described a much lower rate of 13.8% heart failure hospitalisation post-discharge during a mean follow-up of 4.9 years in a younger Taiwanese cohort (n=333) compared to 29.2% of patients in our study with a similar mean follow-up duration (34). While Dreyfus et al did not report on rates of post-discharge PPM insertion, Wong et al observed a 5.2% incidence of post-discharge PPM insertion by end-of-study, compared to 7.6% in our study. Notably, these and other studies have not reported on rates of PE, ICD insertion, or de novo infective endocarditis post-discharge. Reassuringly, these events appear to be low.

TVSx for Rheumatic TV

Our cohort had a high proportion (66.5%) of patients with rheumatic TV disease. While increasingly uncommon in developed countries, rheumatic heart disease (RHD) remains prevalent in Indigenous Australians and immigrants from countries with endemic RHD (35). Organic TV involvement occurs in 4.9 – 9% of RHD, although autopsy studies have suggested much higher rates of invovlement (36). Both repair and replacement are established surgical techniques for treating organic RHD TV disease, although several studies have reported higher mortality rates with tricuspid valve replacement compared with repair (36-38). While highly prevalent in our population, a rheumatic TV was not associated with increased mortality (Supplementary Table 2).

Pathomechanistic reasons for high mortality and morbidity associated with open-heart isolated-TVSx

There are two main hypotheses which attempt to explain why open isolated-TVSx has consistently been associated with high in-hospital mortality and morbidity rates, despite not being considered technically more difficult than left sided-valvular surgery. The first is that patients are referred late for surgery, by which time the consequences of severe TR are, at best, partly remediable by surgery (e.g., right ventricular (RV) dilation and/or dysfunction, cardiac cirrhosis) (32, 33). Furthermore, patients with impaired RV size and/or function may not tolerate the increased afterload created by surgical correction of TR, and consequently further decompensate. Supporting this hypothesis, Hamandi et al (19) reported a dramatically lower in-hospital mortality of 3.2%, highlighting early referral as a defining feature of their

single-centre 95 patient cohort study. However, in-hospital mortality in their cohort was still higher than that reported for left-sided valve surgery in the literature (11, 16-18). The second hypothesis is that severe TR patients form a more comorbid cohort of patients, whose comorbidities often exacerbate the severity of their TR. (e.g. pulmonary disease). Indeed, our study showed chronic pulmonary disease to be associated with a 2.7-fold increased risk of death post-surgery. Interestingly, while type of TV surgery was associated with mortality in the univariate analysis, with replacement being higher risk that repair, this association did not persist in multivariate analysis. One explanation may be that those with more advanced disease are more likely to require replacement and not be appropriate candidates for repair.

Comparison with percutaneous tricuspid valve interventions

There is presently little published data on outcomes following isolated TV intervention, and no long-term data. Published international registry data (n=312) has reported a 30-day all-cause mortality rate of 3.6% following percutaneous TV intervention, varying depending on the technique used from 2.8% with MitraClip to 7.6% with Cardioband (mean age 76.6yo) (39). More recently, the TRILUMINATE trial (n=85), an international, prospective, single arm study examining safety and efficacy of the TriClip edge-to-edge repair system, reported a 1-year all-cause mortality rate of 7.1% (40). Mean ages for patients in both above trials were greater than 75 years of age. While comparison between isolated-TVSx and percutaneous interventions is currently limited by their different cohorts with respect to age, comorbidities, and indication, our data forms an important benchmark against which to compare emerging data on mid-long term outcomes following percutaneous TV intervention.

Strengths and limitations

This study's strengths lie in the large cohort of patients who underwent open isolated-TVSx, a relatively rare procedure compared to other cardiac valve surgery. In addition, our study cohort was derived from a statewide unselected population and included patients from all public and private healthcare facilities that performed cardiothoracic surgery, thus reflecting real-world clinical practice. Our long study period also allows for longitudinal trend analysis of medium to long-term outcomes including identifying important clinical predictors of mortality. The use of a death registry with cause-specific data analysis adds important detail to all-cause mortality figures.

However, this study is limited by its retrospective study design, which limits the imputation of causal links in our multivariable analysis. There was also no propensity-matched control group that did not undergo surgery against which to compare outcomes post TVSx. Additionally, this is an observational study reflecting current practise on isolated TVSx which includes a heterogeneous group of procedures (e.g. annuloplasty, repair, replacement) with less clear evidence on the best approach compared to aortic or mitral valve procedures. Furthermore, while redo valvular surgery has been reported to be associated with poorer outcomes, we were unable to assess the impact of redo surgery on outcomes as our dataset only extends back to 2001 (41, 42). Also, our anonymised dataset does not allow for analysis of the association of operator experience with patient outcomes, a parameter that has been shown to be significant in other open valvular surgery (43, 44). While our study used the

Charlson Comorbidity Index (CCI) as a measure of comorbidity and operative risk, our dataset does not have the necessary data to calculate values for more conventional cardiothoracic risk pre-operative scores such as STS PROM or Euroscore II. Finally, our administrative data lacks important granular details such as echocardiographic data (e.g. RV size and function), functional class, medication usage, biochemical data or organ function such as creatinine or liver function tests, exact aetiology of TV disease or its severity, or indication for surgery (longevity vs quality of life). This speaks to the need for a national registry of tricuspid valve surgeries with such granular detail, especially with the development of newer TV interventions.

CONCLUSION

Open isolated-TVSx carries a significant risk of post-operative mortality, with admission for decompensated CCF and new AF the most common morbidities encountered post-surgery. Independent predictors of mortality include age ≥59yo and comorbidities including history of cardiac failure, chronic pulmonary disease and malignancy. This study forms a benchmark against which to compare outcomes with newer percutaneous TV interventions.

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REFERENCES

1. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, Maalouf J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. JACC: Cardiovascular Imaging. 2019;12(3):433-42.

2. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. Journal of the American College of Cardiology. 2004;43(3):405-9.

3. Ruel M, Rubens FD, Masters RG, Pipe AL, Bédard P, Mesana TG. Late incidence and predictors of persistent or recurrent heart failure in patients with mitral prosthetic valves. The Journal of thoracic and cardiovascular surgery. 2004;128(2):278-83.

4. Hahn RT, Asch F, Weissman NJ, Grayburn P, Kar S, Lim S, et al. Impact of tricuspid regurgitation on clinical outcomes: the COAPT trial. Journal of the American College of Cardiology. 2020;76(11):1305-14.

5. Mehr M, Karam N, Taramasso M, Ouarrak T, Schneider S, Lurz P, et al. Combined tricuspid and mitral versus isolated mitral valve repair for severe MR and TR: an analysis from the TriValve and TRAMI registries. Cardiovascular Interventions. 2020;13(5):543-50.

6. McCarthy FH, Vemulapalli S, Li Z, Thourani V, Matsouaka RA, Desai ND, et al. Association of tricuspid regurgitation with transcatheter aortic valve replacement outcomes: a report from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. The Annals of Thoracic Surgery. 2018;105(4):1121-8.

7. Benfari G, Antoine C, Miller WL, Thapa P, Topilsky Y, Rossi A, et al. Excess mortality associated with functional tricuspid regurgitation complicating heart failure with reduced ejection fraction. Circulation. 2019;140(3):196-206.

8. Chen L, Larsen CM, Le RJ, Connolly HM, Pislaru SV, Murphy JG, et al. The prognostic significance of tricuspid valve regurgitation in pulmonary arterial hypertension. The Clinical Respiratory Journal. 2018;12(4):1572-80.

9. Pinamonti B, Dragos AM, Pyxaras SA, Merlo M, Pivetta A, Barbati G, et al. Prognostic predictors in arrhythmogenic right ventricular cardiomyopathy: results from a 10-year registry. European heart journal. 2011;32(9):1105-13.

10. Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, et al. Clinical outcome of isolated tricuspid regurgitation. JACC: Cardiovascular Imaging. 2014;7(12):1185-94.

11. 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. Journal of the American Heart Association. 2017;6(12):e007597.

12. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;63(22):2438-88.

13. Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Journal of Cardio-Thoracic Surgery. 2017;52(4):616-64.

14. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin III JP, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart

Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2021;77(4):450-500.

15. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease: developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European heart journal. 2022;43(7):561-632.

16. Staab ME, Nishimura RA, Dearani JA. Isolated tricuspid valve surgery for severe tricuspid regurgitation following prior left heart valve surgery: analysis of outcome in 34 patients. Journal of Heart Valve Disease. 1999;8(5):567-74.

17. Do QB, Pellerin M, Carrier M, Cartier R, Hebert Y, Page P, et al. Clinical outcome after isolated tricuspid valve replacement: 20-year experience. The Canadian journal of cardiology. 2000;16(4):489-93.

18. Zack CJ, Fender EA, Chandrashekar P, Reddy YN, Bennett CE, Stulak JM, et al. National trends and outcomes in isolated tricuspid valve surgery. Journal of the American College of Cardiology. 2017;70(24):2953-60.

19. Hamandi M, Smith RL, Ryan WH, Grayburn PA, Vasudevan A, George TJ, et al. Outcomes of isolated tricuspid valve surgery have improved in the modern era. The Annals of thoracic surgery. 2019;108(1):11-5.

20. Chorin E, Rozenbaum Z, Topilsky Y, Konigstein M, Ziv-Baran T, Richert E, et al. Tricuspid regurgitation and long-term clinical outcomes. European Heart Journal-Cardiovascular Imaging. 2020;21(2):157-65.

21. Russo A, Grigioni F, Avierinos J-F, Freeman WK, Suri R, Michelena H, et al. Thromboembolic complications after surgical correction of mitral regurgitation: incidence, predictors, and clinical implications. Journal of the American College of Cardiology. 2008;51(12):1203-11.

22. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. The Lancet. 2016;387(10034):2218-25.

23. Centre for Health Record Linkage (CHeReL).Available at http://www.cherel.org.au.

24. Lee A-H, Ng ACC, Yong ASC, Hyun K, Brieger D, Kritharides L, et al. Outcomes of 1,098 patients following transcatheter aortic valve implantation: a statewide population-linkage cohort study. Heart, Lung and Circulation. 2021;30(8):1213-20.

25. Cheng Y-Y, Brieger D, Bannon P, Chow V, Kritharides L, Ng ACC. Outcomes Following Triple Cardiac Valve Surgery Over 17-years: A Multicentre Population-Linkage Study. Heart, Lung and Circulation. 2022.

26. Ng AC, Chung T, Yong AS, Wong HS, Chow V, Celermajer DS, et al. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. Circ Cardiovasc Qual Outcomes. 2011;4(1):122-8.

27. Ng ACC, Lau JK, Chow V, Adikari D, Brieger D, Kritharides L. Outcomes of 4838 patients requiring temporary transvenous cardiac pacing: a statewide cohort study. International Journal of Cardiology. 2018;271:98-104.

28. Brieger DB, Ng AC, Chow V, D'Souza M, Hyun K, Bannon PG, et al. Falling hospital and postdischarge mortality following CABG in New South Wales from 2000 to 2013. Open Heart. 2019;6(1):e000959.

29. Cheng Y-Y, Chow V, Brieger D, Yan TD, Kritharides L, Ng ACC. Outcomes of 16,436 patients requiring isolated aortic valve surgery: A statewide cohort study. International Journal of Cardiology. 2021;326:55-61.

30. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.

31. National Center for Health Statistics. Instructions for Classifying the Underlying Cause-of-Death, ICD-10. 2008:1-259. http://www.cdc.gov/nchs/about/major/dvs/im.htm Accessed June 10, 2009.

32. Kawsara A, Alqahtani F, Nkomo VT, Eleid MF, Pislaru SV, Rihal CS, et al. Determinants of morbidity and mortality associated with isolated tricuspid valve surgery. Journal of the American Heart Association. 2021;10(2):e018417.

33. Dreyfus J, Flagiello M, Bazire B, Eggenspieler F, Viau F, Riant E, et al. Isolated tricuspid valve surgery: impact of aetiology and clinical presentation on outcomes. European Heart Journal. 2020;41(45):4304-17.

34. Wong WK, Chen SW, Chou AH, Lee HA, Cheng YT, Tsai FC, et al. Late outcomes of valve repair versus replacement in isolated and concomitant tricuspid valve surgery: a nationwide cohort study. Journal of the American Heart Association. 2020;9(8):e015637.

35. Katzenellenbogen JM, Bond-Smith D, Seth RJ, Dempsey K, Cannon J, Stacey I, et al. Contemporary incidence and prevalence of rheumatic fever and rheumatic heart disease in Australia using linked data: the case for policy change. Journal of the American Heart Association. 2020;9(19):e016851.

36. Sultan F, Moustafa SE, Tajik J, Warsame T, Emani U, Alharthi M, et al. Rheumatic tricuspid valve disease: an evidence-based systematic overview. J Heart Valve Dis. 2010;19(3):374-82.

37. Bernal JM, Pontón A, Diaz B, Llorca J, García I, Sarralde A, et al. Surgery for rheumatic tricuspid valve disease: a 30-year experience. The Journal of Thoracic and Cardiovascular Surgery. 2008;136(2):476-81.

38. Moutakiallah Y, Aithoussa M, Atmani N, Seghrouchni A, Moujahid A, Hatim A, et al. Reoperation for isolated rheumatic tricuspid regurgitation. Journal of cardiothoracic surgery. 2018;13:1-10.

39. Taramasso M, Alessandrini H, Latib A, Asami M, Attinger-Toller A, Biasco L, et al. Outcomes after current transcatheter tricuspid valve intervention: mid-term results from the international TriValve registry. JACC: Cardiovascular Interventions. 2019;12(2):155-65.

40. Lurz P, Stephan von Bardeleben R, Weber M, Sitges M, Sorajja P, Hausleiter J, et al. Transcatheter edge-to-edge repair for treatment of tricuspid regurgitation. Journal of the American College of Cardiology. 2021;77(3):229-39.

41. Fukunaga N, Okada Y, Konishi Y, Murashita T, Yuzaki M, Shomura Y, et al. Clinical outcomes of redo valvular operations: a 20-year experience. The Annals of thoracic surgery. 2012;94(6):2011-6.

42. Fukunaga N, Sakata R, Koyama T. Short-and long-term outcomes following redo valvular surgery. Journal of Cardiac Surgery. 2018;33(2):56-63.

43. Bolling SF, Li S, O'Brien SM, Brennan JM, Prager RL, Gammie JS. Predictors of mitral valve repair: clinical and surgeon factors. The Annals of thoracic surgery. 2010;90(6):1904-12.

44. Moon MR, Henn MC, Maniar HS, Pasque MK, Melby SJ, Kachroo P, et al. Impact of surgical experience on operative mortality after reoperative cardiac surgery. The Annals of Thoracic Surgery. 2020;110(6):1909-16.

Figure Legends

Figure 1.

Figure shows temporal trend of annual volume of isolated tricuspid valve surgery during study period (n=575), with a mean (±SD) of 34 ± 14 cases per-annum. Annual case volumes significantly increased over the study period with an average rise of 2.73 cases per year (95% CI 1.95-3.50, p<0.001).

Supplementary Figure 1.

Flow chart shows the derivation of the study cohort.
APDC, Admitted Patient Data Collection; CHeReL, Centre for Health Record Linkage; NSW, New South Wales.

* Dataset containing all statewide admitted patients who underwent a broad range of cardiac procedures including coronary angiography, percutaneous coronary intervention, electrophysiology procedures and transesophageal echocardiography.

Supplementary Figure 2

Figure shows temporal trend of tricuspid valve annuloplasty during study period (n=272), with a mean (±SD) of 16.0 ± 7.3 cases per annum. Tricuspid valve annuloplasty caseload increased significantly over the course of the study period by an average of 0.46 cases per year (95% CI 0.21-0.72, p=0.002).

Supplementary Figure 3

Figure shows temporal trend of tricuspid valve replacement during study period (n=245), with a mean (±SD) of 14.4 ± 8.1 cases per annum. Tricuspid valve replacement caseload increased significantly over the study period by an average of 0.53 cases per year (95% CI 0.40-0.65, p<0.001).

Supplementary Figure 4

Figure shows temporal trend of open tricuspid valvotomy during study period (n=5), with a mean (±SD) of 0.3 ± 0.6 cases per annum. There was no significant change in annual caseload valvotomies over the course of the study period (p=0.64).

Supplementary Figure 5

Figure shows temporal trend of tricuspid valve repair during study period (n=85), with a mean (±SD) of 5.0 ± 2.5 cases per annum. Tricuspid valve repairs increased significantly over the study period by an average of 1.13 cases per year (95% CI 0.24-2.02, p=0.02).

Figure 1. Temporal trend of annual isolated tricuspid valve surgical volume during study period.

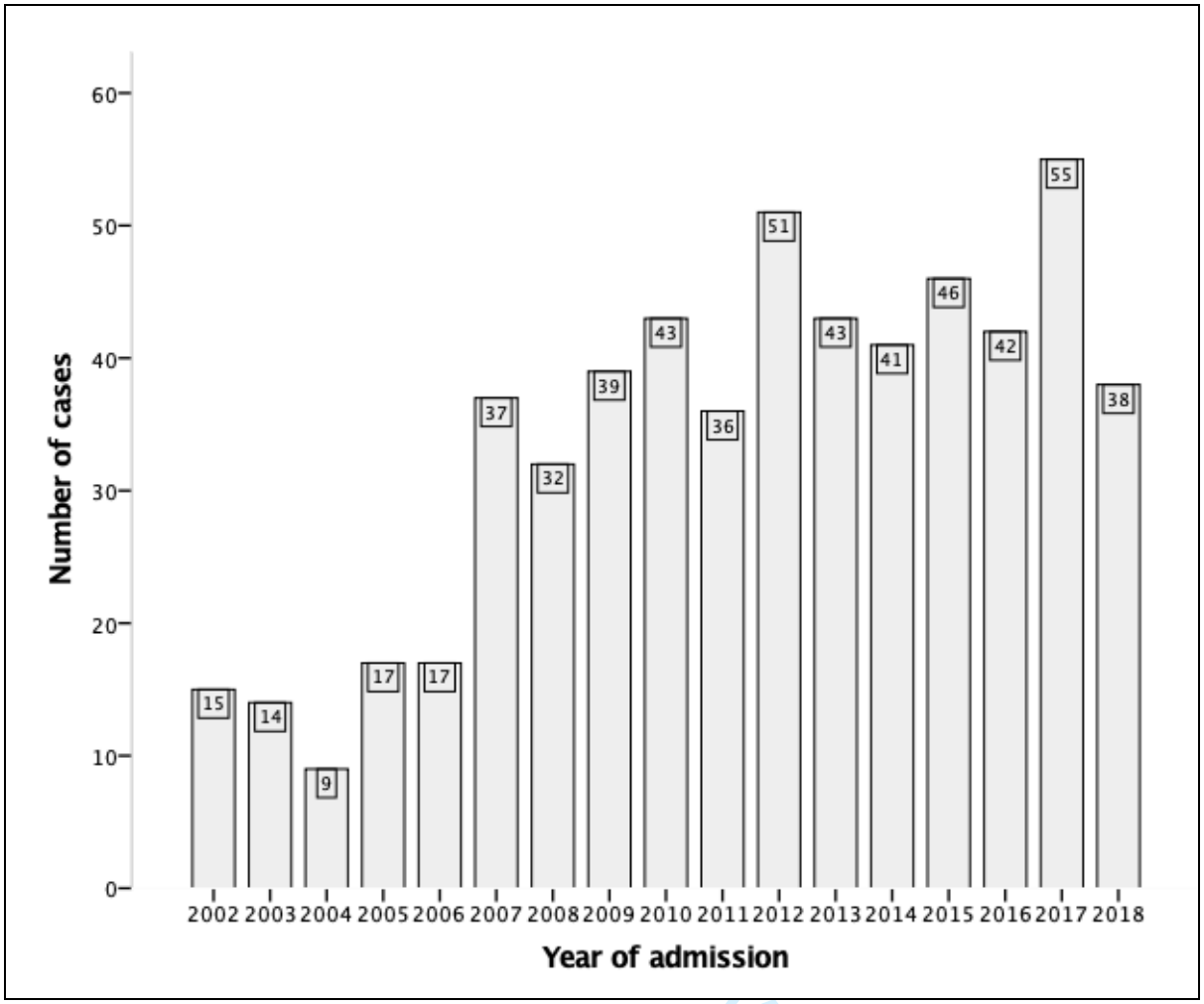

Figure Legend

Figure shows temporal trend of annual volume of isolated tricuspid valve surgery during study period (n=575), with a mean (±SD) of 34 ± 14 cases per-annum. Annual case volumes significantly increased over the study period with an average rise of 2.73 cases per year (95% CI 1.95-3.50, p<0.001).

Figure 1. Temporal trend of annual isolated tricuspid valve surgical volume during study period.

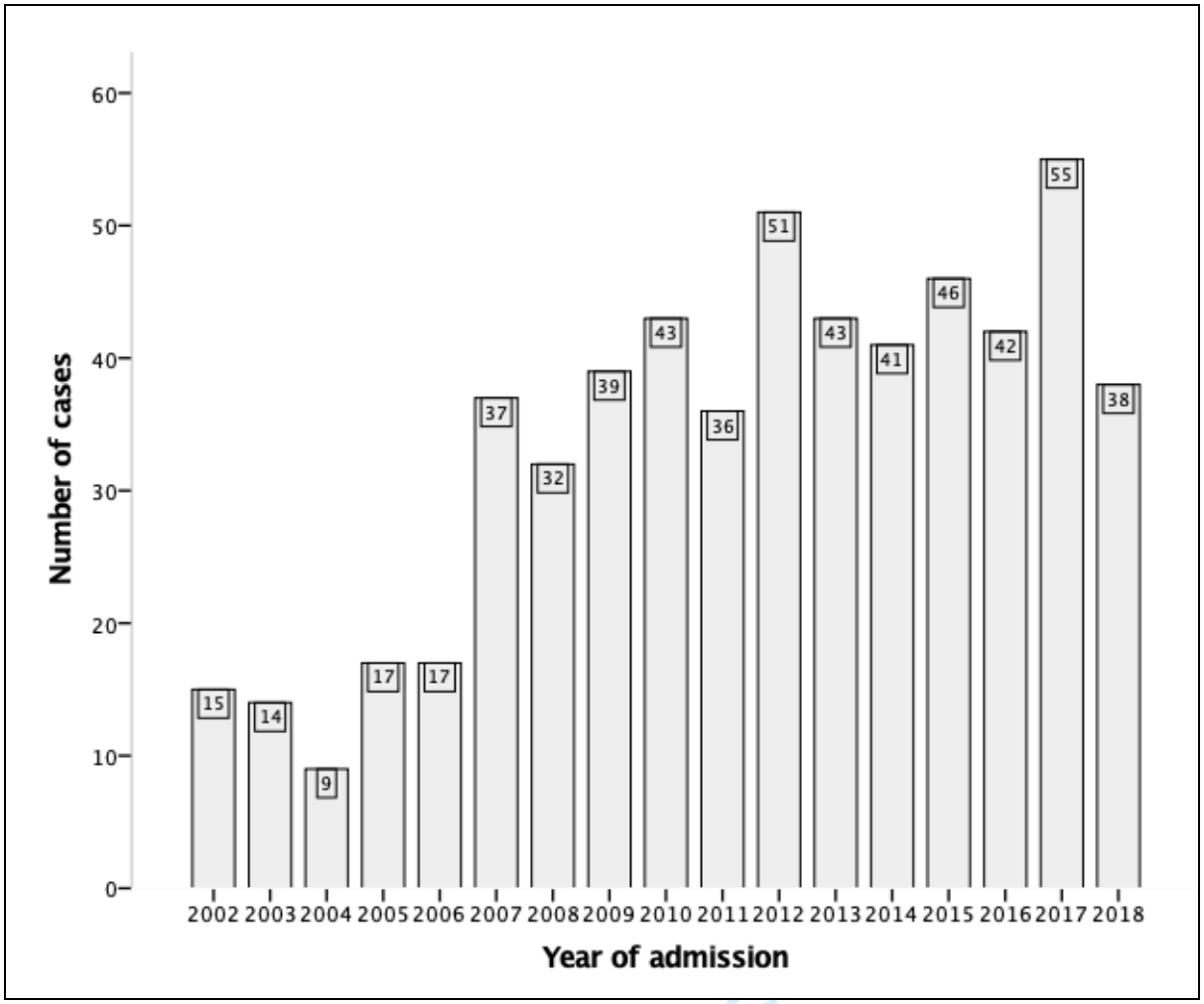

Figure Legend

Figure shows temporal trend of annual volume of isolated tricuspid valve surgery during study period (n=575), with a mean (±SD) of 34 ± 14 cases per-annum. Annual case volumes significantly increased over the study period with an average rise of 2.73 cases per year (95% CI 1.95-3.50, p<0.001).

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	#3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	#4	Present key elements of study design early in the paper	8
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	8
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a (not a matched study)
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect	8-9

		modifiers. Give diagnostic criteria, if applicable	
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-9
Bias	#9	Describe any efforts to address potential sources of bias	9-10
Study size	#10	Explain how the study size was arrived at	8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	11-12
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	11-12
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	11-12
Statistical methods	#12c	Explain how missing data were addressed	8
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a

Statistical methods	#12e	Describe any sensitivity analyses	n/a	
Results				
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.		13
Participants	#13b	Give reasons for non-participation at each stage	13	
Participants	#13c	Consider use of a flow diagram	13 (Figure 1)	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	13-15, Table 1	
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	n/a	

Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	15
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	13-17
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	17-18
Main results	#16b	Report category boundaries when continuous variables were categorized	17-18
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/a
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	17-18

Discussion			
Key results	#18	Summarise key results with reference to study objectives	19
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	23-24
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	19-23
Generalisability	#21	Discuss the generalisability (external validity) of the study results	22-23
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1