Peer Review File

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Reviewer A

Apparently not a single patient within 10 years from Hong Kong underwent lung transplantation after ECMO therapy - this sounds very strange, the authors should comment on that.

Reply 1: Thank you for your important comment. Hong Kong unfortunately has a very low rate of lung transplantations, with the annual number of 2 in 2010, to a highest of 13 in 2015 (1). As a result of the scarcity of lung transplantations, the service is largely offered to patients who have completed extensive workup for chronic lung conditions, and seldom to patients with acute respiratory failure supported on V-V ECMO as an immediate destination therapy. Upon your suggestion, we have reviewed our data again and found 1 patient who had lung transplantation more than 1.5 years after the initial ECMO episode, it was not included as an immediate outcome. We have included the data A in the Results section and expanded the discussion of low rates of lung transplantation after ECMO in Hong Kong.

Changes in the text: See Page 13 lines 250 to 251, and Page 19 lines 390-397.

Reference:

1. Hsin MK, Wong CF, Yan SW, et al. The history of lung transplantation in Hong Kong. J Thorac Dis 2018;10(Suppl 16):S1899-S1904.

Reviewer B

Nice article on trying to delineate outcomes based on high vs low volume centers and utilization of ECMO. It is well written and provides us with good insight, however, there are several critiques I have to strengthen the manuscript.

1. Variations of ECMO configuration and indications have a huge bearing on outcomes. I would recommend the authors divide VA ECMO to categories of post-cardiotomy and other, keep eCPR VA and VV ECMO.

Reply 1: Thank you for your encouraging comments. We agree on the differences in outcomes between the various ECMO configurations. Upon your suggestion, we re-examined the volume-outcome relationship in the 4 ECMO subtypes, and the results are tabulated below. However, they have to be interpreted with caution as we did not have adequate statistical power for multiple comparisons.

Odds ratios for hospital mortality:

ECMO subtype	**Number of Patients**	**Adjusted OR**	**95% CI**	**P value**
Post-cardiotomy	70	0.64	0.14-2.86	0.56
ECPR	157	0.20	0.04-0.93	0.041
Other V-A ECMO	236	1.00	0.54-1.85	0.99
V-V ECMO	448	0.90	0.57-1.42	0.64
Total	911			

Changes in the text: Some of these results have been included in the Sensitivity Analysis (See Page 18 line 369 to line 376).

2. The title is misleading because high volume centers is really a sample size of 2 in this study with a total of 7 centers implanting ECMO. Perhaps something like "low volume ecmo centers do not have a worse outcome extracorporeal membrane oxygenation: A territory-wide longitudinal observational study" would be more apt.

Reply 2: Thank you for your suggestion. Based on your helpful comment, we have completely re-organized the manuscript and now define high- and low-volume centers based on the actual number of ECMO cases performed each year. The number of high-volume centers range from 1 in 2012, to 4 centers in 2018 and 2019. We hesitate to rename the study with a leading title, and are happy to consider other suggestions that may be more neutral.

Changes in the text: See Page 11 lines 200 to 206.

Reviewer C

The authors compared outcomes for ECMO patients between 2010-2019 in low and high case volume centers in public hospitals in Hong Kong in a retrospective observational cohort. The authors found no association with case volume and hospital mortality.

I have some important issues and questions:

Background:

1. There is mention of 7 ECMO centers (line 101) in public hospitals. Are there other ICU's where ECMO is applied? Cardiothoracic ICU's? If so, why are these ICU's not included in the manuscript?

Reply 1: Thank you for your astute observation. ECMO is offered in Hong Kong at more than the 7 ICUs mentioned in the manuscript, including ICUs at district and rural hospitals, coronary care units, and cardiothoracic ICUs. However, the overwhelming majority of ECMO are offered at these 7 "gazetted" centers under the

governance of the Central Organizing Committee in ICU services, which also oversees that these centers have comparable resource allocation and training support. This makes examination of volume effects within these 7 centers, but not beyond, a more reliable analysis. We discuss this limitation in the manuscript.

Changes in the text: Nil.

2. How many private hospitals are in HK with ECMO facilities?

Reply 2: There are 4 private hospitals in Hong Kong that has the capacity to offer ECMO services, but the caseload is sporadic and is less than 5 patients per year.

Changes in the text: Nil.

3. In the manuscript later there is mention of 6 instead of 7 centers (line 156). I will come back to this issue in the results sections

Reply 3: We apologize for the confusion. At the time of manuscript writing, there are 7 ECMO centers in Hong Kong, the last of which was only inducted after the period of data collection, i.e., after 2019.

Changes in the text: We have clarified the wordings in the second paragraph of Introduction (Page 8 lines 143 to 146) and Methods (Page 11 lines 200 to 201).

Methods:

4. Patients with incomplete ECMO details are excluded (128). Main outcome is hospital mortality and SMR with the use of APACHE IV data. Why not exclude patients with missing APACHE IV scores?

Reply 4: In our pre-specified analysis plan, the primary analysis was to examine the effect of annual case volume on patient outcomes, therefore, excluding patients with missing APACHE IV scores would invalidate the annual case numbers per center and prevent us from accurately categorizing centers by volume. Upon your suggestion, we performed sensitivity testing by repeating the analysis in a subcohort excluding patients with missing APACHE IV scores (n=30), the findings remained unchanged (adjusted OR for hospital mortality 0.86 95% CI 0.61 – 1.21, p=0.38; adjusted OR for ICU morality 0.76, 95% CI 0.54 – 1.06, p=0.10). The SMR for high-volume centers was 0.93 (95% CI 0.83 – 1.04) compared with 1.24 (95% CI 1.03 – 1.44) for low-volume centers.

Changes in the text: These results have been added to the "result of sensitivity analysis" in the Supplementary Appendix.

5. Please explain the statement on the need for a power calculation in this is observational study.

Reply 5: Post-hoc power calculation of retrospective observational studies are important to show adequate statistical power to prevent a Type II error (Fagley, 1985; Onwuegbuzie and Leech, 2004). We are aware of the controversies surrounding post-hoc power calculations, and would be happy to remove the power calculation if appropriate.

Changes in the text: Nil.

6. The APACHE IV score is used for comparison between estimated and observed outcomes. How many ECMO patients are included in the original cohort from Zimmerman. Please add literature which shows that APACHE IV is the most appropriate prognostication score for ECMO patients.

Reply 6: Thank you for your important comment. We could not find information on the number of ECMO patients in the original APACHE IV cohort from Zimmerman. APACHE IV scores have been applied to ECMO cohorts with excellent ROC 0.922 (Lin CY, et al. Evaluation of outcome scoring systems for patients on extracorporeal membrane oxygenation. Ann Thorac Surg 2007 Oct;84(4):1256-62.) and ROC 0.98 (Lechiancole A, et al. Heart Transplantation in Patients Supported by ECMO: Is the APACHE IV Score a Predictor of Survival? Artif Organs 2018 Jun;42(6):670-673.)

While we agree that ECMO-specific scoring systems such as the SAVE and RESP scores could add useful information, we were limited in not having access to detailed physiological data in this territory-wide cohort and hence unable to perform the relevant analyses.

Changes in the text: Nil.

7. It's not clear for me why the authors perform a sensitivity-analysis excluding postcardiotomy patients. Please elaborate or consider placing it in the supplements.

Reply 7: Thank you for your suggestion, we have moved the analysis to the Supplement.

Changes in the text: The results are moved to the "Sensitivity analysis excluding post-cardiotomy patients" in the Supplementary Appendix,.

8. The information on the one hospital representing the SAVE and RESP score are scarse. Figure 6 gives numbers of death. For me it's not clear how large the patient population of this center is. Maybe, when small, this part does not add much to the message the authors want to give to the readers.

Reply 8: Thank you for your important question. The total number of ECMO cases in this single institution during the study period (from 2010 to 2019) was 239 (26.2%)

cases. The number of ECMO cases ranged from 3 cases in 2010 and to 39 cases in 2019. We regrettably refrain from publishing potentially identifiable center-specific data as part of the data sharing agreement across Hong Kong.

Changes in the text: Nil.

Results:

My main issue with this manuscript is the use of ECMO patients as one group in comparing outcomes. Looking at the mortality in the ELSO database varying between 30% for ECPR patients to 60% for pulmonary patients it seems unlogical to compare these categories as 1 group.

Reply: Upon your important comment, we re-examined the volume-outcome relationship in 4 subgroups of patients by ECMO configuration and tabulate the results below. However, they have to be interpreted with caution as we did not have adequate statistical power for multiple comparisons.

Odds ratios for hospital mortality:

ECMO subtype	**Number of Patients**	**Adjusted OR**	**95% CI**	**P value**
Post-cardiotomy	70	0.64	0.14-2.86	0.56
ECPR	157	0.20	0.04-0.93	0.041
Other V-A ECMO	236	1.00	0.54-1.85	0.99
V-V ECMO	448	0.90	0.57-1.42	0.64

Total	911			

Changes in the text: Some of these results have been included in the Sensitivity Analysis (See Page 18 line 369 to line 376).

9. Table 1 is meant to describe your population; why did you add p-values in this observational cohort? Is this in line with the recommendations of the STROBE guidelines?

Reply 9: Thank you for your comment, we have removed significance values from in Table 1 - Demographics and comorbidity burden of the study population.

Changes in the text: See Table 1 - Demographics and comorbidity burden of the study population.

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10. Please explain the number of high volume and low volume at the start (figure 1&3). Figure 3 starting with 4 centers in 2010 and < 20 patients in total? Why is the number different in the lines 295-296? Figure 3: all center have increasing runs/year. Please explain when centers cross to the high volume side.

Reply 10: In the original definition, high- and low-volume centers were defined by the average annual number of ECMO cases over the study period. In Figure 4 "Comparison of observed hospital mortality and ICU length of stay against APACHE IV predicted outcomes", there was a total of 4 ECMO cases in the two high-volume centers in 2010.

Based on your helpful comment, we have completely re-organized the manuscript and now define high- and low-volume centers based on the actual number of ECMO cases performed each year. There were 4 low-volume centers in 2010, and the first

center crossover to the high-volume definition in 2012. Results of the primary analysis remained the same, with no significant association between case volume and hospital mortality (adjusted OR 0.86, 95% CI 0.61 – 1.21, p=0.38) or ICU mortality (adjusted OR 0.76, 95% CI 0.54 – 1.06, p=0.10). The SMR for high-volume centers was 0.93 (95% CI 0.82 - 1.03) compared with 1.26 (95% CI 1.06 - 1.47) for low-volume centers (p=0.46).

Changes in the text: See Page 15 line 292 to Page 16 line 315 and the updated Figures 4 and 5.

11. In VA ECMO the most indication is postcardiotomy patients. Please state why this is different in the used study population.

Reply 11: In our cohort, the most common indications of V-A ECMO were myocardial infarction (21.9%) and myocarditis (16.8%). This is similar to other reports such as in a 10-year study by Jang EJ et al. (Trends in Extracorporeal Membrane Oxygenation Application and Outcomes in Korea. Asaio j. 2021;67(2):177-84.) where the most common indication of V-A ECMO was cardiac failure (62.5%) followed by cardiovascular surgery (20.9%).

Moreover, we had only included patients from the 7 "gazetted" centers under the governance of the Central Organizing Committee in ICU services, which oversees that these centers have comparable resource allocation and training support, and make examination of volume effects within these 7 centers a more reliable analysis. Data from other ICUs, CCUs, HDUs were not included.

Changes in the text: Nil

12. The SMR in low volume centers increases over time. Might low volume centers be putting more patients on ECMO to meet volume demands?

Reply 12: With the updated and more stringent definition of low-volume centers, we observed that case volumes in low-volume centers increased from an annual average of 4.5 cases in 2010, to 15.5 in 2019. The SMR of low-volume centers was more variable, although it did not reach statistical significance. The SMR for high-volume centers was 0.93 (95% CI 0.82 - 1.03) compared with 1.26 (95% CI 1.06 - 1.47) for low-volume centers (p=0.46).

Changes in the text: See the updated Figure 4 "Comparison of observed hospital mortality and ICU length of stay against APACHE IV predicted outcomes".

Discussion:

13. Line 333 please elaborate on ECMO patients and prognostic scores.

Reply 13: We now discuss the utility and advantages of APACHE IV and other prognostic scores in ECMO patients in more detail in the Discussion.

Changes in the text: See Page 23 lines 469 to 483.

14. Line 339 this review describes total hospital costs for ECMO patients. Please elaborate on the mentioned difference in costs. Is there literature on incremental costs for ECMO? Or is treatment expensive because of the disease severity.

Reply 14: Thank you for this comment. In a very recent systematic review of 2019 values, hospital costs ranged from US$22,305 to US$334,608 across centers in the US, Europe, Japan, Australia, and Taiwan. US$334,608 (2019 values). The additional costs of ECMO ranged from US$2518 and US$200,658. The variability in costs was related to the indication for ECMO support and geographical location, which likely reflects fundamental differences in the healthcare infrastructure. (Oude Lansink-Hartgring A, et al. Hospital Costs of Extracorporeal Membrane Oxygenation in Adults: A Systematic Review. Pharmacoecon Open 2021 Dec;5(4):613-623.)

Changes in the text: We have included an updated discussion on Page 20 lines 408 to 417.

15. Line 350: This article might add to the discussion on the relationship between volume and outcome. Bailey KL, Downey P, Sanaiha Y, Aguayo E, Seo YJ, Shemin RJ, Benharash P. National trends in volume-outcome relationships for extracorporeal membrane oxygenation. J Surg Res. 2018 Nov;231:421-427. doi: 10.1016/j.jss.2018.07.012. Epub 2018 Jul 31.

Reply 15: Thank you for your helpful suggestion. We have included this reference in our discussion and agree with the possible interpretation that increased hospital mortality in high-volume institutions may represent a selection of patients who are sicker, but would otherwise not have been supported with ECMO in low-volume centers. In multivariable regression, we attempted to adjust for disease severity, but admit there might be effects of residual confounding.

Changes in the text: See Page 22 line 460 to line 466.

Reviewer D

This is a timely and relevant retrospective analysis of outcomes in ECMO programs that are specific to a single country. The stated hypothesis was evaluating care as judged by mortality, rendered at centers with varying case volumes over time between 2010 to 2019.

Overall, the manuscript is well written save for some minor errors in syntax and grammar, all of which are easily editable. The period in question represents an era of exponential growth in technology and expertise in extracorporeal technology and critical care.

The time aspect is likely to exert a confounding effect. It is further compounded by the fact that the volume was evaluated as a static entity without considering that in the course of the decade, a low-volume center might have evolved into a high-volume center and developed a commensurate enhancement in capability and increased exposure to greater complexity.

Reply 1: Thank you for your important comment. Based on your suggestion, we have completely re-organized the manuscript and now define high- and low-volume centers based on the actual number of ECMO cases performed each year. The number of high-volume centers range from 1 in 2012, to 4 centers in 2018 and 2019. Results of the primary analysis remained the same, with no significant association between case volume and hospital mortality (adjusted OR 0.86, 95% CI 0.61 – 1.21, p=0.38) or ICU mortality (adjusted OR 0.76, 95% CI 0.54 – 1.06, p=0.10). We also attempt to adjust for the temporal effect by adjusting for calendar year in our multivariable regression model.

Changes in the text: See Page 15 line 292 to Page 16 line 315 and the updated Figures 4.

Indeed the large proportion of ECPR cases is further evidence as to the conformity with global trends and their results differ from most published accounts. Methodologically, nevertheless, the authors should explicitly specify whether they used logistic regression.

There is widespread interest and preoccupation with the effect of volume, and ECMO has exhibited contradictory volume-outcome relationships. For example, the positive volume-outcome pattern seen in the use of the VV ECMO is not present in the use of postcardiotomy support.

Reply 2: We agree on the differences in outcomes between the various ECMO configurations, especially in light of the increasing proportion of ECPR cases. We re-

examined the volume-outcome relationship in the 4 ECMO subtypes, and the results are tabulated below. However, they have to be interpreted with caution as we did not have adequate statistical power for multiple comparisons. Specifically, we utilized multivariable logistic regression in the primary analysis (see Methods section, page 11 lines 202 to 204).

Odds ratios for hospital mortality:

ECMO subtype	**Number of Patients**	**Adjusted OR**	**95% CI**	**P value**
Post-cardiotomy	70	0.64	0.14-2.86	0.56
ECPR	157	0.20	0.04-0.93	0.041
Other V-A ECMO	236	1.00	0.54-1.85	0.99
V-V ECMO	448	0.90	0.57-1.42	0.64
Total	911			

Changes in the text: Some of these results have been included in the Sensitivity Analysis (See Page 18 lines 369 to line 376).

Further controversy is highlighted by the results from the Japanese study quoted by the authors. A more rigorous approach to identifying the contribution of volume might be the inclusion of a calculation of the C statistic within this model to determine the probability of the outcome, here mortality, that is directly attributable to the outcome in question, namely volume. The authors should be careful not to confuse correlation with causality.

Reply 3: Thank you for pointing this out. We are cautious in the interpretation of our study findings that we did not show an association between ECMO case volumes and hospital mortality. In multivariable logistic regression, ECMO in high-volume centers was not significantly associated with decreased hospital mortality (adjusted OR 0.86, 95% CI 0.61 – 1.21, p=0.38). Upon your suggestion, we computed the C statistic for the unadjusted and adjusted probability of mortality attributable to volume, which was 0.53 and 0.76, respectively.

Changes in the text: Nil.

Previous models have identified that volume is an imperfect predictor of outcome, and the authors should address this. They should comment on the observations that it is commonly the characteristics of the high-volume center, capabilities, constituents, staff, and range of services that permit a center to serve as a solid platform in the landscape of failure to rescue and mitigate the mortality most effectively.

Reply 4: Thank you for this helpful comment. We have incorporated this point to our discussion.

Changes in the text: See Page 22 lines 461 to 467.