

## Peer Review File

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### Reviewer A

I read with interest of this manuscript. There are several issues to be corrected or changed, and there are some recommendations for potential improvement of the manuscript.

#### 1. Introduction:

The author should correct inappropriate use of capital letter; e.g. When patients were treated with Intra-Aortic Balloon Pump (IABP) or Extracorporeal Membrane oxygenation (ECMO), the use of vasopressors and inotropes may be reduced.

**reply:** Thank you for this critical question. The error occurred due to my misunderstanding of the abbreviation used in the paper and I had already rectified the mistake.

Clinical implications of VIS were previously reported in several clinical settings including refractory cardiogenic shock necessitating VA-ECMO support; all types of cardiogenic shock by J Hyun et al. *Circ J* 2022, cardiogenic shock complicated from myocardial infarction by KH Choi et al. *Crit Care Med* 2021. The author should justify and emphasize purpose and uniqueness of their paper, compared with previous literature.

**reply:** Thank you for this critical question. This section will be discussed and compared in the Discussion section.

#### 2. Methods:

The author must specify the way of collecting study data including number of the hospital involved. Furthermore, if the data source was based on the national registry, the protocol of registry should be further specified; was the registry enrolled patients with cardiogenic shock? or with mechanical circulatory support? The baseline information on the Table 1 demonstrated that the study probably included all patients with cardiogenic shock receiving VA-ECMO support, which included post-cardiac surgery settings.

**reply:** Thank you for this critical question. We take our hospital as the core and collaborate with hospitals nationwide on the platform of the Extracorporeal Life Support Branch of the Chinese Medical Doctor Association to build an ECMO data platform. By using an electronic data collection system, we achieve the national data collection and sharing for ECMO-supported patients. Currently, more than 90 units have participated in our work, and this number continues to increase.

The author demonstrated that the study population was divided into two groups according to the maximal VIS of 20 within 6 hours before initiation of VA-ECMO.

However, the study result of reference quoted (J Han et al. J Hear Lung Transplant 2019) was primarily based on VIS information of patients initiated after LVAD support, not before the initiation of LVAD, which was different in terms of VIS “DURING” early period of MCS (mechanical circulatory support) vs “BEFORE” MCS. Strictly speaking, although LVAD is a type of MCS, the study adopted the median value of VIS in the post-cardiac surgery setting.

**reply:** Thank you for this critical question. As mentioned earlier, there are many uncertainties in the current research on VIS. There are significant differences in the timing of VIS selection in various studies. Based on our center's clinical experience, we believe that the VIS score before the installation of ECMO is most helpful in predicting patient prognosis. Additionally, according to the referenced studies and the actual medication practices in our clinic, we have selected the preoperative VIS of patients for research purposes, using a cutoff value of 20 for grouping.

The author should specify “other complications”. (And secondary endpoints were 30 days mortality, length of stay in the ICU and hospital, complications related with ECMO and other complications)

**reply:** Thank you for this critical question. The other complications we mentioned refer to complications not caused by ECMO operations, including renal injury, gastrointestinal bleeding, infections, and neurological complications, among others. We have also provided additional information on these complications in the text.

The abbreviation used once in the manuscript should be consistently mentioned thereafter. (e.g. VISmax for the maximal VIS)

**reply:** Thank you for this critical question. The abbreviation " VISmax " is used to inform readers that we are referring to the maximum value during this period. To avoid ambiguity and for ease of writing, we, like other studies, directly use "VIS" for expression.

A proportion of the missing value should be specified to understand the innate limitation and interpret the result of current study.

**reply:** Thank you for this critical question. When the missing values do not exceed 10% of the total data, we consider them as minor missing and do not take any additional actions. If there are more missing values but not exceeding 20%, we fill these gaps with the mean value.

### 3. Results:

The author demonstrated that patients with acute myocardial infarction (AMI) were associated with higher VIS. However, a proportion of patients with AMI was relatively lower in the high VIS group compared to the lower VIS group. (Patients with cardiac surgery, acute myocardial Infarction and acute myocarditis were connected with higher dose of vasoactive and inotropic agents)

**reply:** Thank you for this critical question. This is just a simple description of the baseline condition of the patients, intended to express which patients among those with

different etiologies of shock will require high doses of vasoactive drugs, rather than to establish a correlation between acute myocardial infarction and high VIS. And I have tried to come up with another more appropriate expression.

Differential preference in inotropes or vasoactive agents by center can be further specified. (Results, line 122–123; And in some experienced medical units, patients with cardiogenic shock had a higher prevalence of lower dose of vasoactive agents) Furthermore, it would be interesting to show differential outcomes according to the different strategy using inotropes or vasoactive agents (=VIS) such as liberal versus strict use.

**reply:** Thank you for this critical question. Due to the collaboration with multiple institutions and the individual preferences of each clinician regarding medication practices, it is challenging to capture this data in the database. However, this is also one of the directions for our future research.

The definition of “experienced medical units” in the Table 1 and “kidney injury” in the Table 2 should be defined clearly.

**reply:** Thank you for this critical question. We define experienced medical units as those that have conducted a total of 50 ECMO cases and continue to perform more than 30 cases annually. The definition of kidney injury is based on the clinical guidelines provided by KIDGO.

The value of lactic acid above 8 mmol/L used in the Table 3 is unusual; the criterion to use this value as a binary cut-off would rather be better justified. If there was no reasonable reference, it would be preferable to present the results of regression analyses using lactic acid as a continuous variable.

**reply:** Thank you for this critical question. We are referring to previous studies for this point (Choi K H, Yang J H, Park T K, et al. Differential Prognostic Implications of Vasoactive Inotropic Score for Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock According to Use of Mechanical Circulatory Support\*[J]. Critical Care Medicine), and we will also conduct further research on lactate in the future.

How can be differentiated between heart failure and cardiomyopathy in the Table 1? In real-world practice, it seems to be very difficult to divide between these two categories. Furthermore, in line with this, the predictive ability of VIS in the Table 4 was somewhat different between patients with heart failure (adjusted HR, 3.75) and cardiomyopathy (adjusted HR, 1.76), which should be discussed specifically.

**reply:** Thank you for this critical question. The heart failure we mentioned refers to chronic heart failure, while cardiomyopathy mainly refers to dilated cardiomyopathy, hypertrophic cardiomyopathy, and other types of cardiomyopathy.

It is inappropriate and better to delete the sentence (the prediction ability of VIS was strongest in patients with acute myocardial infarction), because hazard of AMI was not

directly compared with other etiologies and actually similar with other etiologies (heart failure, acute myocarditis).

**reply:** Thank you for this critical question. Your consideration is reasonable, and I have modified it to 'High VIS exhibited good predictive ability in patients with acute myocardial infarction, heart failure, and acute myocarditis.'

Regarding in-hospital outcomes relevant to the use of VA-ECMO, the rates of ECMO weaning, heart transplant, and LVAD implantation should be specified because these outcomes are also important.

**reply:** Thank you for this critical question. We supplemented data on weaning. However, due to the rarity of heart transplant and LVAD application in China, there is significant data bias and future studies may involve this aspect.

Extracorporeal CPR is known to be strongly predictive of in-hospital outcomes, which should be specified in the Table 1 and added in the regression analyses.

**reply:** Thank you for this critical question. Unfortunately, the data obtained in this study did not include patients undergoing ECPR. We will also acquire more data for further analysis.

#### 4. Discussion

Despite of poor in-hospital outcomes, higher complication and CRRT rates, the length of hospital and ICU stay was significantly shorter in higher VIS group. The author should discuss the reason of this findings.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

The rate of infectious events was unexpectedly and significantly lower in the higher VIS group, which should be discussed.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

The author should discuss the issue regarding different results of 30-day mortality according to the etiology of cardiogenic shock.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

Follow section can be shortened by just pointing out importance of early prediction of mortality (Refractory cardiogenic shock remains one of the leading causes of death in humans worldwide, although early revascularization and improvements of medical therapy have led to significant reductions in mortality in patients with CS over the past many years. Therefore, it is critical to be able to predict the risk of death in patients

with cardiogenic shock in advance by using predictive models. And it is also very important to distinguish patients with CS who are likely to recover with drug therapy from those who may require mechanical support to survive. What's more, we also need to identify patients who are going to die no matter what treatment they receive).

Also, it would not need to demonstrate the history of VIS development, but better to discuss other issues. Beyond predicting in-hospital mortality, the author can discuss deeper for earlier application of ECMO support before increasing the VIS above certain point. Actually, higher VIS may be reflective of more advanced shock possibly resulting more prolonged and profuse end-organ hypoperfusion, in which leads to multi-organ failure. There are several papers reporting delayed initiation of MCS while on higher dose of inotropes/vasopressors was associated with poor outcomes. Deciding the right timing to apply MCS, VIS can give us valuable information not just by chronological shock time but reflecting the degree of concomitant organ failure caused by cardiac failure.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

Using first name instead of surnames for citation in the manuscript appears to be unusual and should be changed. (In addition, a study from Hong[22] showed that VIS > 90 were associated with a higher probability of adverse outcomes in patients with acute myocardial infarction combined with cardiogenic shock and VIS score showed the strongest predictive ability in the medical treatment alone group, followed by the IABP group and the ability was weak in the ECMO group)

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

The optimal VIS value as a cut-off point by the paper quoted (Choi et al. Crit Care Med 2021) was 16.0 for sole medical therapy, 40.1 for IABP, and 84.0 for ECMO; therefore, restricted to patients receiving ECMO, VIS value was actually higher than other literature and quite different with current paper, which should be discussed.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

Unless the author can suggest supporting evidence of following sentence, it is inappropriate to say that VIS can predict well for acute myocarditis owing to little confounding factors. (This may be due to the heart structure of patients with acute myocarditis had not been significantly changed and was less interfered by confounding factors than other cardiovascular disease)

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

Cardiogenic shock cannot actually be following VA-ECMO support, but can be followed by VA-ECMO support. (indicating that VIS score =20 is probably a critical value in patients with cardiogenic shock following VA-ECMO support)

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

The terminology selected (pre-, post-“operative” in the Discussion section, line 223) should be changed because most of VA-ECMO may be implanted percutaneously, not surgically.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

I recommend changing and reviewing overall logics and English expressions in the Discussion section.

**reply:** Thank you for this critical question and I had polished up the whole article. If you are not satisfied with my writing also, would you please recommend me a suitable polishing organization?

#### 5. Limitations:

The authors should discuss important points limiting interpretation of the study including retrospective nature of study design, some discrepant results with existing literature, missing of important variables in the analyses, potential difference in practice by center, etc.

**reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies

#### 6. Conclusion:

Predictive value of VIS was not compared according to the etiologies by head-to-head manner, therefore, inappropriate to conclude that predictive value of VISmax was strongest “compared to” other etiologies.

**reply:** Thank you for this critical question and I had rearranged and rewritten the conclusion section.

7. Lastly, I recommend reviewing and correcting overall English language and grammar. (e.g. inappropriate capital letter, expressions that do not align with the medical journal)

**reply:** Thank you for this critical question and I had polished up the whole article. If you are not satisfied with my writing also, would you please recommend me a suitable polishing organization?

### **Reviewer B**

The topic is quite interesting. The study well designed and the enrolled population is consistent; however, there are major issues.

1. The paper is poorly written and several paragraphs are quite difficult to read.

**Reply:** Thank you for this critical question and I had polished up the whole article. If you are not satisfied with my writing also, would you please recommend me a suitable polishing organization?

2. We suggest to shorten the discussion section focusing on the results of the present investigation.

3. The Authors should hypothesized the reason(s) why VIS is associated with higher mortality.

4. The novelty of the present investigation should be highlightened.

5. This study is retrospective and this should be addressed as a potential limitation,

6. Recent papers on this topic should be cited and discussed: Kaddoura R et al 2022, Dunton K et al 2023 Soltesz A et al 2022

**Reply:** Thank you for this critical question and I had rearranged and rewritten the discussion section, focusing on discussing the results and comparing them with other similar studies