Peer Review File

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Reviewer A

The topic is timely and definitely of interest since ECMO is an evolving technology with growing fields of application.
Although the article is well written, I do have a small number of comments that need to be addressed.

Comment A1: The authors present three cases of their own practice to illustrate the implementation of ECMO in general thoracic surgery. The first case is a patient with an intrabronchial bleeding after bronchoscopic intervention, who was managed well without surgical intervention. The reviewer, therefore, would recommend to omit this case, since it doesn't really fit into the reviewed topic of the article.

Reply A1: Thank you for your review of our manuscript and insightful comments. We appreciate your insight into the applicability of the first case and have since replaced it with a different case. Our new inclusion demonstrates the applicability of ECMO in a case of airway compression in the setting of a large thyroid goiter. This case required the use of V-V ECMO to enable safe intubation and resection.

Changes in the text: Lines 186-205 were deleted from the text. The updated Case 1 is now included at Lines 110-123.

Comment A2: Doing their literature search, the authors missed a couple of publications presenting the use of ECMO during general thoracic surgery. Namely, these would be:
J Clin Med. 2023 May 29;12(11):3750
ASAIO J. 2023 Feb 1;69(2):218-224
ASAIO J. 2020 Aug;66(8):952-959
ASAIO J. 2016 Nov/Dec;62(6):743-746
J Thorac Cardiovasc Surg. 2015 Nov;150(5):e79-81
Since literature regarding the relevant topic is still not available in larger numbers, these should be included into the article, especially because most of them describe application of ECMO for lung volume reduction surgery, a surgical procedure that is otherwise not discussed in the manuscript at all.

Reply A2: We appreciate the multiple references supplied from the Ibbenbueren General Hospital group. The utility of low-flow VV ECMO as a means of ECCO2 removal is discussed briefly on 139-141 in the “Critically Ill Patient with Lung Failure” section of our manuscript and we have edited this section to better reflect its application in lung volume reduction surgery. Additionally, the JTCVS citation regarding VV ECMO use in the setting of a patient unable to tolerate single-lung ventilation was beneficial and has been incorporated into the manuscript.

Changes in the text: Lines 134-141 now reads: When this approach of planned

perioperative ECMO is extrapolated to other thoracic surgery settings, the patient population that may benefit from ECMO utilization drastically broadens. This includes patients undergoing thoracic resection that are unable to tolerate single-lung ventilation as represented in the case report provided by Redwan et al. or those requiring contralateral resection following pneumonectomy.(19, 20) It may also be important to consider the utility of low-flow ECMO for ECCO2R in the setting of anticipated hypercapnia during lung volume reduction surgery as demonstrated by Akil and colleagues (21-23)".

Reviewer B

I was allowed to review your manuscript. You have chosen an interesting and important subject, which I think is also very relevant for thoracic surgery and we thoracic surgeons have to deal increasingly with ECMO. I have some comments:

Comment B1: Sections ECMO modalities pages 4-7: in my view much too long and only conveys basic knowledge about ECMO. I recommend that you focus your manuscript much more on the application of ECMO specifically in thoracic surgery. ECMO has the following indications in thoracic surgery: 1. in technically complex resections of central airways to ensure technical operability (Example: Use of Extracorporeal Membrane Oxygenation for Major Cardiopulmonary Resections. Koryllos A, Lopez-Pastorini A, Galetin T, Defosse J, Strassmann S, Karagiannidis C, Stoelben E. Thorac Cardiovasc Surg. 2021 Apr;69(3):231-239. doi: 10.1055/s-0040-1708486. 2. in functionally borderline operable patients e.g. LVRS or lung carcinoma, to ensure functional operability. 3. for thoracic complications e.g. pleural empyema, thoracic haemorrhage, revisions, trauma, ...

Reply B1: We appreciate the suggestion to improve clarity and cohesiveness of the manuscript. As such, we have deleted the section entitled "ECMO Modalities" and have instead restructured the manuscript to offer an explanation of application in various thoracic surgery settings. The citation from Koryllos et al, was beneficial and has been incorporated into the manuscript. Thank you for these suggestions.

Changes in the text: The prior section entitled "ECMO Modalities" on Pages 4-7 has been deleted. The manuscript has been restructured in an effort to increase cohesiveness and contains new headings to aid in this attempt. Additionally, tables detailing search strategy have been included as Supplemental Tables 1 and 2 on Lines 256 and 259.

Comment B2: You should create a scheme for the application and indications of ECMO in thoracic surgery, this will be much clearer for the reader. You should also structure the manuscript according to the indications and include suitable case studies, ideally with pictures.

Case 1 is interesting, but describes a patient without thoracic surgery. For this manuscript with a focus on thoracic surgery, another surgical case would be more appropriate.

Reply B2: We appreciate your suggestions and have restructured the manuscript accordingly. As such, new headings now read: “ECMO in General Thoracic Surgery”, “ECMO for Potential Airway Compromise”, “The Critically Ill Patient with Lung Failure”, and “ECMO in Complex Resections and Airway Reconstruction”. The appropriate cases are included within these sections for reference. Additionally, Case 1 was deleted and replaced with a new case detailing the utility of V-V ECMO in a complex airway case.

Changes in the text: The new headings can be found on Lines 88, 96, 125, 170 and 220. The new Case 1 is included on Lines 109-123.

Comment B3: ECMO in general thoracic surgery: again, I feel that the text lacks clarity. I recommend a discussion of the relevant literature and structuring the section according to the indications or applications of ECMO in thoracic surgery: technical resectability, functional operability, thoracic complication management and, if applicable, thoracic trauma. At the moment the manuscript lacks a clear structure, good case studies and a focus on thoracic surgery. The manuscript is too general. In addition, the references should be checked and added.

Reply B3: In an effort to increase clarity in this section of the manuscript, we have edited the text to better indicate (1) the use of ECMO in cases of airway compromise (2) ECMO in critically ill patients with lung failure (3) ECMO in complex airway reconstruction and resections

Changes in the text: The text has been largely restructured in an effort to increase cohesiveness. Please see the response to Comment B2 for improved headings and organizational structure of the manuscript.

Reviewer C

Comment C1: Well written review of ECMO applications. Limited meta-analysis compared to introduction/abstract's expectations, but not surprising given limited literature in use in General Thoracic Surgery.

Reply C1: Thank you for your review of our manuscript. In response to other reviewers, we have edited the introduction section to provide more clear expectations for the larger analysis. Additionally, we have shifted search strategy tables to the Supplemental Tables section of the manuscript instead of the main body.

Changes in the text: Supplemental Table 1 and 2 can be found on Lines 256 and 259.

Reviewer D

Dr. D'Cunha and his team submitted the manuscript entitled "Successful Implementation of ECMO for General Thoracic Surgery". The effort his team has put into this work should be admired.

Overall, we find the manuscript well-structured, consisting of three main parts:

Introduction of ECMO, Case series (3 cases), and a Summary of ECMO in thoracic surgery. The introduction of ECMO is well-summarized, providing a clear understanding of the topic. However, we share some concerns regarding the manuscript that need to be addressed:

Comment D1: Author's Opinions and Review Articles: The manuscript appears to include a significant number of the authors' own opinions, and it does not strictly conform to a standard review article format. To enhance the scientific rigor and objectivity of the paper, we recommend reframing the content to provide a more balanced and evidence-based review of ECMO use in general thoracic surgery.

Reply D1: Thank you for taking the time to review our manuscript. We have made changes to provide a more evidence-based review of the literature. Additionally, we have included several additional citations at the direction of other reviewers.

Changes in the text: The text reading "Teams led by the senior author (JD) have been performing complex general thoracic procedures with ECMO support for over a decade" was deleted from Lines 282-283. Additionally, the text reading "multiple studies and our own experience over the last several years has demonstrated reduced complication rates and duration of post-operative mechanical ventilation when utilizing ECMO over CPB in this setting" was removed from 269-271.

Comment D2: ECMO use for lung transplantation is standard practice. It should not be discussed in this manuscript entitled "Implementation of ECMO for General Thoracic Surgery".

Reply D2: Thank you for this comment. At the request of other reviewers, we have edited this section of the manuscript to improve cohesiveness and brevity. We are hopeful that the revisions made will better demonstrate our inclusion of lung transplant as a strong historic example of ECMO use in lung transplant as the foundation from which planned operative ECMO use has developed.

Changes in the text: Lines 126-141 now read: "When considering the applicability of non-emergent ECMO, it is relevant to consider the utilization of ECMO both for diagnostic procedures and as a bridge to recovery or lung transplantation.(14) This patient population, often with varying degrees of concomitant cardiac dysfunction, has demonstrated reduced complication rates and shorter duration of post-operative mechanical ventilation.(15-17) Of note, V-A ECMO is often preferred to V-V ECMO in these cases due to the added cardiac support, particularly in patients with right ventricular dysfunction. Intraoperative V-A ECMO can often be maintained post-operatively or converted to V-V ECMO in patients with adequate cardiac function.(18) In those needing isolated support, V-V ECMO is a reasonable approach throughout the perioperative period. When this approach of planned perioperative ECMO is extrapolated to other thoracic surgery settings, the patient population that may benefit from ECMO utilization drastically broadens." This is under the new heading of "The Critically Ill Patient With Lung Failure" and is supplemented by Case 2.

Comment D3: VV-A ECMO should not be considered as a hybrid cannulation. This is just one type of VV ECMO cannulation.

Reply D3: We appreciate the need for clarification in this section and at the suggestion of other reviewers have removed this section from the text in favor of emphasis on case-based discussion of atypical applications of ECMO in thoracic surgery.

Changes in the text: The section entitled "ECMO Modalities" previously on Pages 4-7 has been deleted. Cases 1, 2, and 3 are included on Lines 109-123, 146-168, and 197-218 respectively.

Comment D4: To prevent limb ischemia, the use of 15 Fr femoral artery cannula without distal perfusion cannula is becoming more standard. The complications of dual lumen canula listed in Line 157-158 is not specific to dual lumen cannulation. Additionally, highlight how the use of fluoroscopy (and TEE) can help avoid these complications.

Reply D4: Thank you for noting this lack of clarity in our manuscript. In response to comments from other reviewers, this section of the manuscript has been deleted.

Changes in the text: The section entitled "ECMO Modalities" previously on Pages 4-7 has been deleted.

Comment D5: The challenges associated with cannulation in the lateral decubitus position should be further elaborated. The cannulation with left lateral decubitus position entails the potential risks of aortic dissection or retroperitoneal hematoma even with the use of micropuncture catheter.

Reply D6: We appreciate the need to further detail potential complications of cannulation in the left lateral decubitus position and have included elaboration to this point.

Changes in the text: Lines 187-188 now read: "This is especially beneficial in cases necessitating left or right lateral decubitus positions, as establishing expedient vascular access after positioning can be quite difficult.

Reviewer E

I have learned from reviewing your narrative review on ECMO for General Thoracic Surgery. The thematic you discuss is interesting despite it has been already discussed in literature. Your single centre experience can add knowledge on the proper use of ECMO in complex thoracic procedure, but the paper has different lack points you should focus on.
Thus, I suggest making major modifications on the article.

Comment E1: Line 35 and line 36: there is a mistake with the acronym EMCO, please correct.

Reply E1: Thank you for identifying this oversight. We have corrected to ECMO.

Changes in the text: “EMCO” was replaced with “ECMO” on Line 42.

Comment E2: Line 60: you have drawn conclusions about the advancement of V-V ECMO too fast. The application of V-V ECLS in COVID-19 patients is partly controversial and the actual benefit of the technique is still debated among experts, as demonstrated in these papers.
Karagiannidis C,Strassmann S, Merten M, Bein T, Windisch W, Meybohm P, et al. High In-Hospital Mortality Rate in Patients with COVID-19 Receiving Extracorporeal Membrane Oxygenation in Germany: A Critical Analysis. Am J Respir Crit Care Med. 2021;204(8):991-4.
Fanelli V, Giani M, Grasselli G, Mojoli F, Martucci G, Grazioli L, et al. Extracorporeal membrane oxygenation for COVID-19 and influenza H1N1 associated acute respiratory distress syndrome: a multicenter retrospective cohort study. Crit Care. 2022;26(1):34.
Dreier E, Malfertheiner MV, Dienemann T, Fisser C, Foltan M, Geismann F, et al. ECMO in COVID-19-prolonged therapy needed? A retrospective analysis of outcome and prognostic factors.Perfusion. 2021;36(6):582-91. VV-ECMO has been approved with good results in mortality rate in other infections like the Middle East Respiratory Syndrome (MERS) and the H1N1 influenza. Therefore, you can cite these two studies if you want to corroborate the advancement of V-V ECMO in ARDS.
Arabi YM, Al-Omari A, Mandourah Y, et al. Critically ill patients with the middle east respiratory syndrome: a multicenter retrospective cohort study. Crit Care Med. 2017;45:1683-1695.Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. JAMA. 2009;302:1888-1895.

Reply E2: Thank you for your suggestions. At the request of other reviewers, we have removed the section of the manuscript entitled “ECMO Modalities” containing much of the information you referenced. We did include reference to the H1N1 and MERS outbreaks at your suggestion, as well as clarify that long-term outcomes regarding the use of ECMO in the COVID-19 pandemic are still being collected.

Changes in the text: The text now reads: “The use of ECMO in the management of acute respiratory distress syndrome (ARDS) during the recent COVID-19 pandemic and previously during the H1N1 influenza and Middle Eastern Respiratory Syndrome (MERS) outbreaks further demonstrates this advancement.(2-5) While long-term data are still being collected, the growing understanding of ECMO has led to an expansion of its use far beyond historic indications” on Lines 69-74

Comment E3: Line 71: how many papers and what kind of articles did you find during your research? Please specify in the Discussion paragraph. In addition, Zhang et al and Reeb et al have recently published, respectively, an original paper and an editorial board about this topic. Please add to your Discussion. (Zhang Y, Luo M, Wang B, Qin Z, Zhou R. Perioperative, protective use of extracorporeal membrane oxygenation in complex

thoracic surgery. Perfusion. 2022 Sep;37(6):590-597 / Reeb J, Olland A, Massard G, Falcoz PE. Extracorporeal life support in thoracic surgery. Eur J Cardiothorac Surg. 2018 Mar 1;53(3):489-494.)

Reply E3: Thank you for your suggestions. At the suggestion of other reviewers requesting increased cohesiveness and brevity, we have restructured the manuscript to better emphasize ECMO applications in thoracic surgery settings as well as case-based applications. As such, the "ECMO Modalities" section of the manuscript was removed. As such, the references you suggested were included in the manuscript. Additionally, our search strategy for this limited review is included in Supplemental Tables 1 and 2, however as this was not a formal literature review and instead a narrative review with case series the exact number of articles reviewed is not provided.

Changes in the text: "ECMO Modalities" was deleted from Pages 4-7. Lines 72-74 now reads: "While long-term data are still being collected, the growing understanding of ECMO has led to an expansion of its use far beyond historic indications.(6, 7)" and includes the provided citations from Zhang and Reeb. Supplemental Tables 1 and 2 can be found on Lines 256 and 259.

Comment E4: The Main Body of the manuscript lacks citation about Novalung device and its use in bridging to LTx patients. (es. Waldemar Bartosik and others, The Novalung interventional lung assist as bridge to lung transplantation for self-ventilating patients – initial experience, Interactive CardioVascular and Thoracic Surgery, Volume 13, Issue 2, August 2011, Pages 198–200).

Reply E4: We appreciate the need for further discussion of advanced technologies serving as a bridge to lung transplant in the current era. At the request of other reviewers we have made an effort to increase the brevity and cohesiveness of the manuscript and feel that discussion of advanced technologies remains outside the scope of this review. We do include discussion about the use of ECMO as a bridge to and adjunct during lung transplantation.

Changes in the text: Lines 126-136 now reads: "When considering the applicability of non-emergent ECMO, it is relevant to consider the utilization of ECMO both for diagnostic procedures and as a bridge to recovery or lung transplantation.(14) This patient population, often with varying degrees of concomitant cardiac dysfunction, has demonstrated reduced complication rates and shorter duration of post-operative mechanical ventilation.(15-17) Of note, V-A ECMO is often preferred to V-V ECMO in these cases due to the added cardiac support, particularly in patients with right ventricular dysfunction. Intraoperative V-A ECMO can often be maintained post-operatively or converted to V-V ECMO in patients with adequate cardiac function.(18) In those needing isolated support, V-V ECMO is a reasonable approach throughout the perioperative period. When this approach of planned perioperative ECMO is extrapolated to other thoracic surgery settings, the patient population that may benefit from ECMO utilization drastically broadens" under the heading "The Critically Ill Patient with Lung Failure".

Comment E5: I would supplement case series with information in order to make it more precious and interesting to the readers. More detailed data can be useful to other ECMO centre to accumulate knowledge and confront similar situations:
If you have any anticoagulation management protocol, please add. It can be interesting in these specific situations where the risk of bleeding is high.
How did you manage ECMO flow and sweep gas in different cases?
Please add information about mechanical ventilation parameters before and during ECMO running.
Please add information about hemodynamic parameters and vasopressors drugs, if used.
Please add detailed information about ECMO discontinuation (postoperative day), mechanical ventilation days, ICU stays and, if available, hospital stays.
You should indicate if any complications (infection, bleeding, thrombosis) occurred during ECMO running.
Case 2: did you perform ECMO placement before or after anaesthesia induction?
Case 3: patient already suffered from idiopathic pulmonary fibrosis (FIP) as described in anamnesis and, maybe, he underwent lung transplantation for his end-stage disease. Please discuss your choice in submitting the patient to biopsy.

Reply E5: We appreciate your comments and critical review of the manuscript, however we are hesitant to include granular data in the case series as our institutional approach for ECMO in thoracic surgery is detailed throughout the manuscript. At the request of other reviewers, we have deleted the "ECMO Modalities" portion of the manuscript as this is well-detailed in current literature. We have updated the cases to provide clarity as to the utilization of ECMO in these thoracic surgery patients. In Case 2 (now Case 3), the patient was placed on ECMO following induction of anesthesia following discussion with our anesthesia colleagues in a multidisciplinary team approach. Case 1 is now included as an example of a patient placed on ECMO prior to induction of anesthesia. The patient in Case 3 (now Case 2) underwent lung biopsy as part of the routine pre-transplant workup at our institution and in an effort to confirm diagnosis and disease progression.

Changes in the text: The "ECMO Modalities" section of the manuscript on Pages 4-7 was deleted. Case 3 (the prior Case 2 referenced) is included on Lines 197-217. Case 1 is included on Lines 110-123. The prior Case 3 (now Case 2) is included on Lines 147-168.

Reviewer F

Comment F1: I was left a bit confused with the structure of the article. Is this a narrative review, literature review, case series? I truly think you do not need whole descriptions of these cases. It just adds to the lack of being precise and concise in writing. This is not a case report/series, and you can simply discuss these alternative applications in separate paragraphs and accompany discussion with supporting literature (if anything was published) or authors own experience/practice. For example, you could have a title "nontraditional applications of ECMO" with subtitles such as for

example “Uncontrolled airway bleeding”, “Elective surgeries with high risk of airway obstruction”, “Lung transplantation” etc…
Overall, interesting and timely topic, however with lack of focus. This is a complex subject, and one should clearly define goals of this review and stick to them. Using more tables would significantly help organization of the article.

Reply F1: We appreciate the need to increase clarity and cohesiveness of the article. As such, and at the request of yourself and other reviewers, we have deleted the “ECMO Modalities” section of the Manuscript. We have included new headings, as well as included the appropriate cases in each of these sections for reference.

Changes in the text:

The following headings are now included in the manuscript:

Line 88: ECMO in General Thoracic Surgery
Line 96: ECMO for Potential Airway Compromise
Case 1: 109-123
Line 125: The Critically Ill Patient with Lung Failure
Case 2: 146-168
Line 170: ECMO in Complex Resections and Airway Reconstruction
Case 3: 197-218
Line 212: When to Avoid ECMO in General Thoracic Surgery

Comment F2: Line 65 “We aim to provide a concise review of current ECMO techniques and applications in thoracic surgery “ I think the article is missing technical details on ECMO management for this sentence to be accurate. It would be useful to have a more structured approach. For example, current common indications and contraindications with an accompanying table. Anticoagulation management differences between VV and VA ECMO. Considerations with low flow states. Other complications. Monitoring of adequacy of perfusion and troubleshooting of issues (malperfusion, AI etc…)
If the focus of this narrative review is to demonstrate ECMO applications outside of traditional indications, then I would suggest to have a small paragraph discussing each individual additional application, and adding a table of those newer indications especially for example performing lung transplants on VA ECMO, other complex surgeries – breaking these down based on pathology and specific considerations. One question reader may have is when do you start ECMO before complex surgery vs. just placing wires/access and “crashing” on ECMO when needed.

Reply F2: Thank you for identifying these areas for improvement. As is addressed in other reviewer comments, we have restructured the manuscript with the goal of providing more concise and clear information regarding our focus. Additionally, we have deleted the “ECMO Modalities” section previously on Pages 4-7. Please see “Changes in the Text” in response to Comment F1 for the new manuscript structure.

Changes in the text: Please see “Reply F1” and the associated “Changes in the text”.

Comment F3: One absolutely needs to touch on ECMO limitations – what if you can't put someone on ECMO?
Use of ECMO in COVID patients is mentioned in several places. We have all experienced serious thrombotic complications in this patient population when placed on ECMO. I suggest reviewing if there is anything published on the subject and discuss utility of ECMO in this population considering pros and cons.

Reply F3: Thank you. The complications and limitations of ECMO are detailed in the manuscript, including infection, thrombosis, cannula dislodgement, recirculation syndromes, and others. We hope that by improving overall manuscript organization as detailed in other comments the limitations and risks of ECMO are now more visible to the reader. We have updated the "When to Avoid ECMO in General Thoracic Surgery" to better reflect the limitations of ECMO.

Changes in the text: Lines 220-229 now reads: "While the utility of ECMO is rapidly advancing in the field of thoracic surgery, it is also worth noting that some patients remain poor or prohibitive candidates for ECMO. As is true of all life-sustaining extraordinary measures, the ultimate goal of bridge therapy must be identified prior to initiation. While absolute contraindications to ECMO remain few (including intracranial processes with likelihood of bleed, irreversible pulmonary destruction without option for transplant, advanced metastatic disease, etc.), the relative contraindications remain widely debated and circumstantial. In certain practices, it may be helpful for the thoracic surgeon become comfortable implementing ECMO into their practice alongside other cardiothoracic surgeons with ECMO expertise. "

Comment F4: Line 249 "The utilization of ECMO has increased exponentially in recent years." – missing a reference.

Reply F4: Thank you for recognizing this. A citation has been included.

Changes in the text: Hadaya and colleagues are now cited on Line 89.

Comment F5: Line 306 typo "my".

Reply F5: Thank you for recognizing this. This has been changed.

Changes in the text: Line 239 now reads: ""toolbox" of approaches for complex general thoracic procedures that may otherwise not have".