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Outcomes of isolated tricuspid valve replacement: a systematic review and meta-analysis of 5,316 patients from 35 studies

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KEYWORDS

- miscellaneous
- tricuspid disease
- TTVR

Abstract

Background: Transcatheter tricuspid valve replacement (TTVR) is rapidly emerging as a therapeutic option amongst patients with secondary tricuspid regurgitation. Historical data from surgical tricuspid valve replacement (TVR) studies may serve as a benchmark for the development of TTVR trials.

Aims: The aim of the study was to investigate the early and late outcomes following isolated surgical TVR.

Methods: Multiple electronic databases were searched to identify studies on isolated surgical TVR. The prespecified primary endpoint was operative mortality; secondary endpoints were early and late outcomes. Overall estimates of proportions and incidence rates with 95% confidence intervals (CI) were calculated using random-effects models. Multiple sensitivity analyses accounting for baseline characteristics, country and the operative period were applied.

Results: A total of 35 studies (5,316 patients) were included in this meta-analysis. The operative period ranged from 1974 to 2019. The overall rate of operative mortality was 12% (95% CI: 9-15), with higher mortality for patients who were operated on before 1995, who had prior cardiac surgeries, or who had liver disease. The most frequent clinical events were pacemaker implantation (10% [95% CI: 6-16]), bleeding (12% [95% CI: 8-17]), acute kidney injury (15% [95% CI: 9-24]) and respiratory complications (15% [95% CI: 12-20]). At follow-up analysis of the bioprosthetic TVR, there was an incidence rate per 100 person-years of 6 (95% CI: 2-13) for death and 8 (95% CI: 5-13) for recurrence of significant tricuspid regurgitation.

Conclusions: This meta-analysis provides an overview of the historical clinical outcomes following isolated surgical TVR. These findings can support the development of future clinical trials in the tricuspid space by providing thresholds for clinical outcomes.

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Abbreviations

CI	confidence interval
HF	heart failure
TR	tricuspid regurgitation
TTVR	transcatheter tricuspid valve replacement
TV	tricuspid valve
TVR	tricuspid valve replacement

Introduction

"One of the most valuable things any person can learn is the art of using the knowledge and experience of others".

Napoleon Hill

The presence of clinically significant tricuspid regurgitation (TR) is common and is independently associated with excess mortality[1,2]. Also, right-sided heart failure is an important public health problem, and several publications support its early treatment[3]. However, symptomatic TR continues to be undertreated in comparison to left-sided valvular diseases[4]. This has been mainly attributed to the high mortality and morbidity rates of tricuspid valve (TV) surgery.

The TV has challenging anatomical features that are known predictors of procedural failure and limit the broad application of repair techniques. In contrast to mitral valve surgery, the great majority of TV patients (59%) undergo surgical replacement[3,5]. Isolated tricuspid valve replacement (TVR) has been found to have an overall mortality risk of ~10%, and this figure has not significantly changed over time[5,6]. Considering the unwavering mortality risk associated with TV surgery, the sizeable gap between patients with TV disease and those undergoing definitive correction is unlikely to be filled by surgery; therefore, several transcatheter solutions are under investigation to address this unmet clinical need at a lower procedural risk[7,8].

Given the growing interest in transcatheter tricuspid valve replacement (TTVR), a more profound understanding of the historical surgical data is fundamental and may serve as a benchmark for developing future therapies[9]. To date, no randomised controlled trials or systematic literature analyses have examined this procedure. With this background, we performed an up-to-date comprehensive meta-analysis to provide a quantitative assessment of evidence regarding the outcomes after isolated surgical TVR.

Methods

The protocol of this meta-analysis has been registered in PROSPERO (international prospective register of systematic reviews; CRD42021284309) and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines **(Supplementary Appendix 1, Supplementary Appendix 2)**[10,11]. Given the nature of the work, ethical approval was not required.

SEARCH STRATEGY AND STUDY SELECTION

Randomised trials and observational studies on isolated surgical TVR were evaluated for inclusion in this meta-analysis. Prespecified criteria to consider the studies eligible for inclusion were: 1) they reported separate outcome data for patients undergoing isolated TVR; 2) they included at least 10 patients; 3) there were no overlapping populations; 4) there were no exclusively congenital TV diseases; 5) there were no paediatric populations. With the aim of investigating all the literature on isolated TVR as a benchmark for TTVR, we excluded the following from the analyses: 1) patients undergoing surgical tricuspid valve repair and 2) non-isolated TVR. No restriction on the publication date was applied.

A systematic search of the literature was performed in PubMed, EMBASE, Scopus, and Web of Science, from the database's inception up to the final search date of October 10th, 2021. In addition, the reference lists of prior systematic reviews and included articles were screened to find further potentially relevant studies (backward snowballing). The search strings are available in **Supplementary Appendix 3**. The data underlying this article will be shared upon reasonable request to the corresponding author.

DATA EXTRACTION AND QUALITY ASSESSMENT

Two reviewers (A. Scotti, M. Sturla) independently searched the electronic bibliographic databases. After the removal of duplicates, the title and abstract were screened to exclude non-relevant studies; subsequently, the full text of the remaining results was retrieved for further appraisal. Discrepancies were discussed and resolved with a senior reviewer (A. Latib). A dedicated electronic database was used for data extraction and included: sample size, operative data, baseline patient characteristics, procedural complications and late outcomes.

Two independent reviewers (A.Scotti, M. Sturla) performed the Risk of Bias In Non-randomised Studies of Interventions (ROBINS-I) assessment tool from the Cochrane handbook assessment for observational studies[12].

OUTCOMES MEASURES

The prespecified primary endpoint was operative mortality, defined as any death that occurred within 30 days after TVR or during the index hospitalisation. Secondary endpoints were early events (stroke, acute kidney injury, renal replacement therapy, bleeding, respiratory complications, pacemaker implantation, and wound infection), late mortality, TV reintervention (surgical or percutaneous), valve thrombosis, structural valve deterioration, and recurrence of at least moderate TR at follow-up. The full list of characteristic and outcome definitions is available in the **Supplementary Appendix 4**.

STATISTICAL ANALYSIS

Baseline characteristics were presented as pooled, weighted means or proportions and 95% confidence intervals (CI). Whenever applicable, the mean±standard deviation was calculated from the reported median and interquartile range according to Wan et al[13]. Study-level and pooled estimates were reported as proportions or incidence rates with 95% CI, for early and late outcomes, respectively. A random-effects model using the logit transformation with the "empirical

Bayes" (Paule-Mandel) estimator was applied for the meta-analysis of proportions[14,15]. A random-effects model using the log transformation and the maximum-likelihood estimator was used to calculate incidence rates. To account for heterogeneity in follow-up, overall incidence rates were estimated per 100 person-years. If available, the collection of the numbers of actual observations at follow-up was preferred over the whole sample size, avoiding assumptions about any participants for whom the outcome was not measured[16]. The indirect methods by Tierney and colleagues were adopted to retrieve missing data (i.e., events, time at risk) for incidence rate estimates; when the available information was insufficient, data were retrieved from Kaplan-Meier curves using follow-up time, estimated rates, and numbers at risk assuming random (non-informative) censoring[17]. A continuity correction of 0.5 has been applied for studies having either zero or all events (i.e., an event probability of either 0 or 1).

Statistical heterogeneity was assessed using Cochran's Q test and I^2 values. I^2 values of less than 25%, 25-50%, or more than 50% were regarded as being indicative of low, moderate or high heterogeneity, respectively[18]. Publication bias and small-study effect were assessed by visual inspection of funnel plots and using Begg's test. A Baujat plot, which is a scatter plot with the contribution of each study to the overall heterogeneity (as measured by Cochran's Q test) on the x-axis and the standardised difference of the overall treatment effect with and without each study on the y-axis, is provided[19].

As a sensitivity analysis, a random intercept logistic regression model was used for the meta-analysis of proportions[20,21]. The potential interaction among continents or operative periods (before 1995 versus after 1995, i.e., median operative time) and treatment effect was investigated with subgroup analyses for the primary endpoint. For this purpose, random-effects models were performed validating the confidence intervals by adjustment according to the Hartung-Knapp-Sidik-Jonkman method[22].

Meta-regressions were performed to evaluate the potential impact of several characteristics (year of publication, operative period, continent, estimated risk of bias, age, left ventricular (LV) ejection fraction, prevalence of females, diabetes mellitus, atrial fibrillation, hypertension, TVR with bioprostheses, endocarditis, secondary TR, liver disease, and previous cardiac surgery) on the outcomes of interest. Cumulative and leave-one-out sensitivity analyses were conducted to show how each study might affect the overall estimates. Further sensitivity analyses included the calculation of proportions and incidence rates with 95% CI using fixed-effects models with the Mantel-Haenszel method. Statistical significance was set at a p-value <0.05 (2-sided). All analyses were performed with R, version 4.0.2 (R Foundation for Statistical Computing), packages meta and metafor.

Results

SEARCH RESULTS

The search strategy results and study selection process are illustrated in **Figure 1** and **Supplementary Appendix 2**. Thirty-five

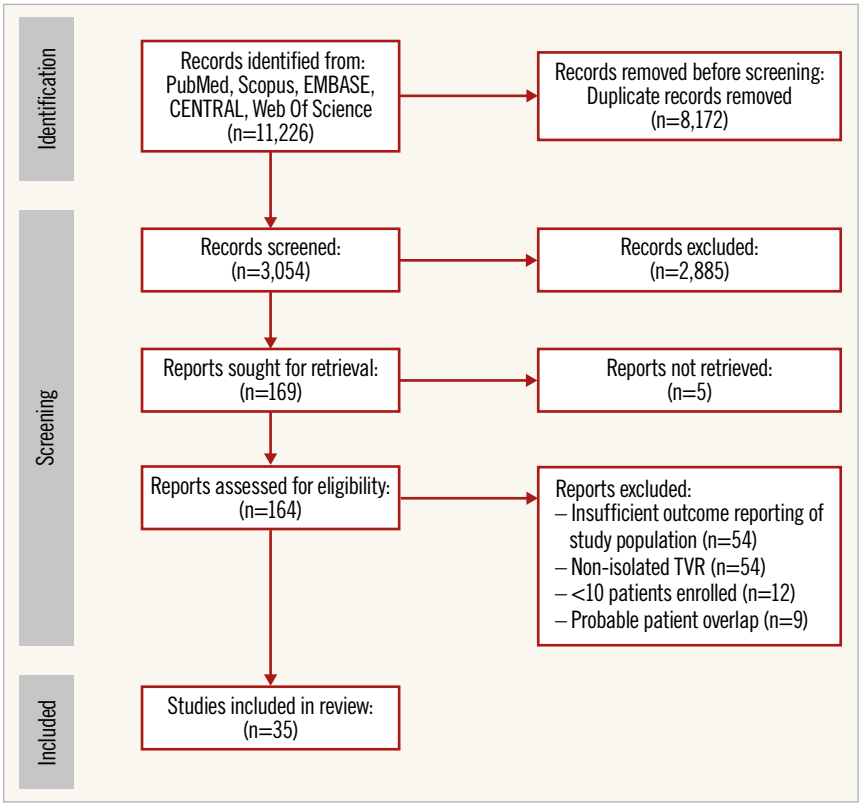

Figure 1. *Flowchart of the study selection progress. TVR: tricuspid valve replacement*

observational studies were found to be eligible for inclusion in this meta-analysis[3,23-54]. The main features of the included studies are presented in **Table 1**. The operative period was up to 2019, and the most represented countries were the USA and China. Apart from 6 studies that showed in-hospital outcomes, the others reported up to 14 years of mean follow-up time.

A total of 5,316 patients undergoing isolated TVR were analysed. The baseline characteristics of the study population are reported in **Supplementary Table 1**. The mean age was 53 (95% CI: 49-56) years, and the majority (63% [95% CI: 57-69]) were female. Six out of 10 patients (60% [95% CI: 27-85]) had previous cardiac surgery. The pooled mean LV ejection fraction was

Table 1. Key study features.

Study	Year	Patients	Bioprosthetic valve (%)	Operative time	Country	Multicentre (n)	Follow-up§ (years)
Sanfelippo et al	1976	15	0 (0)	Up to 1972	USA	No	4
Glower et al*	1995	35	35 (100)	1974-1993	USA	No	In-hospital
Ian Munro et al	1995	30	NR	1975-1992	Canada	No	4
Do et al	2000	29	26 (90)	1978-1998	Canada	No	6
Mangoni et al	2001	15	5 (33)	1984-1994	USA	No	3
Maleszka et al	2004	20	5 (25)	1985-2002	Germany	No	3
Solomon et al	2004	33	25 (76)	1996-2002	N. Zealand	No	5
Iscan et al	2007	20	NR	1987-2004	Turkey	No	6
Tokunaga et al*	2008	31	27 (87)	1975-2004	Japan	No	8
Capoun et al	2010	11	8 (73)	1999-2009	UK	No	2
Baraki et al*	2013	18	14 (78)	1996-2012	Germany	No	6
Kim et al*	2013	14	10 (71)	1996-2010	Republic of Korea	No	3
Bevan et al	2014	29	23 (79)	1995-2011	N. Zealand	No	14
Buzzatti et al	2014	61	NR	1997-2012	Italy	No	5
Farag et al	2017	68	36 (53)	1995-2011	Germany	No	NR
Hanedan et al*	2017	30	10 (33)	2004-2011	Turkey	No	2
Rossello et al	2017	25	0 (0)	1996-2012	Spain	No	5
Çakıcı et al	2018	25	22 (88)	2010-2016	Turkey	No	2
Chen et al*	2018	118	102 (86)	2003-2016	China	No	In-hospital
Fang et al*	2018	90	74 (82)	2007-2016	China	No	9
Moutakiallah et al	2018	11	5 (45)	2000-2017	Morocco	No	6
Di Mauro et al	2019	80	54 (68)	1979-2018	Italy	Yes (21)	19
Kundi et al*	2019	2,670	1,737 (65)	2003-2014	USA	Yes (841)	1
Liang et al*	2019	76	43 (57)	2010-2017	China	No	4
Chen et al*	2020	107	25 (23)	2009-2017	China	No	5
Dreyfus et al	2020	273	264 (97)	2007-2017	France	Yes (12)	3
Sánchez-Espín G et al*	2020	56	48 (86)	1996-2017	Spain	No	4
Wong et al	2020	137	NR	2000-2013	Taiwan	Yes (NA)	4
Yan et al*	2020	49	49 (100)	2012-2019	China	No	2
Kawsara et al*	2021	552	468 (85)	2016-2017	USA	Yes (NA)	In-hospital
Lee et al	2021	216	NR	2000-2013	Taiwan	Yes (NA)	4
Leviner et al	2021	33	31 (94)	2007-2018	Israel	Yes (2)	4
Liu et al*	2021	186	145 (78)	1999-2018	China	Yes (2)	11
Park et al	2021	106	23 (22)	1996-2018	Republic of Korea	No	4
Tafti et al#	2021	47	41 (87)	2010-2018	Iran	No	5

§Mean follow-up. *Studies reporting outcome data for bioprosthetic valve group. #Reported data were clarified and confirmed upon contacting corresponding authors. NA: not applicable; NR: not reported

within normal limits (58% [95% CI: 54-61]). Comorbidities, such as diabetes, hypertension and liver disease, were present in less than one-third of patients.

RISK OF BIAS AND PUBLICATION BIAS

The risk of bias was assessed for every observational study, as shown in **Supplementary Table 2**. The majority of included studies presented an overall moderate risk of bias. Possible concerns were raised for some studies in the domain of "bias due to confounding" because baseline prognostic characteristics were found to influence the choice of intervention (i.e., TVR).

Visual inspection of the funnel plot and the Begg's and Mazumdar's rank correlation tests indicated the absence of significant publication bias and small-study effects. The Baujat plot identified the studies by Tafti et al and Sanfelippo et al as introducing significative heterogeneity and the results of Kundi et al[45] as having a higher impact on the summary estimate **(Supplementary Figure 1)**.

OUTCOMES

The overall random-effects rate of operative mortality, the primary endpoint, was 12% (95% CI: 9-15), with a high degree of heterogeneity (I_2: 68%) **(Figure 2)**.

Secondary endpoints were divided into early and late outcomes. Among the early outcomes, we found a 2% (95% CI: 1-4) rate of stroke, 15% (95% CI: 9-24) of acute kidney injury, 7% (95% CI: 3-15) of renal replacement therapy, 12% (95% CI: 8-17) of bleeding, 15% (95% CI: 12-20) of respiratory complications, 10% (95% CI: 6-16) of pacemaker implantation, and 3% (95% CI: 2-6) of wound infection **(Table 2)**. Late outcomes are reported as incidence rates per 100 person-years and are as follows: 6 (95% CI: 4-9) for mortality, 2 (95% CI: 1-3) for the need for percutaneous

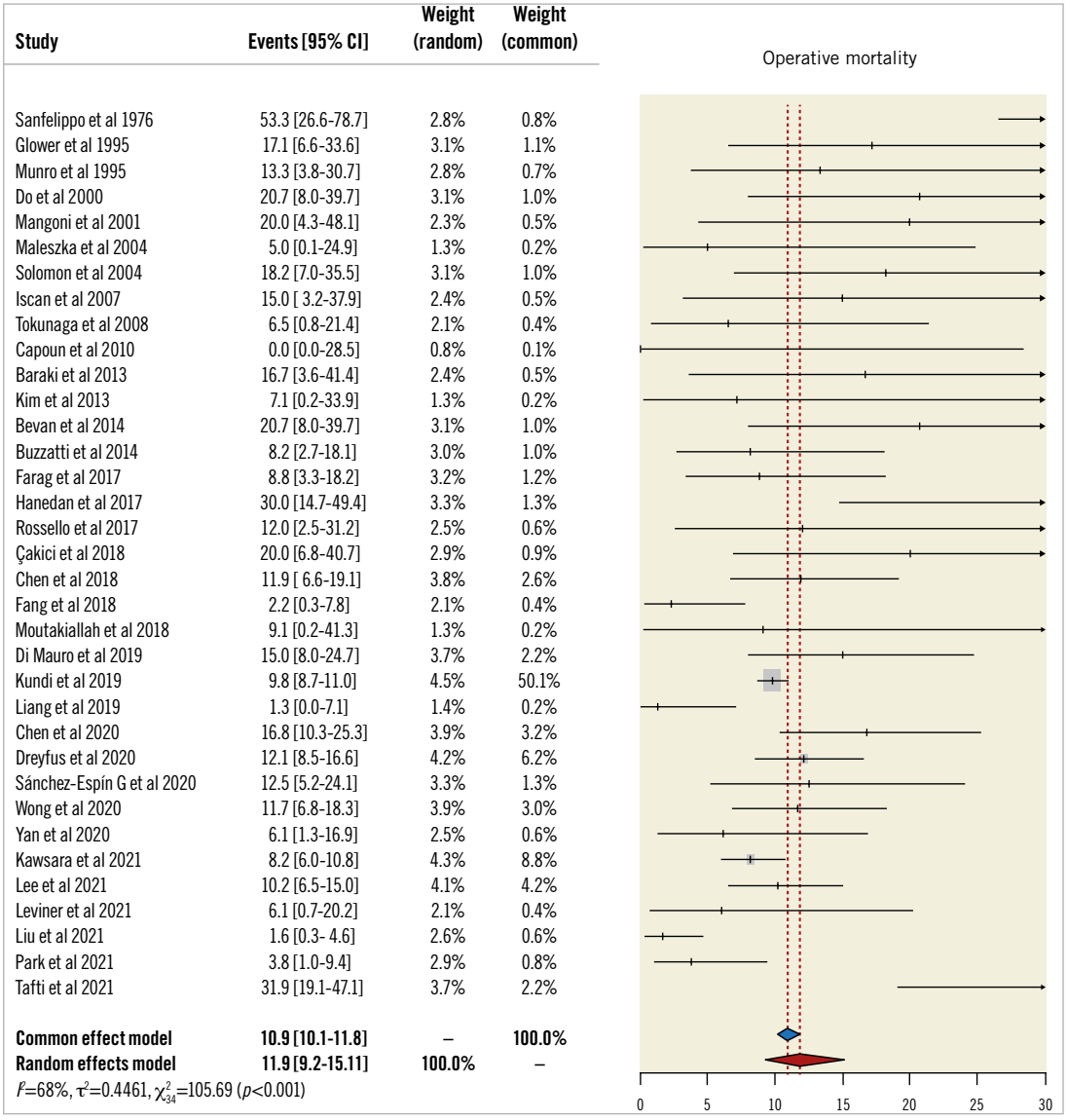

Figure 2. *Primary endpoint. Forest plot of operative mortality. CI: confidence interval*

Table 2. Early and late outcomes – random effects models.

Outcome	Proportion/incidence rate % (95% CI)	I^2 % (X^2 *p*-value)	N. of studies
Early outcomes			
Bleeding	12 (8-17)	83 (<0.01)	17
Acute kidney injury	15 (9-24)	89 (<0.01)	11
Renal replacement therapy	7 (3-15)	63 (0.01)	7
Pacemaker implantation	10 (6-16)	75 (<0.01)	13
Respiratory complication	15 (12-20)	0 (0.56)	7
Stroke	2 (1-4)	74 (<0.01)	9
Wound infection	3 (2-6)	81 (<0.01)	10
Late outcomes			
Late mortality*	6 (4-9)	96 (<0.01)	23
Reintervention*	2 (1-3)	64 (<0.01)	15
Structural valve deterioration*	3 (1-6)	82 (<0.01)	9
Valve thrombosis*	1 (0-2)	49 (0.07)	8
Recurrence of TR ≥2*	5 (2-13)	85 (<0.01)	4
Bioprostheses			
Late mortality*	6 (2-13)	97 (<0.01)	8
Reintervention*	1 (1-3)	77 (<0.01)	5
Structural valve deterioration*	3 (1-9)	91 (<0.01)	4
Valve thrombosis*	0 (0-1)	68 (0.04)	3
Recurrence of TR ≥2*	8 (5-13)	33 (0.22)	3

*per 100 person-years. CI: confidence interval; TR: tricuspid regurgitation

or surgical reinterventions, 3 (95% CI: 1-6) for structural valve deterioration, 1 (95% CI: 0-2) for valve thrombosis, and 5 (95% CI: 2-13) for the recurrence of moderate or greater TR **(Table 2)**.

BIOPROSTHESES

A total of 14 studies reported outcome data for patients undergoing TVR with bioprostheses **(Supplementary Table 3)**. Late outcomes after bio-TVR differed from those observed in the overall cohort for a higher rate of significant TR recurrence (8 [95% CI: 5-13] per 100 person-years), with a similar incidence rate of mortality (6 [95% CI: 2-13] per 100 person-years) **(Table 2)**.

SUBGROUP ANALYSIS AND META-REGRESSION

A subgroup analysis of the primary endpoint, stratifying for the operative period (i.e., before 1995 versus after 1995), found that the mortality rate of 18% (95% CI: 8-35) from the studies examining procedures performed before 1995 was greater than the 11% (95% CI: 8-14) obtained from operations carried out after that date **(Figure 3)**. However, the estimated mortality computed for the most recent studies was similar to the overall one. While investigating the influence of hospital locations (i.e., by continent) on operative mortality, the findings were consistent with the primary analysis, with no significant differences among the 3 subgroups (i.e., North America, Europe, Asia).

Meta-regression analysis detected a significant impact of previous cardiac surgery, liver disease, and the year of publication on the overall estimate of operative mortality **(Supplementary Table 4, Supplementary Figure 2)**. A trend for lower hospital mortality was apparent with increasing values of left ventricular ejection. Further meta-regression analyses found no significant interactions of baseline clinical and echocardiographic characteristics, risk of bias, endocarditis aetiology and the type of prosthetic valve with the primary endpoint rates.

SENSITIVITY ANALYSES

The overall estimates of primary and secondary endpoints were computed excluding the studies with patients having an endocarditis aetiology of their tricuspid valve disease, and the results were consistent with the primary analysis for every investigated outcome **(Supplementary Table 5)**. Using fixed-effects models for the overall cohort, the only difference was in late mortality, whose estimate was mainly influenced by the study of Kundi et al[45] (19 [95% CI: 18-20] per 100 person-years) **(Supplementary Table 6)**. An alternative meta-analysis using a random intercept logistic-regression model was performed and resulted in similar results compared to the primary analysis **(Supplementary Figure 3)**. Leave-one-out random-effects meta-analyses were used to assess the absence of significant influential studies on the

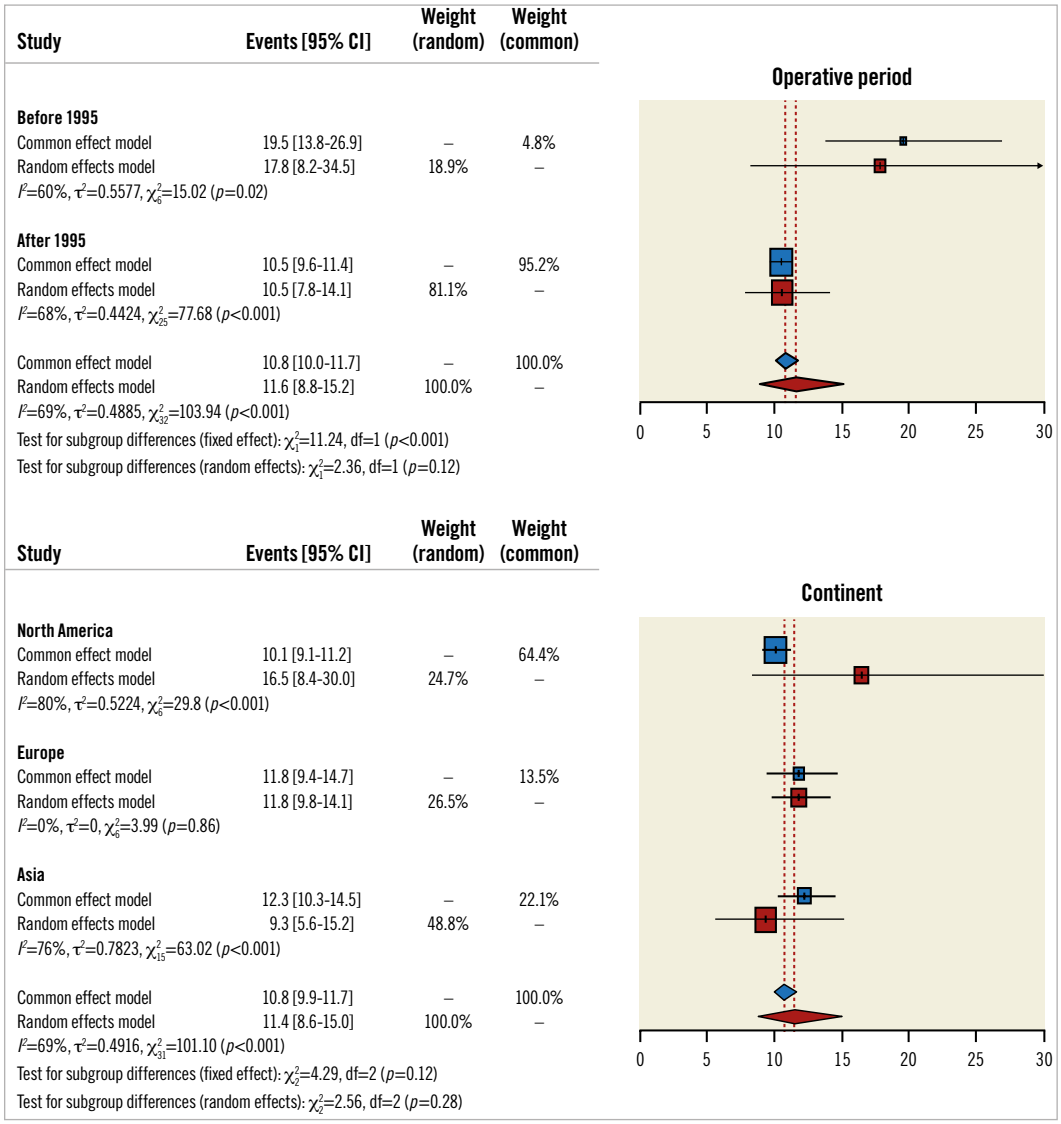

Figure 3. *Subgroup meta-analysis. Forest plot of subgroup meta-analysis investigating the impact of the operative period* and continent# on the primary endpoint. * The studies by Iscan et al and Di Mauro et al were excluded because of their operative period. #Africa (n=1) and Oceania (n=2) were excluded because of their underrepresentation. CI: confidence interval*

primary endpoint **(Supplementary Figure 4)**. A cumulative meta-analysis confirmed the higher rates of operative mortality for older studies **(Supplementary Figure 5)**.

Discussion

This large systematic review and meta-analysis of 5,316 patients provides an overview of outcomes after isolated surgical TVR **(Central illustration)**. With the aim of guiding future perspectives in the development of transcatheter systems, there are several important takeaways from our study: 1) the overall operative mortality and the need for permanent pacemaker implantation in patients undergoing isolated TVR were 12% (95% CI: 9-15) and 10% (95% CI: 6-16), respectively; 2) long-term data concerning device durability deepen the knowledge regarding the extended efficacy of the bioprosthetic implantation on the TV; 3) providing the first systematic assessment of isolated TVR, this analysis gives critical insight and sets a benchmark for anticipated future TTVR trials.

Although no data restriction has been applied in the screening phase, a total of 35 studies throughout all the existing literature reported data on isolated surgical TVR. This limited amount of evidence is partially due to the considerable mortality rate of TV surgery[6]. The risk of treating these patients combined with the perception that TR has minimal prognostic impact are the reasons for the marked undertreatment of TR. However, recent evidence has demonstrated that untreated TR is associated with worse outcomes[1,2]. Moreover, the natural history of TV disease inexorably leads to progressive right heart failure (HF), resulting in excess mortality and recurrent hospitalisations. If we combine these adverse outcomes with the increasing prevalence of significant TR

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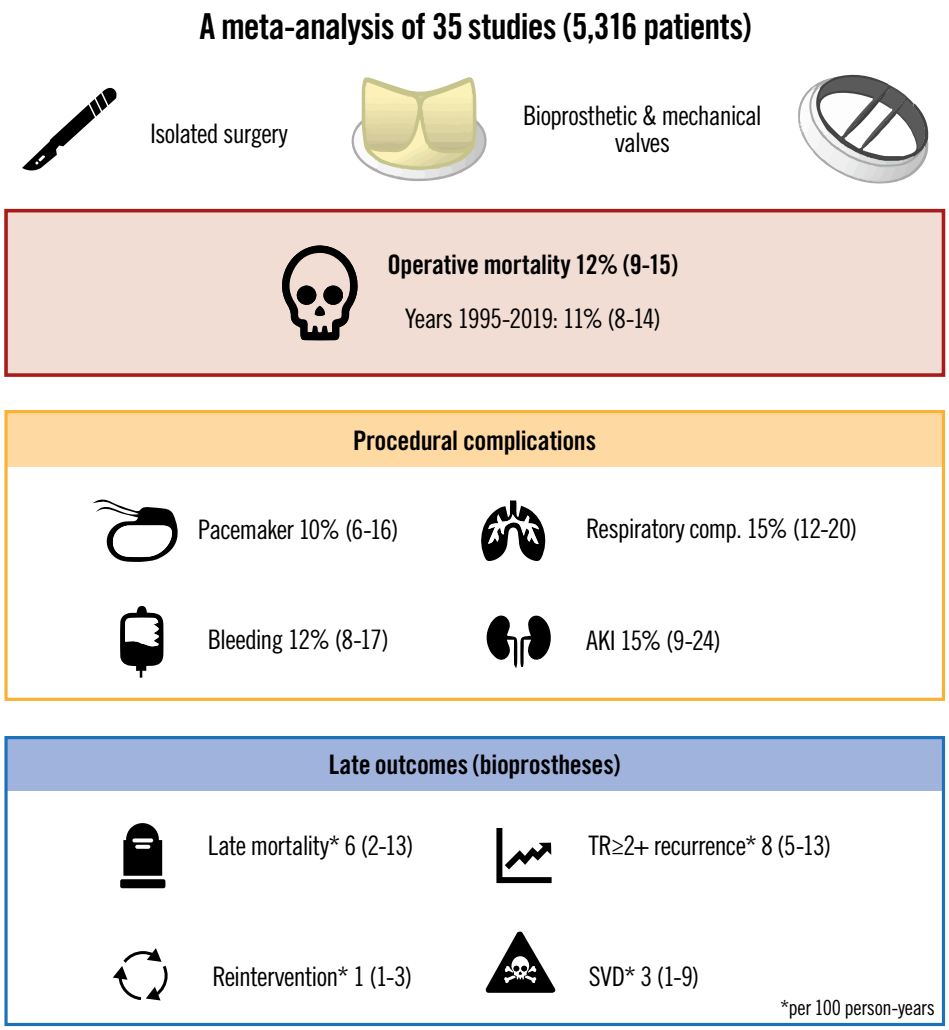
CENTRAL **ILLUSTRATION** Surgical outcomes of isolated tricuspid valve replacement.



The 35 included studies investigated isolated surgical tricuspid valve replacement. The pooled outcomes for 5,316 patients are reported as proportions and incidence rates (late) with confidence intervals. AKI: acute kidney injury; SVD: structural valve deterioration; TR: tricuspid regurgitation

in an ageing population, it is clear that we are facing an important public health problem.

The absence of evidence-based trial data, the heterogeneous nature of TV disease and the unknown ideal timing for surgery makes it difficult to provide concrete recommendations for TV surgery. Indeed, guideline recommendations are currently based upon expert opinions, with the strongest classes of recommendation assigned to cases undergoing left-sided valve surgery. Isolated TV surgery is reserved for patients with primary TR who have signs and symptoms of right-sided HF (IIa) or progressive right ventricular dilation or systolic dysfunction (IIb), and for patients with severe secondary TR who have signs and symptoms of right-sided HF with a poor response to medical therapy and annular dilation (IIa), or prior left-sided valve surgery and the absence of severe pulmonary hypertension or severe right ventricular dysfunction (IIb)[55].

Therefore, the aim of this study was to fill this critical gap. The use of bioprostheses is currently the preferred approach, with a growing trend[3], and constitutes an option for emerging TTVR systems. Despite this, the choice to include trials investigating TVR with mechanical valves was made on the basis of several factors. First, there is no impact of prosthetic valve selection on the surgical technique or the periprocedural medical therapy, such as the anticoagulation regimen. Indeed, the incidences of early outcomes were consistent when comparing the bioprosthetic-only group with the overall one, and no effects of valve type were detected on the primary endpoint **(Table 2, Supplementary Table 4)**. Second, the inclusion of

studies which did not discriminate between bioprosthetic and mechanical valves allowed us to provide more robust results. This is observed by the addition of 21 studies and 2,529 patients (regarding primary endpoint data) to the overall population, making this analysis the largest and most comprehensive assessment on isolated TVR to date.

OPERATIVE MORTALITY

The overall estimated operative mortality was 12%, with a CI ranging from 9 to 15%. After the exclusion of studies with an operative period prior to 1995, the estimated operative mortality for the most recent ones (i.e., after 1995) was in line with the overall one previously reported (11% [95% CI: 8-14]). This finding identifies isolated TVR as having a considerable surgical risk even in recent times, especially when compared to the replacement of other cardiac valves.

Since high-risk patients with aortic valve disease are nowadays treated with the transcatheter solution, data from clinical trials report operative mortality rates for isolated surgical aortic valve replacement of 0.9-1.3% and 1.7-4.1%, for low- and intermediate-risk, respectively[56-59]. On the other hand, isolated mitral valve replacement in ~150,000 patients in US hospitals was found to have an operative mortality rate as low as 4%[60].

The discrepancy between right- and left-sided surgery might be explained by several concomitant factors. First, patients with TV diseases, especially in the case of secondary TR, present with poor functional classes and significant comorbidities, such as a long history of atrial fibrillation and pulmonary hypertension. Second, isolated TVR is usually performed after previous interventions, particularly on left-sided valves. Third, the timing is usually too late: right ventricular function is already impaired and associated with signs of advanced right HF such as liver dysfunction[3]. Indeed, even if hypothesis-generating, the results of the meta-regression analysis found a history of prior cardiac surgery and the presence of liver disease as having a significant impact on the overall estimate of operative mortality. These findings support the insights derived from both surgical and transcatheter TV procedures[61,62].

EARLY OUTCOMES

The procedural complication rates shown in **Table 2**, in addition to operative mortality, contribute to the reluctance to perform an isolated TVR. While most are common to all major invasive cardiac interventions, the risk of having to implant a permanent pacemaker is typical of this surgery. Since the atrioventricular node is in close proximity to the septal leaflet of the TV, its manipulation can lead to trauma of the surrounding area with subsequent heart block. On the contrary, the risk of stroke could be related to other concomitant factors. Prosthetic valves are associated with thromboembolism, but due to the position of the TV this phenomenon would result mostly in pulmonary emboli, unlike left-sided valve replacements which would lead to strokes.

LATE OUTCOMES FOR BIOPROSTHETIC TVR

The incidence rate of mortality after a bioprosthetic TVR was found to be 6 per 100 person-years in the random-effects model, and 22 per 100 person-years in the fixed-effects model **(Table 2, Supplementary Table 5)**. This discrepancy is due to the great heterogeneity among the studies, which, as a result of being observational, included populations with different characteristics that might have influenced this outcome. This is reflected in the discordance of existing literature on the role of TVR on survival. While some studies report an improved survival rate after TV surgery, even in patients with TR and congestive HF[63], others found no difference in long-term survival regardless of whether patients with isolated severe TR underwent surgery or medical therapy alone, after accounting for immortal time bias[64].

The recurrence of at least moderate TR in the follow-up was not negligible (8 [95% CI: 5-13] per 100 person-years). However, this was accompanied by a much lower rate of reintervention (1 [95% CI: 1-3] per 100 person-years). This could reasonably be due to the growing risk of an already very compromised population having to undergo further major cardiac surgery.

FUTURE PERSPECTIVES

Epidemiological data show that secondary TR is the most prevalent aetiology in patients undergoing surgical interventions (92.6%) and the one with the lowest indication rates for surgical correction (53.2%)[65]. As a matter of fact, isolated TV surgery was performed only in 5% of patients included in the EuroSCORE II database[66].

In this context, emerging percutaneous procedures appear to be an attractive solution for this substantial unmet clinical need. However, in order to advance TTVR technology, clinical researchers and regulatory bodies need comparative data from surgical isolated TVR. Our results provide a comprehensive extraction of published data surrounding isolated TVR. Results of either mechanical or bioprosthetic TVR are applicable to early outcomes, while results from only bioprosthetic TVR can be used for insight into TTVR durability studies. Among all TVR, the outcome data for operative mortality and permanent pacemaker implantation, critical outcomes of interest in the development of TTVR devices, should be set as the thresholds for outcomes to be utilised in prospective TTVR trials.

Of note, patients undergoing surgical TVR were relatively young (mean age 53 years), with good left ventricular function (mean ejection fraction 58%), and with few comorbidities, such as diabetes (13%), hypertension (23%), or liver disease (31%). These figures underline a selection bias in the surgical series, which include only patients deemed at an acceptable surgical risk and exclude the most advanced population. This warrants precaution when generalising the results of this meta-analysis to extreme-risk patients, such as those treated in compassionate-use studies of pioneering TTVR devices[7–9]. However, despite the baseline risk profile of patients and the absence of an appropriate learning curve, the outcomes observed in these studies are promising. As soon as

further data proves TTVR to be efficacious and acceptably safe, it will be possible to push even more in favour of this technology. For this purpose, having an in-depth knowledge of surgical TVR, with its results and pitfalls, is essential for a rigorous evaluation and to promote those developing percutaneous therapies by serving as the legitimate benchmark.

Limitations

The results of the present meta-analysis have to be interpreted whilst acknowledging the following limitations. Since no randomised controlled trials investigated surgical TVR, all the included studies were observational and, thus, susceptible to error regarding patient selection and characteristics. As such, the results were affected by significant degrees of heterogeneity and should be interpreted according to their range distribution rather than point estimates. This is a study-level meta-analysis, and its findings are average pooled rates. The computation of person-years at risk was performed using study-level follow-up time when no data on the dropout date or number of days were available. Since a patient-level analysis for these 35 studies was not feasible, meta-regression analyses tested study-level characteristics, and their results should be considered as hypothesis-generating. The population was heterogeneous in terms of TV disease aetiologies, prior cardiac surgeries, and surgical experience or hospital operating volume. However, given the paucity of published evidence, the findings of this meta-analysis depict the full spectrum of patients undergoing isolated TVR.

Conclusions

This systematic review and meta-analysis provides an overview of the early and late outcomes after isolated surgical TVR. The results can support patients and doctors in the clinical decision-making for TVR and may serve as a benchmark for developing percutaneous therapies.

Impact on daily practice

Transcatheter tricuspid valve replacement (TTVR) is rapidly emerging as a therapeutic option amongst patients with secondary tricuspid regurgitation. The findings of this meta-analysis can support the clinical decision-making for tricuspid valve replacement (TVR) and may set the threshold for outcomes to be utilised in prospective TTVR trials. Surgical long-term TVR data may serve as a benchmark for developing TTVR systems. Late outcomes may inform on the bioprosthetic durability of the tricuspid valve.

Conflict of interest statement

The authors have no conflicts of interest relevant to the contents of this paper to disclose.

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Supplementary data

Supplementary Appendix 1. PRISMA checklist.
Supplementary Appendix 2. MOOSE reporting checklist.
Supplementary Appendix 3. Database search results.
Supplementary Appendix 4. Definitions.
Supplementary Table 1. Baseline characteristics of included patients.
Supplementary Table 2. Risk of bias assessment – observational studies.
Supplementary Table 3. Key study features – bioprosthetic tricuspid valve replacement.
Supplementary Table 4. Meta-regression analysis.
Supplementary Table 5. Early and late outcomes – no endocarditis.
Supplementary Table 6. Early and late outcomes – fixed effects models.
Supplementary Figure 1. Funnel plot and Baujat plot.
Supplementary Figure 2. Bubble plots for meta-regression analysis.
Supplementary Figure 3. Meta-analysis using a random intercept logistic regression model.
Supplementary Figure 4. Leave-one-out meta-analysis.
Supplementary Figure 5. Cumulative meta-analysis.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-22-00442

Supplementary data

Supplementary Appendix 1. PRISMA checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, supplementary data
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	supplementary data
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5, figure 1, supplementary data
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5, 6, 7

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6, 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6, 7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6, 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6, 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, supplementary data
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8, 9
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8, 9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8, 9, supplementary data
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-	9, 10,

		regression [see Item 16]).	supplementary data
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11, 12, 13, 14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14, 15, 16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Appendix 2. MOOSE reporting checklist.

Reporting of background should include
Problem definition ***page 4***
Hypothesis statement ***pages 4, 11-14***
Description of study outcome(s) ***page 6***
Type of exposure or intervention used ***page 5***
Type of study designs used ***page 5***
Study population ***page 5***

Reporting of search strategy should include
Qualifications of searchers (eg, librarians and investigators) ***page 5***
Search strategy, including time period included in the synthesis and keywords ***page 5, supplementary method 3***
Effort to include all available studies, including contact with authors ***page 5***
Databases and registries searched ***page 5, supplementary method 3***
Search software used, name and version, including special features used (eg, explosion) ***page 5, suppl method 3***
Use of hand searching (eg, reference lists of obtained articles) ***page 5, supplementary method 3***
List of citations located and those excluded, including justification ***figure 1***
Method of addressing articles published in languages other than English ***page 5***
Method of handling abstracts and unpublished studies ***page 5***
Description of any contact with authors ***page 5***

Reporting of methods should include
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested ***pages 13-15***
Rationale for the selection and coding of data (eg, sound clinical principles or convenience) ***pages 5-7***
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability) ***pages 5-7***
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate) ***pages 5-7***
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results ***page 5-7***
Assessment of heterogeneity ***pages 5-7***
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated ***pages 5-7***
Provision of appropriate tables and graphics ***Table 1,2, Figures 1-3***

Reporting of results should include
Graphic summarising individual study estimates and overall estimate ***Figures 1-3, Central Illustration***
Table giving descriptive information for each study included ***Table 1, Supplementary Tables 1,3***
Results of sensitivity testing (eg, subgroup analysis) ***pages 9-10***
Indication of statistical uncertainty of findings ***page 8-10***

Reporting of discussion should include
Quantitative assessment of bias (eg, publication bias) ***Supplementary Table 2***
Justification for exclusion (eg, exclusion of non–English-language citations) ***Figure 1***
Assessment of quality of included studies ***Table 1 and Supplementary Table 3***

Reporting of conclusions should include
Consideration of alternative explanations for observed results ***pages 11-15***
Generalisation of the conclusions (ie, appropriate for the data presented and within the domain of the literature review) ***pages 11-15***
Guidelines for future research ***page 15***
Disclosure of funding source ***page 1***

Supplementary Appendix 3. Database search results.

Database	Search strategy	Search results
PubMed/MEDLINE	(tricuspid[ti]) AND ((replacement[tiab]) OR (bioprosthetic[tiab]) OR (mechanical[tiab]) OR (intervention[tiab]) OR (surgery[tiab]))	3054
Web of Science	(TI=(tricuspid)) AND (AB=(intervention) OR AB=(replacement)OR AB=(surgery)OR AB=(bioprosthetic) OR AB=(mechanical))	1801
SCOPUS	TITLE (tricuspid) AND (TITLE-ABS (replacement) OR TITLE-ABS (intervention) OR TITLE-ABS (surgery) OR TITLE-ABS (bioprosthetic) OR TITLE-ABS (mechanical))	3222
EMBASE	tricuspid:ti AND (replacement:ab,ti OR surgery:ti OR intervention:ab,ti OR bioprosthetic:ab,ti OR mechanical:ab,ti)	3149
www.escardio.org www.acc.org www.heart.org www.pcronline.com www.tctmd.com www.crtonline.gov www.clinicaltrials.gov www.clinicaltrialsregister.eu	Keywords: “tricuspid”, “replacement”, “surgery”, “bioprosthetic”, “mechanical”.	

MEDLINE: Medical Literature Analysis and Retrieval System Online; EMBASE: Excerpta Medica Database

Supplementary Appendix 4. Definitions.

Study	Acute kidney injury	Liver disease	Bleeding	Structural valve deterioration	Respiratory complications
Sanfelippo et al. 1976	-	-	Not defined		Not defined
Munro et al. 1995	-	-	-	Chronically thickened and rolled leaflets in the open position	-
Do et al. 2000	-	-	Requiring re-exploration		-
Mangoni et al. 2001	Creatinine > 3 mg/dl	Hepatomegaly	Not defined	Thickening and stiffening of the cusps	Mechanical ventilation > 72 hours of or reintubation
Tokunaga et al. 2008	-	-	-	Primary tissue failure	-
Capoun et al. 2010	-	-	-	Not defined	-
Kim et al. 2013	Not defined	Cirrhosis	Requiring re-exploration	Not defined	-
Bevan et al. 2014	Acute renal failure requiring renal replacement therapy	Hepatomegaly	Requiring re-exploration		-
Buzzatti et al. 2014	Not defined	Ascites	Requiring re-exploration		-
Farag et al. 2017	Not defined	Liver enlargement	-		-
Hanedan et al. 2017	-	Hepatomegaly	Requiring re-exploration		Not defined
Çakıcı et al. 2018	-	-	Not defined		-
Chen et al. 2018	One or more of the following: 1) creatinine > 2 mg/dl or >50% from baseline 2) Need for dialysis	Liver congestion	Requiring re-exploration		Mechanical ventilation ≥ 72 hours, tracheostomy, or re-intubation.
Moutakiallah et al. 2018	Not defined	-	Major internal or external bleeding that causes death, hospitalisation, permanent injury, or required transfusion	Not defined	Mechanical ventilation ≥ 24 hours, tracheostomy, or re-intubation.
Kundi et al. 2019	Not defined	-	Not defined		Not defined
Liang et al. 2019	Not defined	-	Requiring re-exploration	Not defined	Not defined

Chen et al. 2020	-	Hepatomegaly	-		-
Wong et al. 2020	-	Cirrhosis	-		-
Yan et al. 2020	Not defined	Congestive liver failure or hepatic insufficiency	Need for blood transfusion		Severe pulmonary infection
Lee et al. 2021	-	Cirrhosis	Transfusion of >10 units of packed red blood cells		-
Leviner et al. 2021	Need for hemodialysis	-	Requiring re-exploration		-
Liu et al. 2021	-	Total bilirubin >2 mg/dl or hepatic transaminase > 5x normal upper limit	Not defined	Not defined	-
Park et al. 2021	-	-	Requiring re-exploration		-
Tafti et al. 2021	-	-	-	Not defined	-

Supplementary Table 1. Baseline characteristics of included patients.

Study (year)	Age (years ± SD)	Female (%)	NYHA III/IV (%)	Prior cardiac surgery (%)	Secondary etiology (%)
Sanfelippo et al. 1976	-	-	-	14(93)	-
Glower et al. 1995	-	-	-	21(60)	-
Munro et al. 1995	-	-	-	-	-
Do et al. 2000	48	18(62)	27(93)	22(76)	-
Mangoni et al. 2001	61±3	9(60)	11(73)	13(87)	-
Maleszka et al. 2004	-	-	13(65)	-	-
Solomon et al. 2004	-	-	-	26(79)	-
Iscan et al. 2007	-	-	-	-	-
Tokunaga et al. 2008	-	-	-	-	-
Capoun et al. 2010	-	-	-	-	0(0)
Baraki et al. 2013	-	-	-	-	-
Kim et al. 2013	56.1±10.7	8(57)	8(57)	0(0)	-
Bevan et al. 2014	46.0	21(72)	7(24)	20(69)	-
Buzzatti et al. 2014	61.7±10.7	44(72)	48(79)	61(100)	-
Farag et al. 2017	55.7±15.9	37(54)	-	37(54)	37(54)
Hanedan et al. 2017	51.1±10.5	24(80)	19(63)	30(100)	-
Rossello et al. 2017	-	-	-	-	-
Çakıcı et al. 2018	-	-	-	-	0(0)
Chen et al. 2018	49.1±12.9	76(64)	101(86)	49(42)	-
Fang et al. 2018	-	-	-	90(100)	90(100)
Moutakiallah et al. 2018	-	-	-	11(100)	1(9)
Di Mauro et al. 2019	-	-	-	-	0(0)
Kundi et al. 2019	-	-	-	-	-
Liang et al. 2019	45.7±13.2	51(67)	19(25)	0(0)	0(0)
Chen et al. 2020	53.6±12.5	69(64)	81(76)	107(100)	-
Dreyfus et al. 2020	-	-	-	-	135(49)
Sánchez-Espín G et al. 2020	-	-	-	-	-
Wong et al. 2020	53.5±15.9	61(45)	-	0(0)	-
Yan et al. 2020	54.8±6.5	40(82)	38(78)	49(100)	49(100)

Kawsara et al. 2021	-	-	-	0(0)	-
Lee et al. 2021	37.6±13.1	78(36)	-	19(9)	0(0)
Leviner et al. 2021	60.7±11	24(73)	30(91)	21(64)	-
Liu et al. 2021	39.0±16	116(62)	99(53)	17(9)	37(20)
Park et al. 2021	59.8±11.5	71(67)	49(46)	65(61)	83(78)
Tafti et al. 2021	48.8±13.5	31(66)	-	-	-
Pooled estimates: mean/incidence (95% CI)	53 (49-56)	63 (57-69)	67 (53-78)	60 (27-85)	22 (4-69)

Continued…

Study (year)	Endocarditis (%)	Diabetes (%)	Hypertension (%)	Atrial fibrillation (%)	Liver disease (%)	LVEF (% ± SD)
Sanfelippo et al. 1976	-	-	-	-	-	-
Glower et al. 1995	-	-	-	-	-	-
Munro et al. 1995	-	-	-	-	-	-
Do et al. 2000	-	-	-	-	-	-
Mangoni et al. 2001	2(13)	4(27)	5(33)	-	12(80)	-
Maleszka et al. 2004	6(30)	-	-	-	-	-
Solomon et al. 2004	-	-	-	-	-	-
Iscan et al. 2007	-	-	-	-	-	-
Tokunaga et al. 2008	4(13)	-	-	-	-	-
Capoun et al. 2010	11(100)	-	-	-	-	-
Baraki et al. 2013	18(100)	-	-	-	-	-
Kim et al. 2013	0(0)	2(14)	3(21)	6(43)	0(0)	59.6±6.9
Bevan et al. 2014	5(17)	-	-	-	13(45)	-
Buzzatti et al. 2014	0(0)	9(15)	-	54(89)	24(39)	54.4±8.3
Farag et al. 2017	32(47)	15(22)	30(44)	-	21(31)	-
Hanedan et al. 2017	-	-	-	24(80)	22(73)	-
Rossello et al. 2017	-	-	-	-	-	-
Çakıcı et al. 2018	25(100)	-	-	-	-	-
Chen et al. 2018	-	5(4)	17(14)	62(53)	45(38)	66.0±6.3
Fang et al. 2018	-	-	-	-	-	-
Moutakiallah et al. 2018	-	-	-	-	-	-
Di Mauro et al. 2019	80(100)	-	-	-	-	-
Kundi et al. 2019	-	-	-	-	-	-
Liang et al. 2019	0(0)	-	7(9)	30(39)	-	61.8±7.5
Chen et al. 2020	-	6(6)	-	68(64)	53(50)	51.6±6.2
Dreyfus et al. 2020	78(29)	-	-	-	-	-
Sánchez-Espín G et al. 2020	0(0)	-	-	-	-	-
Wong et al. 2020	0(0)	23(17)	44(32)	57(42)	18(13)	-
Yan et al. 2020	0(0)	7(14)	20(41)	44(90)	12(24)	57.9±3.5
Kawsara et al. 2021	0(0)	-	-	-	-	-
Lee et al. 2021	216(100)	17(8)	18(8)	-	16(7)	-

Leviner et al. 2021	0(0)	9(27)	16(48)	27(82)	-	-
Liu et al. 2021	22(12)	23(12)	19(10)	62(33)	19(10)	62.0±6.0
Park et al. 2021	0(0)	12(11)	27(25)	59(56)	-	57.9±3.5
Tafti et al. 2021	-	6(13)	-	-	-	47.4±7.8
Pooled estimates: mean/incidence (95% CI)	18 (4-52)	13 (10-17)	23 (15-33)	63 (48-75)	31 (18-48)	58 (54-61)

CI: confidence interval; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; NR: not reported; SD: standard deviation.

Supplementary Table 2. Risk of bias assessment – observational studies.
Risk of bias in non-randomized studies of interventions assessment tool from the Cochrane handbook (ROBINS-I) for the outcome of operative mortality.

Study		**Pre-Intervention**		**At Intervention**	**Post-intervention**				**Overall risk of bias**
Study	***Year***	***Bias due to confounding***	***Bias in selection of participants into the study***	***Bias in classification of interventions***	***Bias due to deviations from intended interventions***	***Bias due to missing data***	***Bias in measurement of outcomes***	***Bias in selection of the reported result***	***Low/ moderate/ high***
Sanfelippo et al.	1976	✗	✓	✓	✓	✓	✓	✓	✗
Glower et al.	1995	⚠	✓	✓	✓	✓	✓	✓	⚠
Munro et al.	1995	✗	✓	✓	✓	✓	✓	✓	✗
Do et al.	2000	NA	NA	NA	NA	NA	NA	NA	✗
Mangoni et al.	2001	⚠	✓	✓	✓	✓	✓	✓	⚠
Maleszka et al.	2004	NA	NA	NA	NA	NA	NA	NA	✗
Solomon et al.	2004	✗	✓	✓	✓	✓	✓	✓	✗
Iscan et al.	2007	⚠	✓	✓	✓	✓	✓	✓	⚠
Tokunaga et al.	2008	✗	✓	✓	✓	✓	✓	✓	✗
Capoun et al.	2010	⚠	✓	✓	✓	✓	✓	✓	⚠
Baraki et al.	2013	✗	⚠	✓	✓	⚠	✓	✓	✗
Kim et al.	2013	⚠	✓	✓	✓	✓	✓	✓	⚠
Bevan et al.	2014	⚠	✓	✓	✓	✓	✓	✓	⚠
Buzzatti et al.	2014	⚠	✓	✓	✓	✓	✓	✓	⚠
Farag et al.	2017	⚠	✓	✓	✓	✓	✓	✓	⚠
Hanedan et al.	2017	✓	✓	✓	✓	✓	✓	✓	✓
Rossello et al.	2017	⚠	✓	✓	✓	✓	✓	✓	⚠
Çakıcı et al.	2018	⚠	✓	✓	✓	✓	✓	✓	⚠

Chen et al.	2018	⚠	✓	✓	✓	✓	✓	✓	⚠
Fang et al.	2018	⚠	✓	✓	✓	✓	✓	✓	⚠
Moutakiallah et al.	2018	⚠	✓	✓	✓	✓	✓	✓	⚠
Di Mauro et al.	2019	✗	⚠	✓	✓	✓	⚠	✓	✗
Kundi et al.	2019	⚠	⚠	✓	✓	✓	✓	✓	⚠
Liang et al.	2019	✗	⚠	✓	✓	✓	✓	✓	✗
Chen et al.	2020	⚠	✓	✓	✓	✓	✓	✓	⚠
Dreyfus et al.	2020	⚠	✓	✓	✓	✓	✓	✓	⚠
Sánchez-Espín G et al.	2020	⚠	✓	✓	✓	✓	✓	✓	⚠
Wong et al.	2020	⚠	✓	✓	✓	✓	✓	✓	⚠
Yan et al.	2020	⚠	✓	✓	✓	✓	✓	✓	⚠
Kawsara et al.	2021	⚠	✓	✓	✓	✓	✓	✓	⚠
Lee et al.	2021	⚠	✓	✓	✓	✓	✓	✓	⚠
Leviner et al.	2021	⚠	✓	✓	✓	✓	✓	✓	⚠
Liu et al.	2021	⚠	⚠	✓	✓	✓	✓	✓	⚠
Park et al.	2021	⚠	✓	✓	✓	✓	✓	✓	⚠
Tafti et al.	2021	⚠	✓	✓	✓	⚠	✓	✓	⚠

✓ = low risk; ⚠ = moderate risk; ✗ = high risk

Supplementary Table 3. Key study features – bioprosthetic tricuspid valve replacement.

Study	Year	Patients	Operative Time	Country	Multicenter (n)	Follow-up (years)
Glower et al.	1995	35	1974-1993	USA	No	In-hospital
Tokunaga et al.	2008	27	1975-2004	Japan	No	8
Baraki et al.	2013	14	1996-2012	Germany	No	6
Kim et al.	2013	10	1996-2010	Korea	No	3
Hanedan et al.	2017	10	2004-2011	Turkey	No	2
Chen et al.	2018	102	2003-2016	China	No	In-hospital
Fang et al.	2018	74	2007-2016	China	No	9
Kundi et al.	2019	1737	2003-2014	USA	Yes (841)	1
Liang et al.	2019	43	2010-2017	China	No	4
Chen et al.	2020	25	2009-2017	China	No	5
Sánchez-Espín G et al.	2020	48	1996-2017	Spain	No	4
Yan et al.	2020	49	2012-2019	China	No	2
Kawsara et al.	2021	468	2016-2017	USA	Yes	In-hospital
Liu et al.	2021	145	1999-2018	China	Yes (2)	11

Supplementary Table 4. Meta-regression analysis.

Covariate	β	Lower bound	Upper bound	Standard Error	p value
Operative Mortality					
Year of publication	-0.037	-0.063	-0.011	0.013	0.006
Operative period >1995 (ref. <1995)	-0.626	-1.392	1.140	0.7376	0.105
Europe (ref. North America)	-0.467	-1.332	0.398	0.423	0.278
Asia (ref. North America)	-0.593	-1.357	0.171	0.373	0.123
Low Risk of Bias (ref. High)	0.858	-0.747	2.462	0.788	0.285
Moderate Risk of Bias (ref. High)	-0.423	-1.090	0.245	0.328	0.206
Bioprostheses	-0.006	-0.018	0.006	0.006	0.337
Age	0.006	-0.066	0.078	0.034	0.865
Sex (female)	0.005	-0.038	0.048	0.020	0.798
Hypertension	0.014	-0.027	0.054	0.018	0.461
Diabetes	-0.002	-0.081	0.076	0.036	0.948
Atrial Fibrillation	0.020	-0.013	0.053	0.015	0.201
Liver disease	0.021	0.006	0.037	0.007	0.013
Secondary TR	-0.008	-0.024	0.007	0.007	0.264
Previous Cardiac Surgery	0.010	-0.000	0.021	0.005	0.056
Endocarditis	0.006	-0.001	0.013	0.003	0.092
LV Ejection Fraction	-0.116	-0.241	0.010	0.053	0.065

LV: left ventricle; TR: tricuspid regurgitation

Supplementary Table 5. Early and late outcomes – no endocarditis.

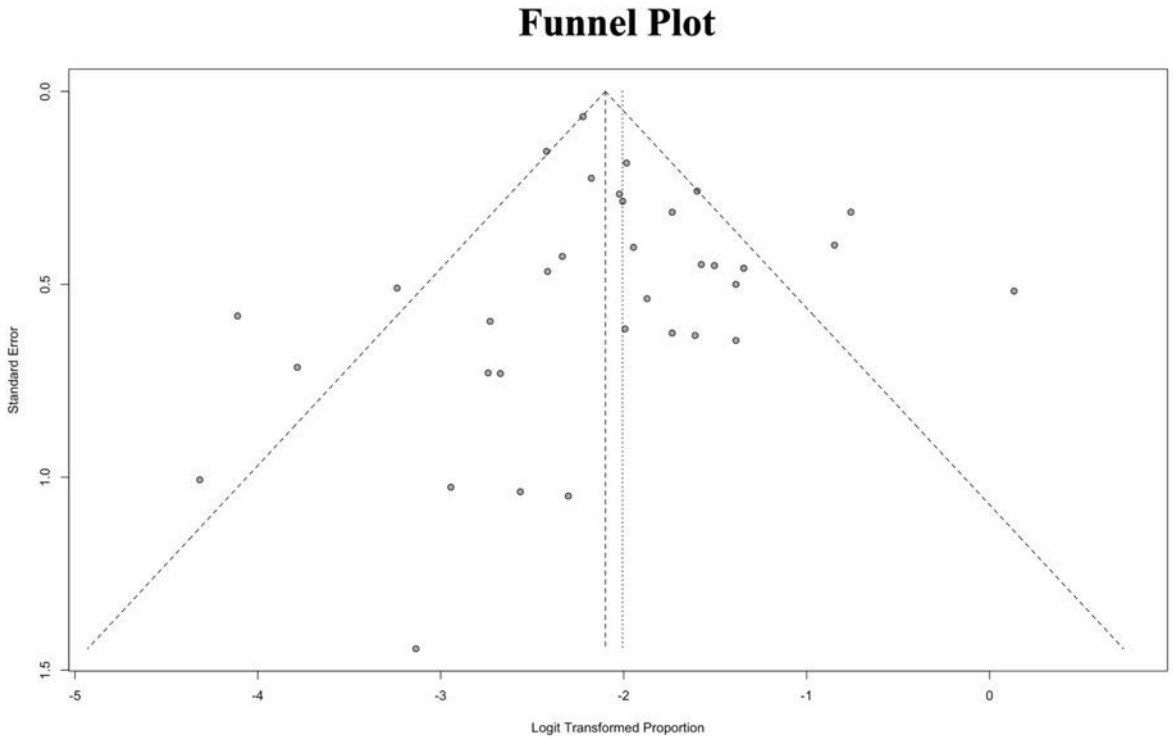
Outcome	Proportion/Incidence rate % (95% CI)	I^2 % (χ^2 P-value)	N. of studies
EARLY OUTCOMES			
Operative Mortality	12 (9–17)	74 (<0.01)	23
Bleeding	11 (6-19)	85 (<0.01)	12
Acute Kidney Injury	14 (7-25)	90 (<0.01)	8
Renal Replacement Therapy	6 (2-19)	70 (<0.01)	4
Pacemaker	9 (5-16)	71 (<0.01)	9
Respiratory Complications	15 (11-19)	0 (0.64)	6
Stroke	2 (1-5)	80 (<0.01)	6
Wound Infection	3 (1-5)	80 (<0.01)	7
LATE OUTCOMES			
Late Mortality*	7 (4-12)	94 (<0.01)	15
Re-intervention*	2 (1-3)	31 (0.17)	9
Structural Valve Deterioration*	4 (3-6)	44 (0.13)	5
Valve Thrombosis*	1 (0-3)	0 (0.56)	3
Recurrence of TR ≥2*	5 (2-13)	85 (<0.01)	4
BIOPROSTHESES			
Late Mortality*	7 (2-23)	91 (<0.01)	6
Re-intervention*	1 (0-3)	0 (0.58)	4
Structural Valve Deterioration*	5 (3-9)	34 (0.22)	2
Valve Thrombosis*	1 (0-2)	0 (0.77)	2
Recurrence of TR ≥2*	5 (2-15)	89 (<0.01)	3

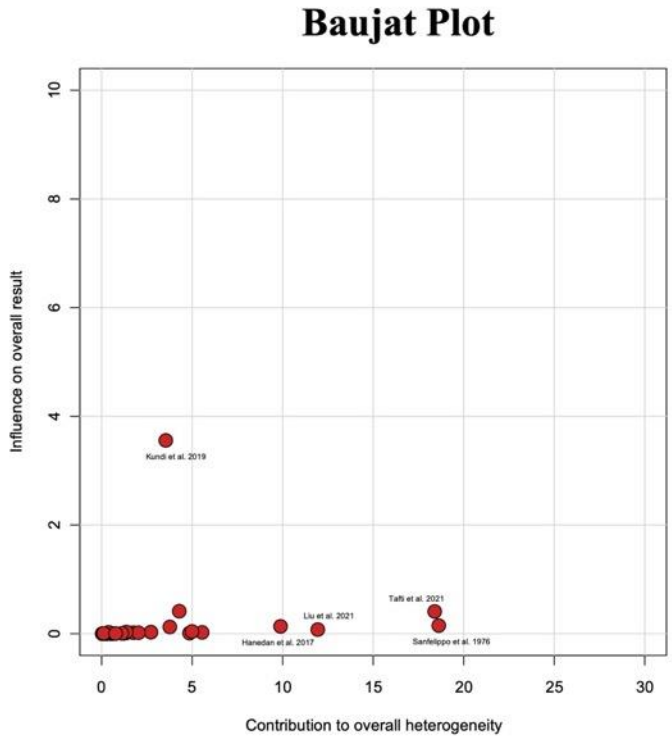
* per 100 person-years
CI: confidence interval; TR: tricuspid regurgitation

Supplementary Table 6. Early and late outcomes – fixed effects models.

Outcome	Proportion/Incidence rate % (95% CI)	I^2 % (χ^2 P-value)	N. of studies
EARLY OUTCOMES			
Bleeding	10 (9-12)	83 (<0.01)	17
Acute Kidney Injury	12 (11-14)	89 (<0.01)	11
Renal Replacement Therapy	11 (8-14)	63 (0.01)	7
Pacemaker	11 (9-14)	75 (<0.01)	13
Respiratory Complications	15 (12-20)	0 (0.56)	7
Stroke	1 (1-2)	74 (<0.01)	9
Wound Infection	2 (1-2)	81 (<0.01)	10
LATE OUTCOMES			
Late Mortality*	19 (18-20)	96 (<0.01)	23
Re-intervention*	2 (2-3)	64 (<0.01)	15
Structural Valve Deterioration*	2 (2-3)	82 (<0.01)	9
Valve Thrombosis*	1 (0-1)	49 (0.07)	8
Recurrence of TR ≥2*	5 (3-8)	85 (<0.01)	4
BIOPROSTHESES			
Late Mortality*	22 (20-24)	97 (<0.01)	8
Re-intervention*	1 (1-2)	77 (<0.01)	5
Structural Valve Deterioration*	2 (2-4)	91 (<0.01)	4
Valve Thrombosis*	0 (0-1)	68 (0.04)	3
Recurrence of TR ≥2*	8 (5-13)	33 (0.22)	3

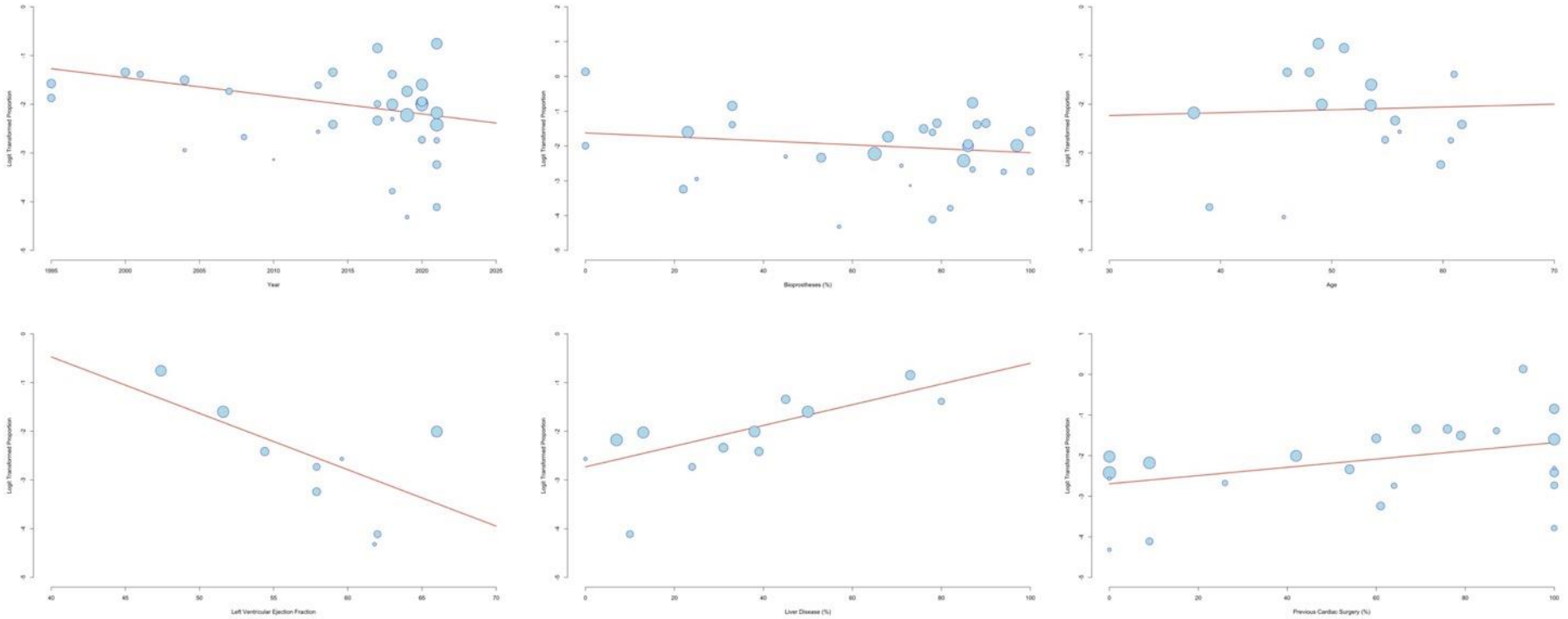
* per 100 person-years
CI: confidence interval; TR: tricuspid regurgitation



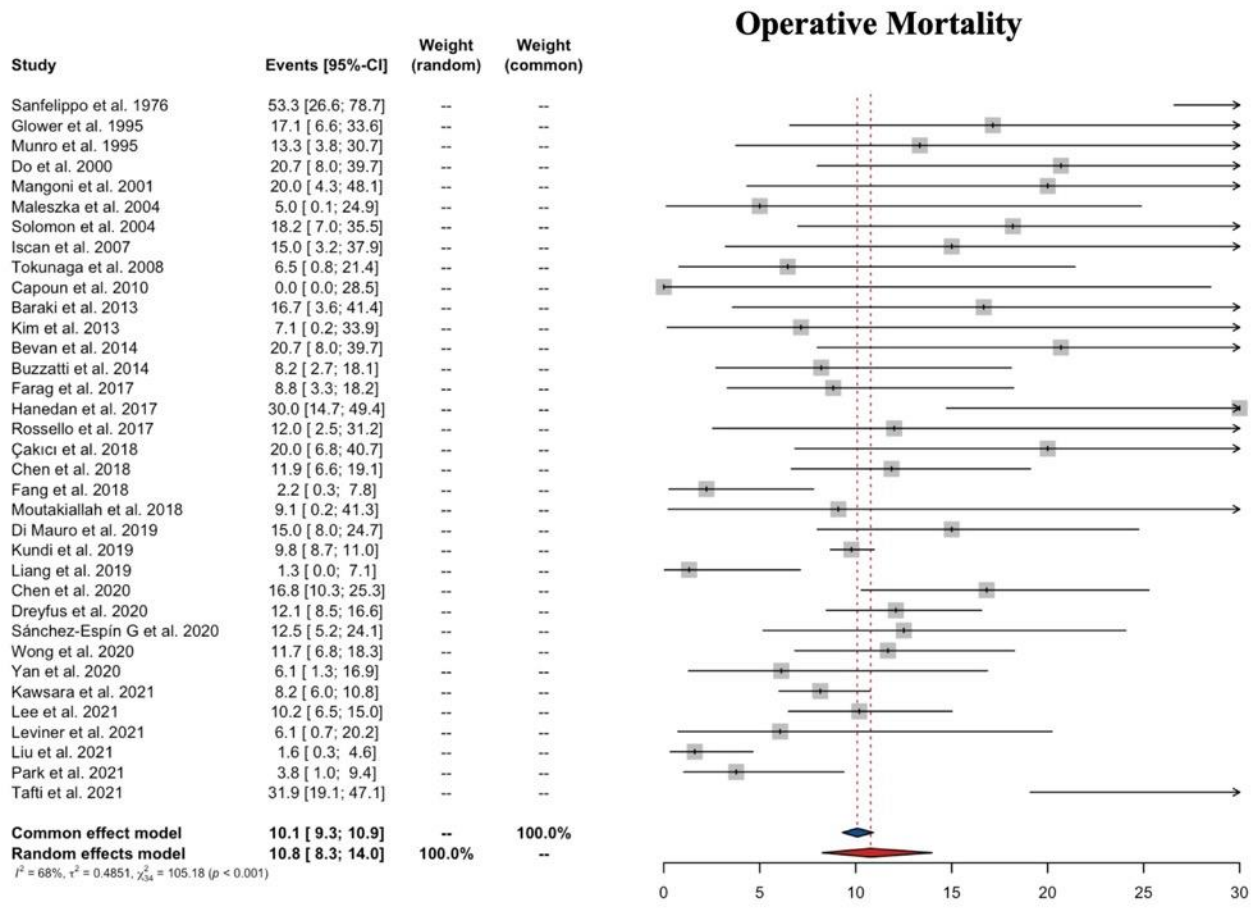


Supplementary Figure 1. Funnel plot and Baujat plot.

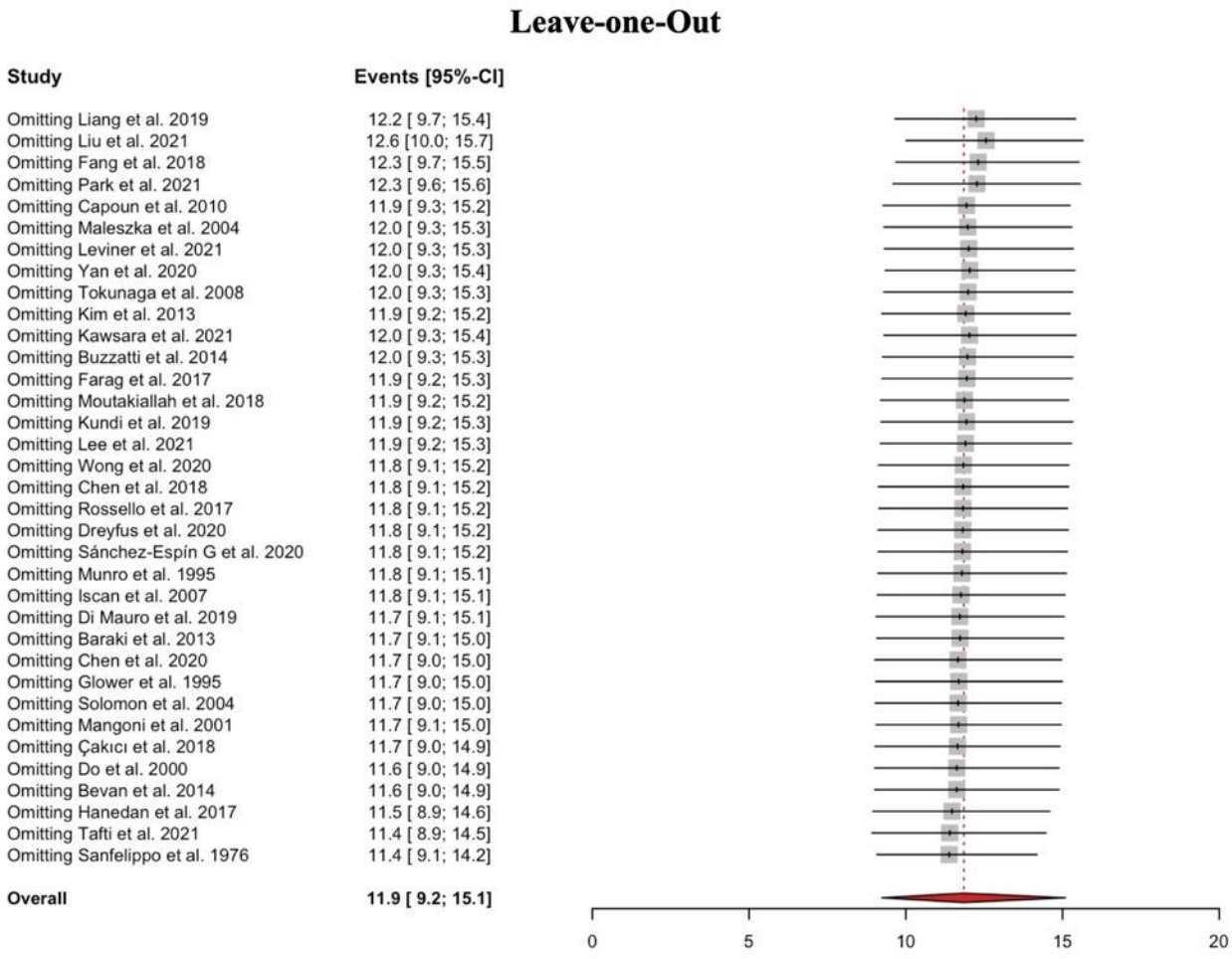
Funnel plot and Baujat plot of primary endpoint (operative mortality).



Supplementary Figure 2. **Bubble plots for meta-regression analysis.**
Bubble plots of the effect of continuous covariates on the overall estimate of primary endpoint (operative mortality) with predicted regression line (red). The size of the bubbles is proportional to the study weights

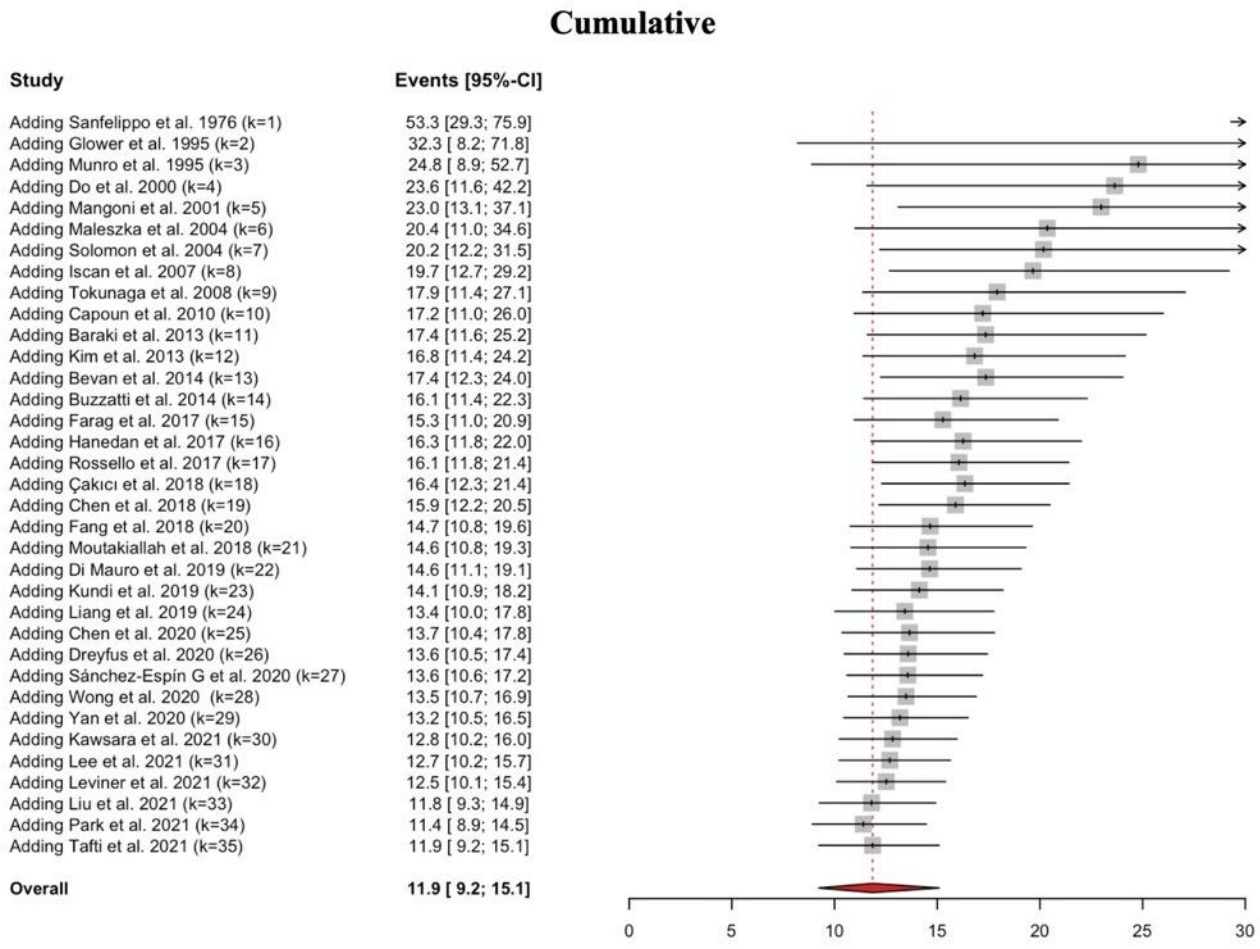


Supplementary Figure 3. **Meta-analysis using a random intercept logistic regression model.** Forest plot of primary endpoint (operative mortality) assessed with a random intercept logistic regression model. CI = confidence interval.



Supplementary Figure 4. Leave-one-out meta-analysis.

Forest plots of primary endpoint (operative mortality) assessed excluding one study per analysis (leave-one-out) with random-effects models.
CI = confidence interval



Supplementary Figure 5. Cumulative meta-analysis.
Forest plots of primary endpoint (operative mortality) assessed adding one study at a time (cumulative) with random-effects models analysis. *CI = confidence interval.*