Peer Review File

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Reviewer A

Thank you for acknowledging the value of our trial, and we appreciate the insightful comments provided for our article. You mentioned that our paper investigates the effectiveness of the "eSAS-based Nomogram" in predicting the risk of postoperative complications and suggests that it can effectively predict such risks. However, our primary aim was to assess the effectiveness of this nomogram system in reducing postoperative complications as a post-op triage system. We did not focus on the predictive power of this system as it has already been thoroughly investigated in our previous study[1]. The results of our trial demonstrate that our nomogram system, as a triage tool, can effectively reduce the overall occurrence of postoperative complications.

1. It is unclear how this nomogram compares directly with existing triage systems in terms of its predictive accuracy, practical application, and cost-effectiveness. Can you demonstrate the access to ICU care using the eSAS-based nomogram?

Respond to Comment 1:

As previously mentioned, the primary objective of our study was not to directly compare the predictive accuracy of the nomogram system with traditional triage methods. Due to the experimental design, assessing predictive accuracy in this manner is not feasible.

For example, one patient underwent surgery and the nomogram scour was calculated on time in the OR, and the system triage this patient into ICU. On this circumstance, comparing to the ward management, the patient is less likely to develop postoperative complications due to ICU not only "detect complications more sensibly" but also prevent complications. ICU admission based on the nomogram is likely to reduce postoperative complications by detecting and preventing them before they occur. Therefore, direct comparison of predictive accuracy is not feasible.

Additionally, we cannot ascertain which patients in the nomogram group would have been assigned to the ward without using the nomogram, nor can we determine which patients in the control group would have been admitted to the ICU if the nomogram had been applied. In other words, we cannot compare the prognostic differences between the two assessment methods on an individual patient basis, whether a different approach would lead to complications or the absence of complications. This may be considered a limitation of the study. Therefore, the researchers believe that conclusions in this phase II clinical study can only be drawn from overall data.

Here is the process of accessing ICU care using the eSAS-based nomogram:

Intraoperative data, including lowest HR, lowest MAP, and EBL, was collected during

surgery. The eSAS was calculated immediately after surgery completion, and the nomogram score was determined before patients left the operating room. Patients with a score higher than 60 (indicating high risk for postoperative complications) were promptly admitted to the ICU, while low-risk patients were transferred to the ward for grade I nursing care.

2. It remains unclear whether the eSAS-based nomogram can effectively predict the risk of postoperative complications. For example, one patient developed severe postoperative complications (Grade III or IV). Thus, the authors should demonstrate that admission to the ICU following surgery prevents complications after esophagectomy.

Respond to Comment 2:

You mentioned that it remains unclear whether the eSAS-based nomogram can effectively predict the risk of postoperative complications. However, the effectiveness of our nomogram system was thoroughly demonstrated in our previous study, where it effectively predicted the risk of major morbidity after esophagectomy, with an area under the receiver operating characteristics curve higher than 0.9 for both internal and external validation[1].

Regarding the patient who developed severe postoperative complications (Grade III or IV), it's important to note that they were in the Control Group, where the nomogram system was not applied.

Regarding the effect of ICU admission, it's widely recognized that admission to the intensive care unit (ICU) following surgery is crucial for preventing, promptly identifying, and managing life-threatening complications[2]. Selective ICU admission after major surgery has been shown to reduce short-term mortality and morbidity, particularly for complex procedures with prolonged operating time[3,4] Furthermore, While the purpose of our trial design was not to explore whether ICU admission can reduce the incidence of postoperative complications, it's evident from the experimental results and discussion that without the role of the ICU in reducing complications, different screening mechanisms would be meaningless.

3. The authors should focus on postoperative pneumonia because of the significant differences between the Nomogram and Control groups. The eSAS-based nomogram appears to be a good approach for predicting postoperative pneumonia.

Respond to Comment 3:

Certainly, we agree that the reduction in major complications is largely attributed to the decrease in the incidence of pneumonia. We also acknowledge the potential of the nomogram system in effectively reducing the occurrence of pneumonia in practical application. Besides, it's worth noting that these observations are somewhat distinct from predictive accuracy. In our previous research, the system was designed specifically to identify independent factors influencing major complications, and its predictive efficacy has been thoroughly validated. We greatly appreciate your recognition of the capabilities of this nomogram model.

4. There has been no evaluation of the prediction of postoperative complications using the eSAS-based nomogram, which seems to be useful for evaluating the eSAS-based nomogram to calculate sensitivity, specificity, recall, precision, and accuracy.

Response to Comment 4:

It seems there might be a misunderstanding from the reviewer's end. The design of this trial wasn't specifically aimed at evaluating "predictive ability", but rather to determine whether employing a more quantitative triage method could reduce the incidence of complications, shorten hospital stays, decrease hospitalization costs, and improve overall quality of life. The predictive ability of the nomogram has been well-validated in previous studies, both internally and externally. It's important to reiterate that the exploration of predictive ability wasn't the primary endpoint of this phase II clinical trial.

5. This study was limited to patients who met certain inclusion criteria. What do you think about evaluating the effectiveness and safety of the nomogram for patient groups with different underlying diseases, the elderly, and those with various risks of complications?

Response to Comment 5:

Indeed, that's one of the limitations of our study. However, considering this is the first study utilizing the nomogram as a postoperative triage system, introducing too many uncontrollable variables, such as different underlying diseases, elderly patients, or various risks of complications, could significantly confound the final endpoint results. Therefore, we decided to take a step-by-step approach and initially define our target population within the inclusion criteria outlined in the original study. Additionally, based on previous experiments, we have already identified various independent risk factors influencing the occurrence of postoperative complications, and we considered these factors when determining our inclusion criteria.

6. This study demonstrates that using the nomogram can reduce the incidence of complications and the duration of hospital stay without increasing hospital costs. However, there is a lack of specific economic evaluations (cost-benefit or cost-effectiveness analyses). Is there any analysis of the substantial impact of implementing this nomogram on hospital revenue?

Response to Comment 6:

Admittedly, this is another limitation of our study. As a secondary endpoint, we did not conduct a more detailed analysis. Instead, we opted for an overall assessment of patients' hospitalization expenses to obtain a macroscopic comparison of patient expenditures.

Reviewer B

#1 The authors conclude that there is less COMPLICATION in the NG group. However, this may be due to the fact that many of the patients in the NG group were admitted to the ICU. A comparison of postoperative complications in patients admitted to the ICU in the NG and CG

groups should also be made, as well as a comparison of postoperative complications in patients admitted to the ward in the NG and CG groups.

Response to Comment 1:

The nomogram was exclusively utilized for triage purposes in the NG group. We suggest that it was the sensitivity and high efficiency in identifying high-risk patients for ICU admission that contributed to the lower complication rate in the NG group. As discussed by Janowak CF in his article, the nomogram could accurately identify high-risk patients, redirecting those who would have been admitted to the general ward to the ICU, potentially reducing the occurrence of complications. Therefore, we believe it's not simply the increased number of patients sent to the ICU that resulted in fewer complications, but rather the sensitivity of this quantified triage system.

Further explanation for the difference in ICU usage and significant outcomes: Based on the high accuracy of nomogram system shown in the previous study, patients in the Nomogram group who would not have been assigned to the ICU were accurately identified and directed to the ICU. Even though the number of patients benefiting from this "rescue" action might seem small, when compared to the control group, where many patients who should have been in the ICU were not, the rate of complications are statistically different between two groups.

In the NG, 12 patients were sent to the ICU, of which 4 experienced major complications (1 Dysrhythmia, 3 Pneumonia, 1 Recurrent nerve paresis). Conversely, in the CG, 6 patients were sent to the ICU, with only 1 case of Pneumonia observed.

Regarding ward admissions, in the NG, 45 patients were sent to the ward, resulting in 10 cases of major complications (9 Pneumonia, 1 Anastomotic leak, 3 Recurrent nerve paresis). In contrast, in the CG, 54 patients were admitted to the ward, with 29 cases of major complications (22 Pneumonia, 6 Anastomotic leak, 5 Recurrent nerve paresis, 1 Chylothorax, 1 Reintubation, 1 Other Clavien-Dindo class III or IV).

One patient could experience more than one major complication.

Patients admitted to the ICU in the NG were considered high-risk individuals, significantly more prone to developing postoperative complications. Despite their admission to the ICU, the rate of complications remained similar to those admitted to the ICU in the CG. Conversely, in the NG, patients sent to the ward were deemed low-risk, resulting in a consistently low rate of complications even under ward management. In contrast, in the CG, some high-risk patients may have gone unidentified, resulting in an increase in major morbidity.

#2 CONSORT diagram in Figure 2 is complicated. It should be corrected. Also, the ICU admission Ward admission for the NG and CG groups should be entered.

Response to Comment 2:

I apologize for any confusion. Figure 2 was originally drawn according to the standard

model of the CONSORT diagram and was previously corrected by other reviewers. I have made efforts to update the figure to enhance clarity. I acknowledge that it can be challenging to represent our trial process clearly within the constraints of the standard CONSORT diagram model.
Change in the text: I have included the number of patients sent to the ICU as well as the ward in both groups for further clarity. (see page 16. Figure 2.)

#3 "Methods" paragraph is too long. It should be written in a concise manner.
Response to Comment 3:
We apologize for the inconvenience. We aimed to provide comprehensive details of the experimental design. We received feedback from some peers who encouraged us to enhance the Methods section by including more procedural details to improve replicability.
Change in the text: We have made efforts to streamline the content appropriately.(see page 5-6, result section, line 163;172-175)

#4 The paragraph on "Results" is also too long. The description of Table 4 is particularly long and confusing.
Response to Comment 4:
We for the length of the result section and we are sorry for any confusion.
Change in the text: We have made efforts to streamline the content appropriately.(see page 8, line 255-264)

#5 Page 8, line 244, morality is a mistake for mortality.
Response to Comment 5:
Thank you for your diligence!
Change in the text: We have corrected the spelling errors.(page 8, line 240)

1. Xi Y, Shen W, Wang L, Yu C. An esophagectomy Surgical Apgar Score (eSAS)-based nomogram for predicting major morbidity in patients with esophageal carcinoma. *Transl Cancer Res.* 2020;9(3):1732-1741.
2. Pearse RM, Holt PJ, Grocott MP. Managing perioperative risk in patients undergoing elective non-cardiac surgery. *Bmj.* 2011;343:d5759.
3. Janowak CF, Blasberg JD, Taylor L, Maloney JD, Macke RA. The Surgical Apgar Score in esophagectomy. *J Thorac Cardiovasc Surg.* 2015;150(4):806-812.
4. Fahim M, Visser RA, Dijksman LM, Biesma DH, Noordzij PG, Smits AB. Routine postoperative intensive care unit admission after colorectal cancer surgery for the elderly patient reduces postoperative morbidity and mortality. *Colorectal Dis.* 2020;22(4):408-415.