

Peer Review File

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Reviewer A

In this retrospective investigation, two different strategies for ECMO as bridge to lung transplantation were analyzed in two centers: a traditional protocol versus an extended selection protocol (violation of at least one of the following exclusion criterium: age \geq 55y, steroid use, musculoskeletal deconditioning, BMI \geq 30 or \leq 18.5 kg/m², non-pulmonary organ dysfunction, unmanageable infection). In the traditional patient cohort 9 of 15 patients were successfully transplanted, while 16 of 30 patients of the expanded criteria group underwent LTx. No difference was detected between both groups in terms of delisting/death on waiting list, 1y-post LTx survival or 1y-post ECMO survival.

The authors are to be congratulated for their results in a challenging patient population. This investigation represents a step towards more rationale rather than dogmatic use of ECMO-BTT-criteria (e.g. acceptance of elderly IPF patients, and candidates without prior waitlisting). The results compare well with the strict Columbia criteria.

Comment 1: Only drawback: From my point of view donor information should be included in the analysis.

Reply 1: Thank you for the comment. We agree with the reviewer that lack of donor data is one of the limitations of the study. Unfortunately, we do not have the donor information available currently secondary to changes in our electronic recording systems.

Changes in Text 1: We have revised study limitations “Our study did not evaluate and report the details of transplant donors. Consideration for ECMO as bridge therapy is likely impacted by the availability of donors, but this is beyond the scope of the current study”. (Page 9, line 8-10)

Reviewer B

This study is a two-center retrospective observational study, whose objective was to determine whether one-year post-transplant and post ECMO survival are impacted by the selection of lung transplant recipients in accordance, or not, with an institutional protocol («traditional» versus « expanded » criteria).

Patients under ECMO as bridge-to-transplant and as bridge-to-transplant decision were considered as «traditional criteria » if they conformed to the institutional protocol which excludes patients \geq 55 years, maintained on steroids, unable to participate in physical therapy or unable to achieve 6-minute walk distance \geq 200 meters prior to hospitalization, have a BMI \geq 30 or \leq 18.5 Kg/m², end-organ dysfunction (including

creatinine clearance < 50 mL/min), or unmanageable infections. Patients who received ECMO as bridge to lung transplantation or decision and did not conform to the protocol were named « expanded criteria ».

Taking into account the limited organ availability, and the invasiveness of ECMO BTT therapy, this study could provide useful information to improve the selection of patients who really benefit from this rescue therapy. However, there are some major limitations with regard to the interpretation and extrapolation of the results.

Comment 1: Firstly, the very small size of the cohort strongly limits the power of the statistical analysis to detect differences in one-year survival. The « traditional criteria » group consists in 15 patients (9 of them being successfully transplanted). The « expanded criteria » group consists in 30 patients (16 of them being successfully transplanted). Statistical analysis of one-year post transplant survival consisted in an univariate analysis of two very small cohorts, with differences in the indications of lung transplantation, making impossible to perform a multivariate analysis in order to assess independent risks factors for one-year post transplant mortality.

Reply 1: Thank for your comment. We agree with the reviewer that due to small sample size it was not possible to the assess the independent risk factors for one year post transplant mortality.

Changes in Text 1: We have clarified that in the study limitations: “The small cohort size limited some of the statistical comparisons; underpowered to detect differences between number of deviations.” (Page 9, line 6-7)

Comment 2: Secondly, the choice of the primary outcome is debatable. I think the primary outcome should be one-year post-transplant survival; and never transplanted patients should be excluded of the analysis. Comparing one-year survival of the all patients, transplanted and not, together, seems not to be relevant.

Reply 2: Thank you for the comment. Our first primary outcome was one year post transplant survival and table 2 consists of outcomes of only those patients who received transplant. Other primary outcome was One year post ECMO survival (Table 4-last Row).

Changes in Text 2: “Our primary outcomes were: the odds of one-year post-transplant survival amongst those who received a transplant and one-year post-ECMO survival” (Page 4, line 22-23):

Comment 3: Thirdly, this study compares one-year survival depending on the adherence of an institutional protocol. This limits the extrapolation of the results.

Reply 3: Thank you for the comment. We agree with the reviewer that result of our study may not be applicable to other centers.

Changes in Text 3: We have included this in the study limitations: “Results of our study may not apply to other transplant centers due to different patient selection processes, availability of ECMO and donor organs, and individual center’s transplant and ECMO experience.” (Page 9, line 11-12)

Comment 4: Can the authors explain why some COPD / emphysema patients received ECMO as bridge to transplant?

Reply 4: 22 patients had more than 1 underlying lung disease. Patients with COPD/ Emphysema all had another contributing lung disease, most commonly pulmonary fibrosis (CPFE) and one had tension pneumothorax with a broncho-pleural fistula.

Changes in Text 4: We have updated the footnote on Table 2: “†22 Patients had more than 1 underlying lung disease; All patients with COPD/ emphysema had more than 1 underlying lung disease.”

Comment 5: The number of ECMO complications is very high (intracranial bleeding: 56%) and should be discussed in the discussion section.

Reply 5: Thank you for the comment. It looks like rows in the previous table 3, now table 4 (pdf file sent to reviewers) were moved up that mixed the numbers and the percentages.

We have modified that table with clearly marked rows. (Table 4 in the revised manuscript)

Please see the response below the next comment.

Comment 6: How do the author explain the very high rate of one year survival in transplanted patients (higher than Bennazzo et al, Hoezeneger et al.) despite the very high rate of ECMO complications? This should be added in the discussion section.

Reply 6: Thank you for the comment. We have revised the manuscript and added text to the results and discussion sections.

Changes in Text 6:

Result section “Extracranial bleeding of any severity was the most common complication. Intracranial bleeding occurred in 3 patients (7%) all from the expanded group and was fatal in one patient who was also the only patient to suffer from cerebral infarction (Table 4). Among the other two patients with intracranial bleeding, one had subdural hematoma without neurologic deficit, and one was with subarachnoid hemorrhage that was reported as small and resolved on follow up imaging in a week (Page 6, line 8-13)

Discussion section “Despite significant progress in ECMO techniques and devices, patients receiving ECMO as a bridge therapy are at higher risk of complications due to their underlying diagnosis, pretransplant mechanical ventilation and ability to participate in

physical therapy while on ECMO (13, 14). Previous reports of complications in ECMO-BTT patients have varied from center to center and how the complications were reported. In our study we reported ECMO related complications during the bridging period and post-transplant for those patients who needed ECMO post operatively. Biscotti et al and Tipograf et al from Columbia medical center reported higher complication rates in patients who did not receive the transplant despite following strict selection criteria and delisting high percentage of patients, suggestive of increased risk of complications in sicker patients (6, 9). Hoetzenecker et al reported an overall cerebrovascular rate of 4.2% and bleeding complications in 35% of ECMO-BTT patients (10). Benazzo et al reported very few complications during the bridging period. However, majority of their patients remained on ECMO after receiving the transplant and had higher rates of complications including ECMO site complications (11). In our study complications occurred more in the expanded group as compared to traditional group that might be because those patients were older and sicker. Offering bridge therapy to such a sick patient population does come with the risk of complications but it brings the possibility of getting transplant without which death is certain for them.” (Page 8, line 7-22)

Comment 7: How do the authors explain the high rate of one year survival in patients with ECMO BTT but not transplanted (20%)?

Reply 7: Thank you for your comment. Among the 20 patients who did not receive the transplant, 16 patients died while they were on ECMO (detailed in results section Page 6, line 21-25). Among the 4 surviving patients at 1-year, these were placed on ECMO secondary to an inflammatory lung disease (e.g. COVID, other viral ARDS, or vaping induced lung injury). They completed transplant evaluation but were ultimately not listed secondary to sign of clinical improvement and were able to be de-canulated.

Comment 8: How do the authors explain the low adherence rate to their local protocol (twice as many patients in the « expanded criteria » group)?

Reply 8: Thank you for the comment. As we detailed in the method section (Page 4, line 9-14) “Exceptions to the protocol are permitted on a case-by-case basis based on the assessment by a multidisciplinary team. These exceptions are granted after review by the medical transplant and surgical transplant team for patients who do not have other therapeutic options in the absence of absolute contraindications to transplant. At our institution patients are evaluated for ECMO eligibility even if they are not active on transplant wait list”. In general, our center’s protocols are intended for general guidance. Individual decisions are made on a case-by-case basis.

Comment 9: Abstract section (page 3 line 14-15) and results section (page 7 line 20 – 21) : percentages are unclear, I suggest to clarify.

Reply 9: Thank you for the comment.

Change in Text 9: We have clarified the text in the abstract and result section of manuscript “A total of 45 patients received ECMO as bridge therapy. Out of those 29 patients (64%) received ECMO as bridge to transplant (ECMO-BTT) and 16 patients (36%) as bridge to decision to transplant. Page 2, line 11-12 and Page 5, line 11-13

Comment 10: Result section (page 10, line 5): the percentage of 56% is unclear, I suggest to clarify

Reply 10: Thank you for the comment.

Change in Text 10: We have clarified the percentage and added text “56% (25 out of 45 patients) (Page 7, line 19)

Comment 10: Table 3: I think there is a mistake in the number of patients of the « expanded criteria » group (30 patients in the expanded criteria group, 13 died in hospital and 18 survived at one-year)

Reply 10: Thank for the comment. We have revised the last row of table 3. (New Table 4)

Reviewer C

This is a nicely written study that describes the outcomes in 2 center lung Transplant program. In the small population, the investigators show that outcomes are not different when using traditional candidate selection as opposed to expanded candidate selection. This study is limited by the small size, retrospective nature and somewhat subjective nature of selection of transplant candidates for this specific patient population.

Comment 1: Please described traditional as well as expanded selection criteria at your institution in a table format which will make it easier for the readers.

Reply 1: Thank you for the comment. We have included a table of exclusion criteria from institutional ECMO-BTT protocol. (Table-1 in the revised manuscript)

Comment 2: Please provide clear definitions ECMO-bridge to transplant and ECMO-bridge to transplant decision.

Reply 2: Thank you for the comment.

Changes in Text 2: We have added to the method section “Patients were categorized as ECMO bridge to transplantation if they had an active transplant listing status, and bridge to decision to transplant if they did not have active listing status prior to ECMO cannulation. (Page 4, line 2-3)

Comment 3: Correct typo in the word expanded in figure 1.

Reply 3: Thank you for noticing this. It has been corrected.

Reviewer D

This is a brief report abstracting the experience of two transplant programs and their outcomes bridging patients to decision or to lung transplant with ECLS.

The manuscript is very well written and clear. The discussion is comprehensive, and the limitations are well-stated.

I have a few questions and recommendations.

Comment 1: Title, since the authors include Heart/Lung Transplants in their analysis this should be added to the title, or they should remove H/L patients from their analysis.

Reply 1: Thank you for the comment. We have updated the title.

Comment 2: Results, since this is a 17-year experience it is difficult to understand from the manuscript if their findings are associated to the extension of their selection criteria for bridge to transplant or there are associated to changes in cannulation strategies, ECLS management and patient care.

Per Table 1, the extended criteria group had twice the number when compared to the traditional group.

Did you have era related differences between the groups? Meaning early in the experience adoption of criteria was more uniform as the programs felt more comfortable their started liberalizing them? Particularly since more often than not you extended your recipient criteria according to this data.

This in a way can also explain the finding of a better 1-year survival in the extended criteria group.

Reply 2: Thank you for the comment. During the study period (2009-2021) total number of transplant patients who received ECMO as bridge therapy increased significantly. We have included Figure 2 and 3 to show the trends.

Changes in Text 2: We have added text in the result section “Total number of patients who received ECMO as bridge therapy increased during the study period. During the first half of the study both groups had almost same number of patients. However, in the second half the expanded group had more than twice the number of patients as compared to the traditional group (Figure 2 and 3)” (Page 5, Line 14-17)

Changes in Text 2: We have also added text in the methods section “During the time frame of the study (2009-2021), there were no significant changes in institutional ECMO management practices. Type of anticoagulation utilized (heparin to bivalirudin) and antibiotic prophylaxis use shifted.” (Page 4, line 19-21).

Comment 3: Table 3 raises some concerns. Are these ECMO related complications during bridging or after transplant? it is also unusual to see this high percentage of CVA and intracranial hemorrhage. Do you attribute this to your anticoagulation practices? These outcomes are not discussed in the results. Maybe this is related to the brief report word limitation.

Reply 3: Thank you for the comment. It looks like rows in the previous table 3, now table 4 (pdf file sent to reviewers) were moved up that mixed the numbers and the percentages.

We have modified that table with clearly marked rows. (Table 4 in the revised manuscript)

Changes in Text 3:

Result section: “Extracranial bleeding of any severity was the most common complication. Intracranial bleeding occurred in 3 patients (7%) all from the expanded group and was fatal in one patient who was also the only patient to suffer from cerebral infarction (Table 3). Among the other two patients with intracranial bleeding, one had subdural hematoma and one was with subarachnoid hemorrhage that was reported as small and resolved on follow up imaging in a week” (Page 6, line 8-13)

Discussion section: “Despite significant progress in ECMO techniques and devices, patients receiving ECMO as a bridge therapy are at higher risk of complications due to their underlying diagnosis, pretransplant mechanical ventilation and ability to participate in physical therapy while on ECMO (12, 13). Previous reports of complications in ECMO-BTT patients have varied from center to center and how the complications were reported. In our study we reported ECMO related complications during the bridging period and post-transplant for those patients who needed ECMO post operatively. Biscotti et al and Tipograf et al from Columbia medical center reported higher complication rates in patients who did not receive the transplant despite following strict selection criteria and delisting high percentage of patients, suggestive of increased risk of complications in sicker patients (6, 9). Hoetzenecker et al reported an overall cerebrovascular rate of 4.2% and bleeding complications in 35% of ECMO-BTT patients (10). Benazzo et al reported very few complications during the bridging period. However, majority of their patients remained on ECMO after receiving the transplant and had higher rates of complications including ECMO site complications (11). In our study complications occurred more in the expanded group as compared to traditional group that might be because those patients were older and sicker. Offering bridge therapy to such a sick patient population does come with the risk of complications but it brings the possibility of getting transplant without which death is certain for them”. (Page 8, line 7-22)

Comment 4: Lastly, bridge to decision can be significant stressor for the health care team caring for the patient and family. This is the reason why some programs only bridge patients that are known to them. How does your program decide who to cannulate and bridge to decision? Do you consent to transplant by proxy?

Reply 4: We agree with the reviewer, that the bridge to the decision can be challenging for the healthcare team and very stressful for patient and family. Eligibility for ECMO-BTT or bridge to transplant decision is assessed by the medical transplant and surgical transplant team for patients who do not have other therapeutic options in the absence of absolute contraindications to transplant. At our institution patients are evaluated for ECMO eligibility even if they are not active on transplant wait list. For the most part, we strive to obtain first person consent for transplant and transplant evaluation. For ECMO, we consent the patient's family member with the understanding that recovery or transplant may not be ultimately possible.

Reviewer E

Comment 1: My biggest concern of this study is the statistical analysis. I believe they cannot prove the non-inferiority with their analysis. If they want to discuss about the non-inferiority, they need to set up the noninferiority margin beforehand and needs to compare with confidence interval. With small sample size, confidence interval tends to be wider and might be difficult to discuss the non-inferiority.

Reply 1: Thank you for the comment. We agree with the reviewer that our study was not aimed to prove non-inferiority. We believe that a randomized controlled trial would be a suitable study to prove non-inferiority.

Their analysis is based on the null hypothesis that the primary endpoints of standard criteria and expanded criteria are similar. And p value was higher than 0.05. That does NOT mean "outcome of standard criteria and expanded criteria are similar". It means "we cannot tell that there was difference in outcomes between standard criteria and expanded criteria". Also the p value might have not reach to statistical significance because of the small sample size. I understand the challenge how to set up the cohort and how to measure the outcome to correctly evaluate the appropriateness of expanded criteria in this study. I am not convinced including ECMO bridge to decision is appropriate way to discuss the ECMO criteria.

Reply 2: Thank you for the comment. We agree that this is a hypothesis generating study and results would need to be confirmed in a prospective nature. We have outlined this in our limitations section and conclusion section.

Changes in Text 2: "The limitations of our study include the inherent bias of a two-center, retrospective data collection, and analysis. The small cohort size limited some of the statistical comparisons; underpowered to detect differences between number of deviations. Outcomes may be limited by selection bias by who was selected to proceed to ECMO as a bridge to transplant versus recovery. Our study did not evaluate and report the details of transplant donors. Consideration for ECMO as bridge therapy is likely impacted by the availability of donors, but this is beyond the scope of the current study. Also, our study did not evaluate detailed descriptions of different ECMO modalities. Results of our study may not apply to other transplant centers due to different patient selection processes, availability of ECMO and donor

organs, and individual center's transplant and ECMO experience. Also, the outcomes may be affected by local immunosuppression protocol, surgical and ECMO techniques.

This two-center study suggests that stringent selection criteria may limit the transplant opportunity for patients who may otherwise have favorable outcomes with ECMO- BTT. Future multicenter, prospective studies are needed to evaluate the impact of individual selection criteria, develop better prediction tools, and prove non-inferiority with expanded selection criteria." (Page 9, Line 5-17)

Comment 3: I encourage the authors to describe more detail regarding the de-listed patients, patients weaned from ECMO, patients never listed. Some of them showed improvement and the candidacy was differed. We do see this happens among the patients with ARDS.

Reply 3: Thank you for the comment.

Changes in Text 3: We have revised the manuscript and added text "table 5 shows outcomes of 20 patients who were not transplanted, 4 patients died (1 patient had right ventricular dysfunction, 1 suffered from stroke and 2 patients developed hemorrhagic shock) while on the waitlist, and 8 patients were delisted. Most common reason for delisting was multiorgan failure 5 (62%) followed by human leukocyte antigen sensitization in 2 patients (25%) and 1 patient (13%) developed biventricular failure. Among the 8 patients who were never listed, 4 patients (3 with pulmonary fibrosis and 1 with hypersensitivity pneumonitis) died due to multiorgan failure prior to being listed. Remaining 4 patients were weaned off ECMO, 1 had underlying pulmonary hypertension and the three were with acute respiratory distress syndrome" (Page 6, line 21-25, Page 7 line 1-3).

Comment 4: I believe the authors are overstating the result. P8 Line 23: Less likely to receive a transplant with the result of OR: 0.46, CI: 0.12-1.78, $P = 0.26$.

Reply 4: We agree with the reviewer that the results on the Page 6, line 7-11 did not reach statistical significance likely due to small sample size and those results are not conclusive.

Changes in Text 4: "While this did not reach statistical significance possibly due to small sample size, patients who had > 1 reason for deviation from traditional selection criteria appeared to be less likely to receive a transplant (OR: 0.46, CI: 0.12-1.78, $P = 0.26$), had higher odds of being delisted or dying while on waitlist (OR: 2.65, CI: 0.64-10.97, $P = 0.17$), and had higher odds of receiving renal replacement therapy (OR: 3.61, CI: 0.82-15.90, $P = 0.08$)." (Page 6, line 16-20)

Comment 5: With these concerns, I believe this manuscript does not meet the expectation of the manuscripts published from your journal.

Reply 5: Thank you for your suggested edits. These edits have greatly improved our manuscript.

Reviewer F

The study by Wahab et al is about ECMO bridge in lung transplant candidates. It's an important topic relevant for the cardiopulmonary transplant community. The paper is well written and includes data from 2 centers.

I have some minor comments for the authors to clarify

Comment 1: The patients who were bridged on ECMO to decision did not have an active waitlist status? This should be stated in the methods section.

Reply 1: Thank you for the comment.

Change in Text 1: we have added to the Methods section: "Patients were categorized as ECMO bridge to transplantation if they had an active transplant listing status, and bridge to transplant decision with no active listing status prior to ECMO cannulation." (Page 4, line 2-4)

Comment 2: Table I: There were patients with an unknown HLA status. Does this mean there was no data available or did the Tx teams listed patients without information about the HLA status?

Reply 2: Thank you for the comment. Data was missing from the electronic medical record for those patients. Out of 5, one patient had active transplant listing status, four were never listed.

Comment 3: Table I: could the authors specify coronary artery disease? Do they refer to no significant coronary stenosis, single vessel disease with/without intervention? Please clarify?

Reply 3: Thank you for the comment. Patients with obstructive coronary artery disease who had already received intervention, or they were planned to undergo coronary artery bypass graft during transplant surgery were included in the analysis. We updated the table to say, "Obstructive Coronary Artery Disease".

Comment 4: Table I: 7 patients were listed for a HLTx. Please specify what the need or a HLTx was in these patients?

Reply 4: Thank you for the comment. Out of 7, 6 patients had severe Pulmonary hypertension with concern for lack of right ventricular recovery and one had cryptogenic organizing pneumonia and non-ischemic biventricular failure. 5 patients were successfully transplanted, 2 were delisted due to very high levels of HLA antibodies.

Comment 5: Is there data on LAS?

Reply 5: Thank you for the comment. We don't readily have available the LAS for the listed patients. We had a change in our transplant database/ EMR during the timeframe of this study,

and unfortunately, the listing LAS or LAS at time of transplant is not presently available.

Comment 6: Table III: The authors should at least discuss their findings in this table, since complications between the groups were different and mainly due to ECMO site complications. Please discuss?

Reply 6: Thank you for the comment. It looks like rows in the previous table 3, now table 4 (pdf file sent to reviewers) were moved up that mixed the numbers and the percentages.

We have modified that table with clearly marked rows. (Table 4 in the revised manuscript)

Changes in Text 6:

Result section: “Extracranial bleeding of any severity was the most common complication. Intracranial bleeding occurred in 3 patients (7%) all from the expanded group and was fatal in one patient who was also the only patient to suffer from cerebral infarction (Table 3). Among the other two patients with intracranial bleeding, one had subdural hematoma and one was with subarachnoid hemorrhage that was reported as small and resolved on follow up imaging in a week” (Page 6, line 8-13)

Discussion section: “Despite significant progress in ECMO techniques and devices, patients receiving ECMO as a bridge therapy are at higher risk of complications due to their underlying diagnosis, pretransplant mechanical ventilation and ability to participate in physical therapy while on ECMO (12, 13). Previous reports of complications in ECMO-BTT patients have varied from center to center and how the complications were reported. In our study we reported ECMO related complications during the bridging period and post-transplant for those patients who needed ECMO post operatively. Biscotti et al and Tipograf et al from Columbia medical center reported higher complication rates in patients who did not receive the transplant despite following strict selection criteria and delisting high percentage of patients, suggestive of increased risk of complications in sicker patients (6, 9). Hoetzenecker et al reported an overall cerebrovascular rate of 4.2% and bleeding complications in 35% of ECMO-BTT patients (10). Benazzo et al reported very few complications during the bridging period. However, majority of their patients remained on ECMO after receiving the transplant and had higher rates of complications including ECMO site complications (11). In our study complications occurred more in the expanded group as compared to traditional group that might be because those patients were older and sicker. Offering bridge therapy to such a sick patient population does come with the risk of complications but it brings the possibility of getting transplant without which death is certain for them”. (Page 8, line 7-22)

Comment 7: Adjust table 4: the numbers concerning Died prior..... should follow this sentence. The numbers are in the line above.

Reply 7: Agreed and adjusted.

Comment 8: Figure 1: the first box should state expanded

Reply 8: Agreed and corrected.

Comment 9: In the discussion the authors should refer and compare to a recent paper by Gan et al JHLT, covering a similar topic.

Reply 9: Thank you for suggesting the study by Gan et al (Long-term outcome and bridging success of patients evaluated and bridged to lung transplantation on the ICU). Authors in this study defined bridging as only Mechanical ventilation to transplant, ECMO only to transplant or mechanical ventilation with ECMO to transplant. Among 70 bridged patients, 28 were bridged to transplant via ECMO with or without mechanical ventilation. Remaining 42 patients were bridged to transplant via mechanical ventilation only.

Authors did not include subanalysis of the ECMO with or without mechanical ventilation to transplant, so we are not able to compare our results directly to this study.

Changes in Text 9: “Moreover our study results corroborate the findings of Gan et al: very sick patients can be bridged to transplant with ECMO (or mechanical ventilation) and have positive long-term outcomes” (Page 7, line 21-23)