

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-326>

Reviewer A

Comment: This is a systematic review and metanalysis for time-to-event long-term outcomes following the Ross procedure. It confirms the benefits of the Ross procedure in adults and the long-term survival benefit. The authors mentioned the limitations of the study and I believe it is a good addition to the literature supporting the benefit of the Ross procedure in the adult population.

Reply: Thank you for the positive comments on our manuscript. We believe that findings from our study would be a valuable addition to the current evidence of the Ross procedure. We also appreciate the time and effort you have dedicated.

Reviewer B

In this manuscript, Dr. Shimamura and colleagues have performed a meta-analysis of long-term outcomes following the Ross procedure. They have identified 6 recently published manuscripts reporting long-term Ross outcomes in nearly 5,000 patients; reported outcomes overall survival and rates of reintervention on the autograft or homograft valves following the Ross. The authors have presented a sophisticated analysis with good clarity and have appropriately acknowledged the limitations of their findings. I believe this manuscript may represent the best current summary of the available long-term data on the Ross procedure, but I do have several comments that I hope will help strengthen their study:

Major comments:

Comment 1: The authors have identified six manuscripts that met their inclusion/exclusion criteria. I believe they have identified the available literature from the main centers that have reported Ross outcomes in recent years. Of note, Dr. David and his group from Toronto have reported long-term outcomes of his series of Ross patients in several recent papers. The authors chose the Mazine et al 2022 JACC manuscript to include in their analysis, which includes Ross procedures performed at Toronto from 1990-2014. However, that manuscript was performed as a propensity-match analysis, thus ultimately only reports outcomes on 108/233 available patients who underwent the Ross procedure. Alternatively, the Toronto group also reported outcomes from the complete group of 200+ patients in JTCVS 2019 (David et al), and that paper also had 20+ year follow-up. Can the authors justify why they selected the JACC paper even though the number of patients available to include was less than half of those in the JTCVS paper (and represented a skewed group since less than half of available Ross patients were included in the JACC analysis)? At a minimum, the authors should consider a sensitivity analysis that would repeat the primary analysis after substituting the JTCVS data from the JACC data from the Toronto group to ensure the most complete/accurate outcomes data is reported in their meta-analysis.

Reply 1: As the reviewer pointed out, the largest cohort with long-term outcomes following the Ross procedure from Toronto is the JTCVS data by David et al. However, this report did not report Kaplan-Meier curve for mortality which is the primary outcome of interest of this study, and we could not reconstruct the primary outcome. Therefore, we have included the JACC data by Mazine et al from the same group instead. The only available Kaplan-Meier data in the JTCVS study was reintervention from either autograft/RVOT. Thus, we performed a sensitivity analysis by substituting the JTCVS data which showed quite similar results from the current study in terms of freedom rate from any valve reintervention data. (Freedom from any valve reintervention (either autograft or RVOT) at 5, 10, 15, and 20 years was 95.8 ± 0.6 , 92.6 ± 0.9 , 88.5 ± 1.2 , $80.8 \pm 2.5\%$ with JACC data and 95.9 ± 0.6 , 92.6 ± 0.9 , 88.7 ± 1.2 , $79.7 \pm 2.6\%$ respectively). We also added the following sentence in the limitation because we could not include studies that did not report Kaplan-Meier curves.

Changes in the text: (line 354) Fifth, studies that did not report Kaplan-Meier curve were not included in the current study.

Comment 2: Each of the included primary manuscripts handled reporting of autograft/homograft reinterventions in slightly different ways. Most did assess these outcomes as a competing hazard (accounting for concomitant risk of mortality; ie, a patient who dies is no longer at risk for valve reintervention). However, the authors seem to have analyzed this outcome using Kaplan-Meier techniques. Did the authors account for the competing risk of mortality in their analysis? If not, please justify this approach.

Reply 2: The reviewer has raised an important point. As the reviewer mentioned, one of the major limitations regarding the results of reintervention is the potential competing risk because the outcome was analyzed with the Kaplan-Meier method. Therefore, we have added the following statement in the limitation section.

Changes in the text: (line 361) Because the algorithm for reconstruction of individual patient data from the Kaplan Meier curve is not able to reproduce informative censoring of competing risk, we could only calculate cause-specific Kaplan Meier estimates in the outcome of revascularization.

Minor comments:

Comment 3: Author contributions: contributions from all authors except MO are detailed. Please clarify contributions from MO.

Reply 3: The author contribution of MO has been added.

Comment 4: Abstract: conclusion starts by commenting on reoperations, even though survival was the primary outcome of interest. Would recommend re-ordering conclusion sentences.

Reply 4: The conclusion sentence of the abstract has been revised according to the reviewer's recommendation.

Changes in the text: (Line 58) This meta-analysis demonstrated that the Ross procedure was confirmed to provide excellent survival despite the need for reintervention of autograft or RVOT in approximately 20% of patients at 20 years.

Comment 5: Key findings (line 78): Ross should be capitalized. Also, what makes for “excellent” survival? Would remove this subjective term and report objective findings instead.

Reply 5: The key findings sentence has been revised.

Changes in the text: (Line 82) The Ross procedure was confirmed to provide survival rate of approximately 87 % at 20 years despite the need for reintervention in roughly 20 % of patients.

Comment 6: Intro (line 112): the authors state registry-based studies have shown excellent outcomes of the Ross, but this does not account for perhaps the most rigorous registry-based study of the Ross procedure (Reece et al Ann Thorac Surg 2014), which analyzed all Ross procedures in the STS database from 1994-2010 and showed unacceptable perioperative risks. The authors should acknowledge this study, and place in context of current recommendations that only high-volume centers should perform the Ross procedure.

Reply 6: The reviewer has raised a very important point. We have acknowledged this study and added this article in the context of surgical indication of the Ross procedure.

Comment 7: Methods (line 141): Figure 1, and a brief in-text summary of this information, should be relocated to first paragraph of results (as per PRISMA reporting guidelines).

Reply 7: This part was relocated to the first paragraph of the result section. (Line 136).

Comment 8: Methods: the statistical details are not relevant to the intended audience. I would highly recommend relocating this information to a Statistical Appendix/Supplement. I would also strongly advise expert statistical review of this information.

Reply 8: We have summarized the statistical information as follows and relocated the details to the supplemental section as the supplemental method.

Changes in the text: (line 161-6) The meta-analysis of the time-to-event outcomes was performed as follows. Raw data (time, survival probability) were extracted from each Kaplan-Meier curve. Then, the data were processed in conjunction with the numbers at risk at given time point. Finally, the reconstructed time-to-event outcomes were merged to create the study dataset. The methodological details were described in the previous literature. (14, 15). (Supplemental Method).

Comment 9: Results (lines 203-206): the authors report there is variability in baseline characteristics of patients in each study. Important data should be explicitly stated so that readers can understand which differences matter and how different the groups were at baseline (difference of 1%, 10%, 50%, etc?)

Reply 9: Thank you for pointing this out. We agree with your opinion, and it is beneficial to add the variability of aortic disease. Therefore, the following information has been added.

Changes in the text: (line 228) (aortic insufficiency: 19-36%, mixed lesion: 7-50 %)

Comment 10: Results (line 218): “Supplemental 2” is a typo. Is this a table or figure?

Reply 10: This is Supplemental Table 2. Thank you.

Comment 11: Discussion (line 226): “20% freedom” is a typo. I believe the authors mean 80%

Reply 11: “20%” was removed. Thank you.

Comment 12: Discussion (Line 241-245): this paragraph is out of context. Authors should consider removing or better connect this information to the flow of their discussion on survival after the Ross.

Reply 12: I agree with your opinion. To better connect this information to the discussion, we have added the following sentence.

Changes in the text: (line 271-2) These benefits may result in the favorable long-term survival.

Comment 13: Discussion (line 254-255): the authors should also discuss that operative risk of Ross procedure may be higher than isolated AVR (see Reece paper above, and others). Jury may still be out on whether patients have to accept a slightly higher operative risk for the Ross in exchange for long-term advantages. This should be acknowledged and discussed, even though focus of the paper is long-term.

Reply 13: The reviewer has raised an important point. Despite the long-term benefits, the higher perioperative risk of the Ross procedure should be considered. Therefore, we have added the following sentence at the end of discussion of the survival.

Changes in the text: (line 283-4) However, we need to consider that the Ross procedure is associated with higher perioperative risk compared with isolated AVR despite its long-term survival advantages.

Comment 14: Discussion: several papers have recently been published detailing outcomes of Ross reinterventions (see Varrica et al Ann Thorac Surg 2020, Stelzer et al Ann Cardiothorac Surg 2021, and Shih et al JTCVS 2023). These reports are worth including in the discussion about the risks associated with reintervention after the Ross.

Reply 14: Thank you for your suggestion. They are actually very informative articles regarding the reintervention following the Ross operation. These studies have been added to the discussion.

Comment 15: Discussion (line 309): the authors cannot claim there is a significant advantage of the Ross procedure based on their analysis (which did not compare to any alternative therapies).

Reply 15: This is a valid assessment, and we agree with your opinion. These sentences have been deleted.

Comment 16: Limitations (line 328): how did the authors deal with the possibility of patient overlap? Should not any studies with possible overlap be excluded except for the most comprehensive one?

Reply 16: We acknowledge that the current study has potential patient overlap. There are two multicenter registries in the included study. From the list of participating centers, only one German center was included in both registries. (Department of Cardiac and Thoracic Vascular Surgery, University Heart Center Lübeck, University Hospital Schleswig- Holstein, Lübeck Campus, Lübeck, Germany) However, the information regarding the patients from this center included in those two studies such as number and outcomes could not be obtained. Therefore, we could not remove the potential overlap completely. Also, the study period of these registries is different. (Romeo et al.: between 1991 and 2018. Aboud: between 1988 and 2018).

Comment 17: Figures 2-5: “Kaplan-Meir” is spelled incorrectly in each figure caption. The captions should clarify that dotted lines represent the confidence intervals.

Supplemental Table 2a (20-year column, row 2): “965.2” is a typo that should be corrected.

Reply 17: The typo has been corrected.

Reviewer C

Comment: Congratulations to the authors of this good work. The large volume of cases that have been included for analysis is important, highlighting the main factors associated with Ross surgery. The work is well-written and structured. The conclusions obtained are very useful to value the reality of the results of the Ross surgery and the experience accumulated in the last 20 years of follow-up.

Concerning the statistical methodology for carrying out the meta-analysis, I cannot comment too much, as I am not an expert on the matter. However, from other meta-analyses that I have seen, I miss a forest plot-type graph, where the results obtained could be shown in a very visual way. What is the reason for not having done it?

Without more to add, congratulations on the excellent work.

Reply: Thank you for the positive comments on our manuscript. We also appreciate the time and effort you have dedicated. You have raised an important point; however, we believe that

forest plot-type graph is outside scope of our paper because our study is the meta-analysis of the single-arm and forest plot is utilized for two-arm studies.