Peer Review File

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Reviewer A

The paper is well written, the results nicely presented and the conclusions support the results of the paper.

Reply: We thank the reviewer for the positive comments on the clarity of the manuscript and the consistency of the conclusions with the results.

Change in the text: We did not change.

Reviewer B

Congratulations on a relatively large case study.

PNI studies on various diseases and conditions have been done, but empyema is an interesting one.

I was wondering if there was more emphasis being done on increasing PNI in your most recent empyema patients?

Reply: We sincerely thank the reviewer for this valuable comment. In the present retrospective study, we did not specifically assess interventions aimed at increasing PNI in patients with empyema. As noted in the manuscript (page 16, line 300), we have mentioned the importance of nutritional improvement in this patient population. We agree that nutritional support to improve PNI may have important implications for patient outcomes, and we have included this point as a perspective for future research.

Change in the text: We have modified our text as advised (see Page 16, line 313).

Reviewer C

The authors demonstrated the utility of PNI score predicting postoperative outcomes after acute empyema surgery.

The content and result are reasonable and acceptable, however, that acknowledgement was already published, so the authors investigated more detailed point comparing with another index such as RAPID score.

We described the revision points below.

1) Result

The authors showed postoperative complication, however, how about 30-day or 90-day mortality? Did the authors include those patients into the groups of death within 1 year?

Reply: We appreciate the reviewer's insightful comment regarding short-term mortality. The 30-day and 90-day postoperative mortality have been included in our analysis of overall mortality within 1 year. Specifically, all patients who died within 30 days and 90 days after surgery have been counted in the "death within 1-year" group. To provide more detailed information, we have added the 30-day and 90-day mortality rates to Table 1 and Supplemental Table 1.

Change in the text: we added the 30-day and 90-day mortality rates to Table 1 and Supplemental Table 1.

Open window thoracotomy is one of severe condition for acute empyema.

How was the correlation between an indication of open window thoracotomy and PNI or the RAPID score?

The surgeons have an interest for supporting information whether or not performing open window thoracotomy for severe acute empyema.

The authors should discuss those points in discussion point.

Reply: We sincerely thank the reviewer for this valuable comment. Of the 75 patients, 6 patients underwent open-window thoracotomy, and only one patient underwent the procedure when excluding those undergoing cancer treatments. Among these patients,

4 patients died within 1 year. The median PNI was low at 25.3 (23.2–28.4), and the median RAPID score was high at 5 (4–5), reflecting severe disease. The median time from hospital admission to surgery was also relatively long at 16 days (2–35). These findings suggest that, in severe acute empyema, performing open window thoracotomy before a further decline in PNI or an increase in RAPID score may be preferable. Nevertheless, given the small number of cases, further studies are warranted to clarify the relationship between PNI, RAPID score, and the indication for open window thoracotomy. We have added this discussion in the revised manuscript to provide additional information for surgical decision-making in severe cases.

Change in the text: We added on OWT and PNI (see page 10, line 182). In addition, we have modified our text as this discussion (see page 14, line 276).

2) In inclusion criteria

The authors included patients with acute empyema in this study and indicated exclusion criteria, however, for inclusion criteria, acute empyema within three month is not described, in contrast, chronic empyema over three months was excluded, So the authors should describe correct inclusion criteria; the common criteria and the selected criteria.

Reply: We thank the reviewer for this helpful comment. We have clarified the inclusion criteria in the Methods section: patients were included if they underwent surgery for acute empyema developing within three months from symptom onset. Acute empyema was diagnosed based on clinical presentation and at least one of the following: purulent pleural fluid, positive culture, pH ≤ 7.2 or glucose ≤ 55 mg/dL in pleural fluid, or CT findings suggestive of pleural infection. Patients with chronic empyema lasting more than three months were excluded.

Change in the text: We have modified our text as advice (see page 6, line 96).

3) Comparison between the RAPID score and PNI

The authors calculated both score and both had a significant value for empyema.

How is the difference analyzed between two score?

The authors should make another ROC curve for the RAPID score and compare with that of ONI for each AUC statistically, which may clarify the two score's value.

Reply: We thank the reviewer for this important comment. In response, we additionally performed a ROC analysis for the RAPID score with respect to 1-year postoperative mortality in patients with acute empyema. In the analysis of all patients, the PNI demonstrated an AUC of 0.73, with a sensitivity of 92% and a specificity of 52%, whereas the RAPID score showed an AUC of 0.73, with a sensitivity of 69% and a specificity of 71%. In the supplementary analysis excluding patients with active cancer, the PNI demonstrated an AUC of 0.73, sensitivity of 100%, and specificity of 41%, while the RAPID score demonstrated an AUC of 0.72, sensitivity of 63%, and specificity of 71%. These results indicate that the PNI tends to have higher sensitivity, whereas the RAPID score shows higher specificity. Therefore, the two scores may provide complementary information when used together for risk stratification in patients with acute empyema. We have included these results and the interpretation in the revised manuscript.

Change in the text: We added some data on ROC analysis (see page 11, line 208). Figure 4 and legend was changed according to adding data (see Figure 4 and page 21, line 482). We have added some considerations based on the analysis results (see page 14, line 272).

4) Nutritional intervention

The authors suggested nutritional support may improve their outcomes.

However, the authors did not mention the detailed treatment method.

Please described in this point.

Reply: We appreciate the reviewer's valuable comment regarding the description of nutritional supplementation. While various reports have investigated perioperative nutritional support, to our knowledge, no studies have specifically examined nutritional therapy during the perioperative period of acute empyema. Based on previous findings in related infectious and surgical settings, immunonutrition-focused supplementation may be beneficial, although further studies are warranted to clarify its role in this

specific context.

Change in the text: We have added this description to the manuscript (see page 16, line 312).

Reviewer D

I have read with great interest the submitted manuscript "Impact of Prognostic Nutritional Index on Postoperative Outcome of Acute Empyema". The concept of using a simple blood-based test to help prognosticate surgical outcomes of acute empyema is intriguing. However, there are a number of variables that the authors do not report that limit the applicability of this study. The first, which should be available in a single, institution retrospective study is time from admission to surgery. This variable has been associated with both short-term mortality as well as long-term outcomes. I would encourage the authors to consider the below points to strengthen their manuscript to see if PNI remains associated with surgical outcomes. The "Major Points" need to be addressed. The "Minor Points" are some ideas to consider.

Major Points:

1. The time from admission to surgical intervention was not discussed. This is important as the largest retrospective study on empyema (not cited in this manuscript) demonstrates changes in mortality over the first 5 days after admission prior to surgery and then changes in patient outcomes if surgery is delayed beyond 5 days without a change in mortality.(Towe et al, JTCVS 2018). It would be of value to report the time from admission to surgical intervention (median and ranges) for the group that survives over 1 year and those that die within a year. This is important as those with longer lengths of stay and more complications were more likely to be in the group that did not survival 1-year. Therefore, was there a delay is surgery in this group that set them on this path?

Reply: We sincerely appreciate the reviewer's insightful comment regarding the

interval from hospital admission to surgery. In response, we analyzed this variable in our cohort. Among all patients, the median time from admission to surgery was 2 days (range, 0–42 days) in the survival group and 2 days (range, 0–63 days) in the 1-year mortality group, with no significant difference observed (P = 0.43). In the supplementary analysis excluding patients with active cancer, the median time was also 2 days (range, 0–42 days) in the survival group and 2 days (range, 0–63 days) in the 1-year mortality group, again with no significant difference (P = 0.79).

As our institution generally proceeds to surgical intervention relatively early once acute empyema is diagnosed, the interval from admission to surgery was short in both groups. This likely explains why no significant association between time to surgery and 1-year survival was observed in our cohort.

Change in the text: These results have been added to Table 1 and Supplemental Table 1, and the P-values have been included in the text (see page 9, line 170). We also added a statement regarding this finding (see page 14, line 281). Additionally, we cited Towe et al. (J Thorac Cardiovasc Surg. 2019;157:1288–1297.e4) to provide context regarding the potential impact of surgical timing on outcomes in empyema patients.

2. In the RESULTS section, the variables that are different between the survival and non-survival groups are listed. What is “procedure”? Do the authors mean “operative approach”?

Reply: To clarify, we have changed all instances of “procedure” to “surgical approach” throughout the manuscript, including the text, Table 1, and Supplemental Table 1.

Change in the text: We have changed all instances of “procedure” to “surgical approach” throughout the manuscript, including the text, Table 1, and Supplemental Table 1.

3. As for operative approach, the study mentioned in “Major Point #1” demonstrated lower mortality and complications with VATS compared to open. This is demonstrated in this manuscript also in a univariate analysis. This should be explored in a multivariate analysis.

Reply: We sincerely appreciate the reviewer's insightful comments regarding the impact of surgical approach on treatment outcomes. As the reviewer noted, the number of patients in this study was relatively small (75 cases total, 66 cases excluding patients with active cancer). Consequently, we initially refrained from performing multivariate analysis to avoid instability in the estimated values. Following the reviewer's suggestion, we conducted exploratory multivariate analyses including surgical approach and PNI. However, due to sample size limitations, none of the variables, including surgical approach or PNI, reached statistical significance.

Change in the text: We have added this point to the Results section (see page 12, line 231) and included the multivariate analysis results (see Table 3). Furthermore, in the Discussion section (see page 13, Line 255), we added further consideration, noting that a large-scale study with sufficient sample size is necessary to clarify the independent prognostic impact of PNI. Based on this, we also revised the Methods section (see page 8, line 153) and Limitations section (see page 16, Line 324).

4. If patients already had cancer, it is possible that they might have died within 1 year anyway. Also, a patient with advanced cancer may be malnourished and may be frailer than those without cancer. Therefore, this is a confounding variable and should be addressed. One way is to eliminate patients who were actively being treated for cancer or who had active cancer.

Reply: We sincerely thank the reviewer for this valuable comment. We agree that the presence of active cancer or patients undergoing cancer treatment may represent an important confounding factor, as these patients are more likely to be malnourished and frail, which could influence both PNI and survival outcomes. To address this concern, we conducted a supplementary analysis excluding such patients. The results demonstrated that PNI remained a significant predictor of postoperative outcomes, including 1-year mortality. These findings suggest that the prognostic impact of PNI may be not solely attributable to the presence of cancer.

Change in the text: We have added these results to the Methods (see page 6, line 103) and Results section (see page 9, line 172; page 10, line 180; page 10, line 195; page 11,

line 210; page 11, line 218, and page 11, line 227). We also added a Supplementary Appendix describing the results of these analyses. Based on these findings, we expanded the Discussion (see page 12, line 239).

5. The sentences that begins at line 160 and end at line 162; which PNI is a predictor? The preop or postop? What about a patient that has an improvement between the two?

Reply: We sincerely appreciate the reviewers' valuable comments. To clarify the timing of PNI measurements, we have added “preoperative” or “postoperative” to the PNI section in the Results and Discussion. Regarding the potential impact of postoperative improvement, this point is already addressed in the manuscript (see page 15, line 282 and page 15, line 296). Specifically, we describe that preoperative PNI was used as a predictor of postoperative outcomes, and that patients with low preoperative PNI who experienced improvement within the first 7 days after surgery had a 1-year survival rate comparable to that of patients with high preoperative PNI. We greatly appreciate the reviewers’ careful reading and hope that this clarification addresses the concerns raised.

Change in the text: We added “preoperative” or “postoperative” to the PNI section in the Results and Discussion.

6. The sentence that starts on line 173; so, the authors think that more studies should be done to determine the usefulness of PNI with surgical cases of acute empyema? I thought that was the purpose of this study. Do the authors mean that more studies should be done to validate these findings? Please clarify. This is important and the next sentence (first of the next paragraph, line 175) says that PNI may be a useful marker for prognosis in these cases.

Reply: We sincerely appreciate the reviewer’s careful reading and constructive comments.

Regarding the comment about the clarification of the purpose of further studies on PNI: we agree that the main purpose of our study was to evaluate the usefulness of PNI as a prognostic factor in surgical cases of acute empyema. However, to clarify the wording and prevent potential misunderstanding, we have revised the Discussion to indicate that

further studies are needed to validate our findings in larger, multi-center cohorts and in diverse patient populations, ensuring the generalizability of the results.

We believe that these revisions make it clear that while our study demonstrates the potential utility of PNI as a prognostic marker, additional studies are warranted to confirm and generalize these observations.

Change in the text: We have modified our text as advice (see page 14, line 278).

7. What do the authors mean by "treatment efficacy"?

Reply: We appreciate the reviewer's question regarding the term "treatment efficacy." In our manuscript, this term was intended to refer to the effectiveness of surgical intervention in combination with perioperative management, including nutritional support and infection control measures.

Change in the text: To improve clarity, we have revised the relevant sentences in the Discussion to explicitly describe these components (see page 15, lines 292).

8. The authors state that the goal of surgery for acute empyema "may be to completely irrigate the pleural cavity and re-expand the lung". Most surgeons consider the goals to be 1) source control and drainage of the empyema; 2) decortication; 3) achieve pleural-pleural apposition. In fact, in the study cited by Shen et al, the "2 primary goals" 1) complete evacuation of potentially infected fluid and/or material and 2) complete re-expansion of the lung. In other words: evacuation and expansion. I would encourage the authors to revise their manuscript to appropriately quote the citation.

Reply: We sincerely appreciate the reviewer's insightful comment. In response, we have revised the manuscript to more accurately reflect the primary goals of surgery for acute empyema, based on the cited literature.

Change in the text: We have modified our text as advice (see page 15, line 299).

Minor Points:

1. At line 40, a comma is not needed between "serum albumin level, and total lymphocyte count". In fact, I would consider revising that entire sentence into 2

separate sentences.

a. Consider as an option: The prognostic nutritional index (PNI) is a blood test-based score used to assess the nutritional and immune status of a patient and is considered a prognostic predictor in many respiratory diseases including: lung cancer, transplantation, and pneumothorax.(8-10) It is easily calculated from only the serum albumin level and total lymphocyte count.

Reply: We sincerely thank the reviewer for this helpful suggestion. In accordance with the comment, we have revised the sentence to improve clarity and grammar by separating it into two sentences and removing the unnecessary comma. The revised text now reads:

"The prognostic nutritional index (PNI) is a blood test-based score used to assess the nutritional and immune status of a patient and is considered a prognostic predictor in many respiratory diseases, including lung cancer, transplantation, and pneumothorax.(8-10) It is easily calculated from only the serum albumin level and the total lymphocyte count.".

Change in the text: We have modified our text as advice (see page 5, line 75).

2. In the methods it states that 75 patients underwent surgery for empyema with 5 being excluded for various reasons. However, in the results it states that 80 patients underwent surgery for pleural infections. While this is the same, consider to report only the inclusion and exclusion criteria in the METHODS without any results (80 patients with surgery, 75 with acute empyema, etc.…).

Reply: In accordance with the comment, we have revised the METHODS section to describe only the inclusion and exclusion criteria without reporting patient numbers. The detailed patient numbers are now reported exclusively in the RESULTS section.

Change in the text: We have modified our text as advice (see page 5, line 94).

3. The term "complications of air leak" is not defined. Is this an air leak longer than 5 days? Please define this term.

Reply: We appreciate the reviewer's insightful comment. In our manuscript, the term

"complications of air leak" was intended to describe *empyema with a fistula*, rather than postoperative prolonged air leak. To avoid confusion, we have revised the terminology in the tables and Results section from "complications of air leak" to "empyema with a fistula." We believe this change improves accuracy and clarity.

Change in the text: We have modified our text (see page 9, line 166), Table 1, and Supplementary Table 1 as comment.

4. Were they any patients that the PNI decreased from preop to postop checks? Where there any that had a preop value of > 29.3 and post-op it was less than 29.3? If so, how did those patients do?

Reply: We sincerely appreciate the reviewer's insightful comment regarding potential postoperative decreases in PNI and their impact on outcomes. In response, we have added the following clarification to the Results and Discussion sections: among patients with a preoperative PNI >29.3, 12 patients experienced a postoperative decline below the cutoff value, and 2 of these patients (16.7%) died within 1 year. Although the small number of cases precluded formal statistical analysis, this observation suggests that deterioration of nutritional and immune status after surgery may negatively affect postoperative outcomes. We believe this additional information addresses the reviewer's question and highlights the importance of monitoring and supporting perioperative nutritional status.

Change in the text: We added some analyses (see page 12, line 229). Based on these findings, we expanded the Discussion (see page 15, line 306).

5. It is well known in the literature that nutritional status plays an enormous role in outcomes of patients undergoing surgery for cavitary NTM (non-tuberculosis mycobacterium) disease. In fact, optimizing nutrition is one of the key points pre-operatively that is known to be associated with improved outcomes. Did the authors consider looking into these methods (as it relates to their statement starting at line 187)?

Reply: We sincerely appreciate the reviewer's insightful comment regarding the role of nutritional optimization in surgical outcomes. As noted, evidence from other surgical

populations, including patients undergoing surgery for cavitary NTM disease, demonstrates that preoperative nutritional optimization—such as high-protein diets, immune-modulating nutrients (e.g., arginine, omega-3 fatty acids), and timely initiation of enteral nutrition—can improve postoperative outcomes. In the present study, we did not implement or evaluate specific perioperative nutritional interventions. However, we agree that targeted nutritional support to improve PNI may be an important strategy to enhance postoperative outcomes in acute empyema.

Change in the text: We have added a corresponding statement to the Discussion to highlight this point (see page 16, line 312).

6. While not significant (p-value = 0.11) those that died had a lower C-reactive protein (CRP). This would imply that inflammation may not be as important in the eventual outcomes. Was CRP considered in the multivariable analysis? Was CRP tracked? In patient 7 days after surgery was it higher or lower than those that survived?

Reply: We sincerely appreciate the reviewer's insightful comments regarding CRP. To address this, preoperative CRP was included as a variable in the multivariate analysis. Additionally, we evaluated postoperative CRP measured on day 7. In the overall cohort, there was no significant difference between the survival and death within 1-year groups in either preoperative CRP (P = 0.11) or postoperative CRP (P = 0.25). In the supplementary analysis excluding patients with active cancer, results were similar (preoperative CRP, P = 0.075; postoperative CRP, P = 0.88). These findings have been added to the Results section (page 10, line 176). Our data suggest that, within this cohort, CRP may not be a major determinant of 1-year postoperative outcomes, although further studies could explore other inflammatory markers or dynamic measures of inflammation.

Change in the text: We added some analyses (see Figure 3, Supplemental Figure 2, and page 10, line 198). Based on these findings, we expanded the Discussion (see page 15, line 294).

Reviewer E

The authors conducted a retrospective analysis examining the correlation between preoperative nutritional index and one-year survival after surgery. They found that a prognostic nutritional index (PNI) <29.3 was associated with worse prognosis in their cohort. In addition, among patients with a low PNI at surgery, postoperative improvement in PNI was associated with better survival. I agree with the authors that this convenient evaluation method may be useful for clinicians. The manuscript is interesting and potentially valuable; however, several issues need to be clarified before acceptance.

1. The enrollment criteria were limited to acute empyema, but the definition of "acute" empyema is not clearly described. Please specify the period between disease onset and surgery that was used for this definition.

Reply: We thank the reviewer for pointing out the need to clarify the definition of "acute empyema." In response, we have added a detailed description of acute empyema and the inclusion/exclusion criteria in the Methods section (see paragraph inserted after the sentence describing patient enrollment). We believe this clarifies the criteria used to define acute empyema and ensures reproducibility of the study.

Change in the text: We have modified our text as comment (see page 6, line 94).

2. The operative procedure is an important factor in evaluating the value of PNI, because patients undergoing open-window thoracostomy may find it difficult to recover their PNI postoperatively. The inclusion of cases with bronchopleural fistula, which are known to carry a higher mortality compared to other conditions, could introduce bias. Please clarify this point.

Reply: We appreciate the reviewer's comment regarding the potential bias introduced by patients with bronchopleural fistula. In our cohort, nearly all patients with bronchopleural fistula were also patients with active cancer. Therefore, in the supplementary analysis excluding patients with active cancer or those undergoing

cancer treatment, these patients were effectively excluded as well. Importantly, even after excluding these potential confounders, low preoperative PNI remained significantly associated with poor postoperative outcomes, including 1-year mortality. This suggests that the observed association between low PNI and adverse postoperative outcomes is not solely attributable to the presence of bronchopleural fistula.

Change in the text: We expanded the Discussion (see page 12, line 242).

3. Please provide information on the severity or stage of empyema in Table 1, and include the correlation between empyema severity and the type of surgical procedure performed.

Reply: Thank you for this valuable comment. In response, we have added the empyema stage to Table 1. Furthermore, we performed an additional analysis to evaluate the relationship between empyema stage and surgical procedures. The results are presented in a new table. This analysis showed that advanced empyema stages were more frequently treated with open surgery, which is consistent with the clinical difficulty of performing VATS in organized empyema. Although the supplementary analysis excluding cancer patients did not reach statistical significance, the same trend was observed. We also revised the Discussion section to mention this finding and clarified that empyema stage was assessed retrospectively as an additional analysis, since the surgical indication at our institution was primarily determined by other clinical factors.

Change in the text: We added some analyses (see Table 2, Supplemental Table 2, and page 10, line 178). We also expanded the Discussion (see page 16, line 327).

4. Please confirm whether any patients with poor nutritional status and acute empyema received perioperative nutritional support at your institution.

Reply: Thank you for your valuable comment. As described in the Methods section, patients who underwent surgery for acute empyema at our institution did not receive special nutritional support before or after the operation. We have also expanded the Discussion to address the potential role of perioperative nutritional optimization based on recent evidence and clinical guidelines.

Change in the text: We did not change. We described in the Methods section (see page 7, line 122).

5. The change in PNI before and after surgery seems to reflect the degree of systemic inflammation. Was there any correlation between perioperative changes in PNI and C-reactive protein (CRP) levels?

Reply: Thank you for your comment. We analyzed the correlation between perioperative changes in PNI and CRP levels and found a significant positive correlation ($r = 0.292$, $P = 0.012$), suggesting that improvements in PNI may partly reflect resolution of systemic inflammation. We will add this point to the Discussion section.

Change in the text: We added some analyses. (see page 11, line 203) Based on these findings, we expanded the Discussion (see page 14, line 294).

6. How were patients who underwent negative-pressure wound therapy evaluated for PNI on postoperative day 7?

Reply: Thank you for your comment. For patients who underwent negative-pressure wound therapy (NPWT), the PNI on postoperative day 7 was measured based on the date of the window surgery, not from the start of NPWT. This point has been clarified in the Methods section (page 7, line 128).

Change in the text: We have modified our text as comment (see page 7, line 128).