Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-23-513

Reviewer A

I read with interest the paper of Meshulami et. al on Cardiac transplantation in Adult Congenital Heart Disease: A narrative review, which aims to describe the profile and outcome of patients with ACHD requiring HTx, the unique ACHD HTx challenges and potential solutions, and future opportunities to better serve more patients with ACHD HF. Thank you for submitting your paper to the Journal of Thoracic Disease.

Comment 1: This was broadly narrated, yet I have some issues I would like the authors to address. Line 29: Stating mean age, range would be helpful and informative.
Reply: Added median age of 35-years old and IQR of 24-46 as per UNOS data from 2000-2019 (N=1,159). Line 30 (in the clean version).

Comment 2: Line 46: The prevalence of ACHD HTx is increasing – was this supported in your narrative review?
Reply: Lines 91-97 support the increasing prevalence of heart transplantation in the ACHD population.

Comment 3: Line 46-47: Despite the operational complexity, ACHD HTx recipients have excellent outcomes – please be specific.
Reply: We now state "the majority of ACHD HTx recipients have excellent outcomes with 59% surviving more than 10-years post-transplant." Line 55-56.

Comment 4: Lines 54-55: mild, moderate and severe lesions - please clarify and describe specifically what these lesions are and which belongs to what classification.
Reply: We added that the lesions were categorized as per the Bethesda Conference categories. To further clarify, we also added examples. Line 67, 68, and 74.

Comment 5: Lines 63-64: Reference for the statement "It is often cited that the birth prevalence of CHD is increasing." is necessary.
Reply: Thank you for the suggestion, reference added. Line 71.

Comment 6: Line 85: registry instead of registrar?
Reply: Language changed to registry. Line 93.

Comment 7: Line 97: Pubmed search conducted from December 2022-March 2023 – incomplete sentence.
Reply: Updated the language to "We conducted a Pubmed search from December 2022 – March 2023."

Comment 8: Line 105: What are the specific keywords/ Index terms used to appropriately focus on topics relevant to the search?
Reply: We updated the search terms used to be more specific (line 113). In addition to incorporating your comments, we added language in the methods section on how we reviewed select articles cited by papers in our original search, especially when the referenced article was on a topic of importance for the review (e.g., outcomes for ACHD HTx, organ selection, preoperative coil embolization, and hypothermic circulatory arrest). Line 106-108.

Comment 9: Inclusion and exclusion criteria: All publications indexed in PubMed - do you mean by all include original articles, review articles, case reports, case series, editorial, etc? Please be specific.
Reply: Added language to specify that we included in our search original articles, meta-analyses, reviews, editorials, books, guidelines, case series, and case reports. Line 113.

Comment 10: Lines 107-390: The Findings/Discussion is broad. Several statements have to be edited or re- structured.
Reply: We have streamlined multiple statements in the findings/discussion section. See track changes manuscript.

Comment 11: There were many statements which needed to be referenced.
Reply: We have added references to each relevant statement.

Comment 12: Will you be able to specify the number of patients considered in each study you mentioned instead of just stating the percentages?
Reply: When possible, we have added the number of patients included. See track changes manuscript.

Comment 13: The narrative review lacks a critical and objective analysis of the chosen topic - This must also be included.
Reply: We added the following critical and objective analyses:
- ACHD HTx patients profile: “Further investigation of the underlying diagnoses for ACHD HTx candidates is warranted.” Line 130.
- ACHD HTx outcomes: “Given the risk of death or delisting while waiting for a donor, we would recommend against delaying for a more “perfect” heart.” Line 170-172.
- ACHD HTx outcomes: “While 10-year post-transplant outcomes are well-documented, we anticipate that as more data is collected, ACHD HTx recipients will have significantly better outcomes than non-ACHD HTx over longer timeframes (e.g., 20- years post operation).” Line 197-199.

- Challenges unique to ACHD HTx: “Pre-transplant PH is associated with higher post- operative RV dysfunction and mortality. Severe PH is a relative contraindication to heart transplantation alone (e.g., PVR >5 wood units, TPG >16-20 mmHg).

Mechanical circulatory support (MCS) can be considered as a bridge to transplant in patients with severe PH. Use of a Swan-Ganz catheter can help guide post-operative care. Furthermore, care must be taken to address all pulmonary artery stenosis intra-operatively. This can often be complex, and one may have to deal with old stents. We do not recommend selecting oversized hearts due to the limited data supporting the practice and the potentially prolonged waitlist time associated with waiting for an oversized heart. Pulmonary vasodilatory therapy is often continued post-operatively." Lines 239-247.

- Challenges unique to ACHD HTx "Multiple sternotomies additionally cause a restrictive chest wall and can interfere with post-operative pulmonary mechanics. HTx is an extremely time sensitive operation requiring good coordination between the donor and recipient surgeon teams, careful sternal re-entry, liberal use of peripheral cannulation strategies and extensive pre-operative cross-sectional imaging to help with all the above." Lines 280-283.
- Challenges unique to ACHD HTx "While the literature describes multiple challenges unique to ACHD HTx and potential solutions, research is still required to improve these solutions. Open questions include: What is the optimal desensitization therapy? How can we further reduce ACHD HTx organ ischemic time? How best to employ coil embolization to reduce bleeding? Do patients with FALD receiving combined heart- liver transplantations have better outcomes than those receiving heart-only transplantations?" Line 406-411.
- Future directions mechanical support devices: "MCS for patients with ACHD is an emerging field. Given the shortage of donor hearts and promising initial clinical data, MCS for ACHD HF is a field that warrants further investment. Furthermore, we feel that outcome data for MCS device usage in the ACHD population will improve as clinicians gain experience and continue to refine their practice." Line 451-454.

Comment 14: What is the clinical impact of your findings to the current state of knowledge of the topic?

Reply: Excellent question. While we wrote a review article summarizing the existing literature, we feel there are three novel contributions to the current state of knowledge: 1) we summarized the challenges and potential solutions for ACHD-HTx (table 3), 2) we described the underlying diagnosis for ACHD HTx recipients and candidates (table 2), and 3) we calculated the percent of patients assessed for HTx receiving a donor heart (table 5).

We emphasized these three novel findings in our updated conclusion. Lines 464-470.

Lines 391-396: Conclusion does not correspond to your objectives.

We rewrote the conclusion to correspond to our objectives and highlight our contribution to the current state of knowledge of ACHD HTx.

The new conclusion reads as follows: "The most common underlying diagnoses among ACHD HTx patients are transposition of the great arteries and Fontan/Glenn circulation. There are many complexities to ACHD HTx including PH assessment, immunological sensitization, additional surgical reconstructions, intraoperative bleeding, and Fontan specific complications (e.g., liver failure). Despite these challenges, the majority (59%)

of ACHD HTx recipients survive beyond 10-years post-operation. Unfortunately, less than 40% of patients with ACHD assessed for transplantation receive a donor heart. Further research is warranted to both improve outcomes for ACHD HTx recipients and to better utilize MCS for patients with ACHD HF." Lines 464-470.

Comment 15: Can you please state the Limitations of your narrative review?
Reply: Added a limitations section prior to the conclusion stating "The limitations of our review are that we only included articles in English that were indexed to PubMed and published since 2010. Expanding our search strategy to include other language, databases, and older articles could have resulted in a more comprehensive review." Lines 459-461.

Reviewer B

Comment: Meshulami et al. have reported a narrative review of the results of heart transplantation in adult congenital heart disease recipients. The authors have extensively reviewed the literature on this specific subject and this resulting review is well written and explore different aspects and challenges of this peculiar situation. I enjoyed the reading and have no specific remarks but some minor language errors.
Reply: Thank you for the kind words. We made minor language edits throughout the article utilizing the track-changes functionality.

Reviewer C

Mehulami et al. present a comprehensive overview of heart transplantation in patients with adult congenital heart disease (ACHD). The review is exhaustive of the literature and follows the appropriate guidelines. Some comments include:

Comment 1: The authors state they limit studies included from 2010-2023. Can they please explain why 2010 was set as the earlier date as it seems that inclusion further back (at least to 2000) would potentially be warranted?
Reply: We updated the text to state "We focused our review on articles since 2010 to provide information most relevant to current and future ACHD HTx cases." Lines 109-111.

Comment 2: We wanted a contemporary series that included current medications available, second and third generation MCS devices, and outcomes that reflect contemporary care practices.
Reply: Please note, while we only included papers published since 2010 some of the cases included in these papers date further back (e.g., Cohen et. al., Irving et. al., Kinsella et. al., and Shi et. al., include cases performed in the late 1980's).
Finally, we also included our study range as a limitation in our new limitation section. Line 459-461.

Comment 3: The authors describe the approach to pulmonary hypertension and discuss the lack of need for oversizing the donor allograft as well as treatment algorithms. A small figure describing the algorithm to the ACHD patient with pulmonary hypertension would be useful.
Reply: We added a new figure 1 “Approach to pulmonary hypertension in ACHD HTx candidates” describing the PH assessment and potential pre-transplantation medications. The approach to PH is often patient specific but a general guideline is provided. Line 249.

Comment 4: In line 279 the word "multivariable" should be used in place of multivariate
Reply: Updated the text to multivariable. Line 313.

Comment 5: One aspect that is discussed, but would be more useful from its own section would be a review of donor selection. As these recipients are younger, waiting for a more "perfect" donor is common, but this is weighed against the risk of waitlist mortality. Could the authors better expand on this.
Reply: We added a paragraph discussing the tradeoffs between waiting for a more perfect donor and waitlist mortality in the waitlist outcomes section. “There are no ACHD specific guidelines to inform donor selection. Given the young age of ACHD HTx candidates, physicians are potentially inclined to wait for more “perfect” hearts utilizing non-data-driven practices. Recent studies by Diamant et. al., (N=1,271) and Clark et. al., (N=827) demonstrated no survival benefit from utilizing hearts from non-lung donors nor from utilizing oversized donor hearts. Furthermore, Huntley et. al., found that among listed patients with ACHD waiting for a donor with negative viral serology, no history of alcohol use disorder, and larger size was associated with an increase in waitlist time and no increase in post-operative survival. Given the risk of death or delisting while waiting for a donor, we would recommend against delaying for a more “perfect” heart.” Lines 164-172.

As donor selection is relevant to multiple complications (e.g., PH and donor oversizing, sensitization among ACHD HTx recipients, and extensive artery reconstruction among Fontan/Glenn recipients) we did not want to create confusion/overlap by adding a separate complications section specific to donor selections.

Comment 6: The discussion on MCS is somewhat related, however is not completely in keeping with the rest of the manuscript and as written underdeveloped. Would either suggest expanding this further to include more justification about the limited supply of donor organs and then expand more on current limitations and specific disease processes where it would be useful or removing the section.
Thank you for the feedback, we have improved this section. Given the consistent shortage of cardiac allografts, we think it is important to mention MCS as a future direction to help more patients with ACHD HF.
Reply: Incorporating your feedback, we have restructured this section as follows:
- Shortage of cardiac allografts. Lines 415-418.

- Relative underutilization of MCS in patients with ACHD when compared to patients with non-ACHD HF. Lines 420-431.
- Overview of MCS in ACHD (goal of treatment, lesions treated, types of devices used).
Lines 433-440.
- Outcomes of MCS utilization in ACHD. Lines 442-449.

Comment 7: There are typographical errors throughout the manuscript that should be corrected.
Reply: We have thoroughly edited the article to eliminate typographic errors.