

Peer Review File

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Reviewer A

Comment 1: I agree there almost parts of conclusion although this study could not show high expenses in nosocomial infection group. This conclusion implies me that we need to prevent nosocomial infection. In recent following paper suggested prophylactic antibiotics during ECMO could reduce nosocomial infection and showed lower mortality. This study may give you some insights in your study and therefore please discuss at this point in the Discussion.

Reply 1: Many thanks for your positive comments and suggestions. As you suggest, we have conducted the following discussion on the prophylactic antibiotics during ECMO. Some studies have found that prophylactic antibiotics during ECMO could reduce nosocomial infection and showed lower mortality. Therefore, medical institutions usually increase the use of antibiotics in order to save lives for patients who need ECMO support, no matter whether nosocomial infection occurs or not, which can be reflected from the no statistically significant difference in the use of prophylactic antibiotics and the cost of antibiotics between ECMO infection group and ECMO non infection group.

Changes in the text: We have modified our text as advised (see Page 10, line 217-223)

Comment 2: In table1, I suggest to categorize year because non infectious group showed 0 in 2013, 2014, 2015, and 2016. If the box showed 0, statistical analysis become inaccurate. I therefore suggest to categorize in year variable.

Reply 1: As suggested, we have combined 2013, 2014, 2015, 2016, and 2017 into 2017 and previous groups, and further analysis found that there was still no significant difference in the composition ratio of the years between ECMO infection group and ECMO non infection group.

Changes in the text: We have modified Table 1 as advised (see Table 1)

Reviewer B

Comment 1: Line 78: please reference these papers on the need for standardization of antimicrobial prophylaxis in patients on ECMO. Please include in summary, findings of these papers in the background and discussion.

<https://pubmed.ncbi.nlm.nih.gov/33575744/>

<https://www.else.org/Portals/0/Files/ELSO-ID-Task-Force-Recommendations->

Summary.pdf.

Reply 1: Many thanks for your positive comments and suggestions. As you suggest, we have summarized the findings of these papers in the background and discussion.

Changes in the text: We have modified our text as advised (see Page 4, line 67-70 and Page 11, line 229-235)

Comment 2: It is important to acknowledge and discuss a huge limitation of this study. Costs are hard to estimate in various countries, especially USA. There is lack of clarity on how patients are billed and for what purpose. It is important to discuss this and leave a cautionary point that this paper could be hard to generalize owing to significant difference in cost metrics in various countries and health care systems.

Reply 2: As suggest, we have discussed this limitation. The cost of treatment for ECMO patients due to infection cannot be accurately calculated. Therefore, this study only compares the total hospital expenses between ECMO infection group and ECMO non infection group, as well as detailed expenses such as bed expenses, nursing expenses, radiation expenses, and operational expenses, to evaluate the increased cost of ECMO patients after infection. In addition, our sample size is relatively small and it may be impossible to accurately assess the increase in medical costs for nosocomial infection after ECMO support. Moreover, due to the significant differences in the cost indicators of different countries and healthcare systems, it is necessary to carry out multi-center cohort studies and randomized controlled trials for comparing hospital expenses among ECMO infection populations in different countries and systematically evaluate the economics burden of ECMO infection populations.

Changes in the text: We have modified our text as advised (see Page 11, line 246-251)

Comment 3: This paper needs discussion of cost of infections. I see expenses about radiation, anesthesia etc. But how about the cost of antimicrobials? Cost of blood draws to monitor side effects? Cost of managing adverse effects from antimicrobials? Were there adverse effects from antimicrobials? What about c diff? Antimicrobial resistance?

Reply 3: The cost of infections treatment for ECMO patients cannot be accurately calculated. This was also one of the limitations of this study. We have discussed this limitation in Discussion section.

Changes in the text: We have modified our text as advised (see Page 11, line 240-245)

Comment 4: Without the discussion of the above, we will miss the point of impact of infections. Impact of infections is not just monetary but also outcomes based

Reply 4: The aim of this study was to explore the hospital expenses of nosocomial infection after ECMO support. The characteristics of infection such as c diff and antimicrobial resistance were not analyzed in detail, which is also one of the limitations of this study.

Changes in the text: We have modified our text as advised (see Page 11, line 240-245)

Comment 5: Line 251:I disagree with this statement. I think it should be the case that expenses should be analyzed over the entire hospital period. I think this study needs to do the same. One cannot just estimate costs when on ECMO, complications such as infection impact cost, outcomes, length of stay, mortality over the entire hospital period.

Reply 5: We are very sorry that we did not make this clear. We re-discussed this part in Discussion section. In fact, we analyzed the expenses of ECMO patients over their entire hospital period, and compared the outcomes, length of stay, mortality over the entire hospital period between different groups. The results of these analysis were shown in Table 2.

Changes in the text: We have modified our text as advised (see Page 10, line 223-227)

Comment 6: In the discussion, need to discuss the ill effects of more antimicrobial use in patients with infections. Again, per the recent paper in CID, patients on ECMO are at high risk of future hospitalization and hence the need to make sure they are not over exposed to antimicrobials in the current ECMO stay.

<https://pubmed.ncbi.nlm.nih.gov/33575744/>

Reply 6: As suggested, we have discussed the ill effects of more antimicrobial use in patients with infections. Study have found that ECMO patients are at high risk of hospitalization in the future, and a multidisciplinary team-based antimicrobial stewardship approach can significantly reduce the prophylaxis and overuse of antimicrobial in ECMO patients without increased risk of nosocomial infection. The ELSO ID TASK FORCE Recommendation Summary also suggests that cautious, aggressive use of antifungal prophylaxis in patients deemed to be at particularly high risk. Therefore, we call for the adhering to strict infection control measures in the life-saving process of ECMO support treatment, and antimicrobial prophylaxis follow standard guidelines.

Changes in the text: We have modified our text as advised (see Page 11, line 229-235)

Comment 7: In the tables, it is clear that patients with more infections have more

catheter use. Must discuss how this risks more chance of CLABSI and CAUTI.

Reply 7: First of all, we are very sorry that we did not make this clear. This study found that there was no significant differences in Days of central venous catheter use and Days of catheter use between the two groups after PSM. We have discussed this result in the Discussion section. It is clear that ECMO provides more time and space for the identification of the etiology of cardiac arrest and maintenance of organ perfusion. However, due to the existence of multiple potential entrances, including ECMO intubation, standard invasive catheters, and open chest wounds, etc., patients who receive ECMO are at a high risk of healthcare-associated infection, especially blood stream infection (BSI), central line associated bloodstream infections (CLABSI).

Changes in the text: We have modified our text as advised (see Page 9, line 191-195)

Comment 8: It is also unclear to me who practices western medicine as to how chinese herbal medicine is used or classified.

Reply 8: In fact, some diseases in China, such as respiratory diseases, will adopt the method of integrated traditional Chinese and Western medicine, so the expenses of Chinese herbal medicine will be involved in the hospitalization expenses of ECMO patients. Since Chinese herbal medicine accounts for a relatively small amount, and there is no research showing that Chinese herbal medicine has a role in ECMO patients' infections, we have deleted this part in result.

Changes in the text: We have modified our text as advised (see Table 3)

Comment 9: Would recommend removal of all reference to procalcitonin. This is a "biomarker" which is significantly hampered by kidney dysfunction and the general sense of inflammation in a patient's body, which are both factors patients on ECMO have.

Reply 9: As suggest, we have removed all reference to procalcitonin.

Changes in the text: We have modified our text as advised (see Table 1 and Table 2)

Comment 10: Line 52: more and more, change wording.

Reply 10: As suggest, we have changed wording.

Changes in the text: We have modified our text as advised (see Page 3, line 42-44)

Comment 11: Lack of cost of entire hospital stay, which Indeed is a true reflection of a complication of an infection.

Reply 11: We are very sorry that we did not make this clear. We re-discussed this part in Discusion section. In fact, we analyzed the expenses of ECMO patients over their entire hospital period. The results of these analysis were shown in Table 2.

Changes in the text: We have modified our text as advised (see Page 10, line 217-

227)

Comment 12: Lack of metrics such as c diff, antimicrobial resistance.

Reply 12: The aim of this study was to explore the hospital expenses of nosocomial infection after ECMO support. The characteristics of infection such as c diff and antimicrobial resistance were not analyzed in detail, which is also one of the limitations of this study.

Changes in the text: We have modified our text as advised (see Page 11, line 240-245)

Comment 13: Improper and inadequate classification of infection. Please review this paper to see how better to classify infections.

<https://pubmed.ncbi.nlm.nih.gov/33575744/>.

Reply 13: The aim of this study was to explore the hospital expenses of nosocomial infection after ECMO support. The characteristics of infection not analyzed in detail, which is also one of the limitations of this study.

Changes in the text: We have modified our text as advised (see Page 11, line 240-245)

Comment 14: Lack of discussion how infections lead to more procedures, more devices, more device related infections.

Reply 14: As suggested, we have discussed this issue. The artificial surfaces of the ECMO circuit, such as the membrane oxygenator (MO), drainage cannula, the return cannula, could be the target of microbial adhesion and colonisation, thereby facilitating the development of ECMO-related bloodstream infection.

Changes in the text: We have modified our text as advised (see Page 9, line 195-198)