

Peer Review File

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Reviewer A

This research is about the sarcopenia in patients with adult cardiac surgery in Korea. Sarcopenia was measured by bilateral psoas muscle mass areas at the level of the top of the iliac crest in abdominal CT. The author demonstrated the presence of sarcopenia corresponded to longer mechanical ventilation and longer ICU stay. In addition, the nutritional risk index could predict the presence of sarcopenia. There were several issues to be addressed.

Comment 1: In the abstract, the authors mentioned “NRI could offer a potentially simpler, faster means than muscle strength or mass measurement for screening sarcopenia.” What did the word “muscle strength” mean? I could not find the data about muscle strength in this manuscript.

Reply 1: We apologize for any confusion that may have arisen during the summarization of the manuscript into the abstract. In the introduction, we presented a screening method for sarcopenia, which involves measuring muscle strength, such as grip strength, chair stand test. We included this information in the abstract to aid in comprehension. Unfortunately, due to the retrospective nature of the study, we were unable to obtain preoperative muscle strength data. The study highlights the potential for using the NRI to screen for sarcopenia in patients identified as having low muscle mass prior to undergoing cardiac surgery. As a result, we have revised the conclusion of the abstract.

(Page 2, line 27-28, and page 4, line 46-48)

Comment 2: The topic about BMI suddenly appeared in the last part of the results.

Reply 2: Several studies have analyzed the difference between sarcopenia in individuals who are obese versus those who are not. In our research, we conducted a subgroup analysis divided by BMI, which yielded significant results. As a result, we sought to report the findings of the subgroup analysis for both obese and non-obese sarcopenia in the result section.

Comment 3: I think nutritional marker might directly correspond to perioperative clinical course independently from the sarcopenia. Which is the more appropriate predictor of postoperative clinical course between nutritional score and sarcopenia?

Reply 3: Indeed, we concur that both the nutritional score and sarcopenia are independent factors that impact postoperative clinical outcomes. Our study's primary objective was to investigate the potential of nutritional indices to predict the presence of sarcopenia. Additionally, we aimed to examine whether clinical outcomes might be better predicted when nutritional indices and the presence of sarcopenia are identified together. Going forward, we intend to explore prognosis factors that could affect post-cardiac surgery clinical outcomes, including age, BMI, EuroSCORE II,

sarcopenia, and nutritional index in the future study. We revised the introduction section to clarify the aim of this study.

(page 5, 69-73)

Comment 4: There had been several reports about the association between inflammation and sarcopenia. How about the difference in postoperative inflammatory marker between patients with and without sarcopenia?

Reply 4: After undergoing cardiac surgery, the inflammatory markers of all patients tend to rise and then gradually decline during the recovery phase. The duration of normalization varies depending on the postoperative clinical course. Furthermore, this study is retrospective, and therefore, we were unable to obtain data on the inflammatory markers during the same postoperative period for all patients.

Comment 5: What is the definition of “early mortality”? Did it correspond to in-hospital death in the method section?

Reply 5: Yes, it does. We changed “early mortality” to “in-hospital death” in the manuscript and table to help readers understand clearly.

(page 8, line 134, table3, supplementary table 2 and 3)

Reviewer B

This study reports about the usage of nutritional indices as a screening tool for sarcopenia. In their trial, the researchers examined the predictive capacity of 3 nutritional indices (Controlling NUTritional stats (CONUT score), Prognostic Nutritional Index (PNI) and Nutritional Risk Index (NRI)) for sarcopenia, defined as the lowest sex-specific quartile of the psoas area index. They showed that NRI was the best predictor for sarcopenia with a sensitivity of 68 % and a specificity of 65 %, compared to the other nutritional indices.

You address the need for a sarcopenia screening tool, which is independent from physical activity and therefore applicable in patients in the intensive care unit or patients with restricted physical activity. This is a very interesting paper, which, at least, establishes a link between muscle mass and nutritional status further. The NRI may not only be an easy to perform and available screening tool for sarcopenia. If we could establish this connection further, it could be a monitoring tool for nutritional interventions in our patients, which may improve their outcomes further.

In my opinion, your paper may benefit further from clarification of the following points:

Comment 1: In general, I recommend language editing of the manuscript by a native speaker. There are many unfortunate phrases with grammatical errors, which may impair the understanding of the content.

Reply 1: Thank you for providing your feedback. We have taken it into consideration and revised the manuscript with the assistance of a native speaker.

Comment 2: As cited by you, sarcopenia is defined by the European Working Group on Sarcopenia in Older People 2, by reduced muscle strength AND mass. As no data is available about the muscle strength of your patients, I suggest the usage of “muscle mass” or “muscle areas” instead of “sarcopenia”, as you cannot diagnose sarcopenia in your patients accurately yet.

Reply 2: Indeed, we agree with your statement. We acknowledge that there is no universally accepted definition of sarcopenia, and our study had its limitations. Although sarcopenia is typically associated with elderly patients, younger patients with heart disease can also develop it due to decreased activity levels. For the purpose of this study, we defined sarcopenia as the lowest sex-specific quartile, based on the measurement of muscle mass obtained from abdominal CT scans. We should note that previous studies have employed similar definitions of sarcopenia.

Minor comments:

Abstract

Please spell out abbreviations, when you use them for the first time in the text and in the abstract.;

Reply: We appreciate your comments. We have made an effort to use full terms instead of abbreviations. However, in instances where the same term is repeatedly used, we have utilized abbreviations to ensure the manuscript's brevity.

(page 2, line 33, 44-45)

Line 35: Please provide numbers and percent

Reply: We added numbers and percent.

(page 2, line 37-38)

Line 36-37: Please provide the area under the curve with confidence intervals for each nutritional score

Reply: We fill in the area under the curve with confidence intervals.

(page 2, line 39-42)

Line 38: Consider clarifying, that the stated sensitivity and specificity is for prevalence of sarcopenia, not the postoperative outcome

Reply: We amended the sentence to clarify.

(page 2, line 43-44)

Line 38-39: Please provide the group comparison of the mechanical ventilation time and length ICU stay.

Reply: We added the data of mechanical support and intensive care stay time.

(page 2, line 44-45)

Highlight Box:

Key findings:

I disagree with your conclusion, that a nutritional index could provide a measurement

for muscle strength, nor does your data support this finding, since you did not measure muscle strength in your trial. Please consider revising the sentence, i.e. “Nutritional risk index may be an alternative assessment tool to screen for sarcopenia”.

Reply: Thank you for your valuable comments. We amended the sentence to clarify a meaning.

(page 4, line 52)

What is known and what is new?

Muscle mass is not a screening tool, but a tool for confirmation according to Cruz-Jentoft et al.

Reply: Yes, we revised the sentence. (page 4, line 52)

What is the implication and should change now?

Efforts to keep ventilation time and length of stay in the intensive care unit should be made in every patient, regardless of the presence of reduced muscle mass. Please consider revising this sentence, i.e. “Screening patients with the nutritional risk index may allow to identify sarcopenic patients at special risk for adverse postoperative outcomes with consecutive possibility for intervention.” Also you could mention the possibility to monitor the influence of optimized nutrition on the nutritional/muscle status of the patient.

Reply: Thank you for your valuable comments. We revised the paragraph.

(page 4, line 52)

Methods:

Line 95: This sentence is redundant, as it is described in the section “Statistical Analysis”.

Reply: Thank you for your advice. We removed the sentence.

(page 7)

Line 78 ff: Since there is no internationally acknowledged cut-off value of psoas muscle area indices and most used cut-offs are data-driven, the information about the selection of the cut-off is crucial. You describe your choosing process sufficiently. However, please state the sex-specific cut-off values chosen in your paper to ensure comparability with the literature, especially since they may differ between different ethnic groups.

Reply: To date, there is no universally recognized cut-off value for psoas muscle area indices. However, since several previous studies have defined sarcopenia using the lowest sex-specific quartile, we adopted this approach in our research. We have revised the relevant sentences and included literature to support our choice of definition.

(page 6, line 88-91, reference 12)

Line 85 ff: Please indicate additionally to the given formula, if a lower or higher value

indicates a poorer nutritional state.
Reply: Thanks, we added sentence.
(page 7, line 102-103)

Line 90 ff/ 140 ff: Although perhaps not externally validated, Barge-Caballero et al suggested cut-off values for the NRI, which are widely used and relevantly lower than yours. Please consider adapting their cut-off values or at least include a statement, why those cut-off values are not applicable in your cohort.

Reply Currently, there are no validation studies available for NRI cut-off values. As a result, As a result, we have utilized sex-specific quartiles to define our analysis following the methodology employed in prior research studies.

Is it applicable to calculate the SARC-F score from your clinical data, to compare this from Cruzt-Jenthoft et al proposed screening tool with the NRI?

Reply: We are sorry that we are not able to calculate the SARC-F score because this study is retrospective.

Statistical Analysis:

Please provide information, how you chose the optimal cut-off value for the nutritional indices. Did you use Youden-Index?

Reply: CONUT score was calculated using the CONUT scoring system (Supplementary table 1) that was referred to by validated studies. Undernutrition degree was classified as normal (CONUT 0-1), mild (CONUT 2-4), moderate (CONUT 5-8), or severe (CONUT 9-12). However, there is no valid study for PNI and NRI. Hence, patients were also grouped based on sex-specific quartiles of PNI and NRI, with the lowest quartile of PNI and NRI denoting malnutrition. These details were included in paragraphs on patients and study design.

Results:

Is there a linear correlation between psoas area index and nutritional indices? If you find a correlation, you should discuss, why.

Reply: Thank you for your comments. To assess the significance of differences in the distribution of sarcopenia among the four groups of NRI, PNI, and CONUT, we utilized the Linear by Linear Association test. Additionally, we conducted a linear correlation analysis between the psoas muscle area index and nutritional indices. However, since there were no significant correlation coefficient, we did not discuss this further.

Variable	correlation coefficient	p-value
Psoas muscle area index - PNI	$r = 0.160$	< 0.001
Psoas muscle area index - NRI	$r = 0.152$	0.001
Psoas muscle area index - CONUT	$r = - 0.130$	0.004

A subanalysis of the area under the curves for the different components of the

nutritional indices and the BMI as a prediction tool for sarcopenia would be very helpful, especially in cardiac patients, who experience weight changes with fluid accumulation. It would allow following a discussion, why the NRI may be the best index to predict sarcopenia.

Reply: In the discussion section, we outlined the reasons why NRI might be the most effective index for predicting sarcopenia. Firstly, unlike PNI and CONUT, NRI is calculated based on body weight. Secondly, as malnutrition often results in low albumin levels, and NRI is calculated using serum albumin levels, it is likely to be a reliable indicator of sarcopenia. Finally, the relationship between sarcopenia and malnutrition may be influenced by inflammation, which NRI takes into account.

Please consider an (adjusted) logistic regression analysis to conclude, if the NRI or the psoas area index is more predictive for clinical outcome. Additionally, it would allow adjustment for other known risk factors as the EuroScore, especially, since the clinical risk indicated by the EuroScore differs significantly between sarcopenic and non-sarcopenic patients.

Reply: Thank you for your valuable comments. Our study aimed to investigate the effectiveness of nutritional indices in predicting the presence of sarcopenia, as well as whether nutritional indices and sarcopenia could better predict early outcomes rather than one factor of nutritional indices or sarcopenia. If our objective was to identify risk factors for early outcomes, we would have conducted a logistic regression analysis using variables such as age, EuroScore, psoas muscle area index, and nutritional indices.

Discussion:

Line 168: According to your cited source, gait speed is not a screening tool for sarcopenia, but helps distinguishing between different levels of sarcopenia.

Reply: Thank you for your suggestion. Gait speed is a commonly used measure to assess physical performance. We have made the necessary revisions to the manuscript.

(page 10, line 178-180)

Line 177: nutritional indices are not diagnostic tool for sarcopenia, although they may help to screen for patients at risk.

Reply: Indeed, we concur that nutritional indices are not intended to serve as a diagnostic tool for sarcopenia. However, compared to other modalities, nutritional indices are faster, simpler, and more reproducible. This retrospective study was the first investigation of whether nutritional indices could potentially be utilized to screen for sarcopenia among cardiac surgery patients.

Line 181: As mentioned in your discussion, the proposed definition for sarcopenia by Cruz-Jentoft et al is to screen for sarcopenia with identification of patients with low muscle strength and confirm the diagnosis with measurement of muscle quantity or quality. Due to the retrospective design, it does not seem to be possible to compare the

results of the NRI directly with muscle strength measurements directly. However, it would be helpful to compare the sensitivity and specificity of the NRI with sensitivity and specificity of grip strength measurements etc for impaired muscle mass from the literature in your discussion. There is a lot of research, which describes the link between nutrition and sarcopenia. You should discuss this further in regard of the recent literature.

Reply: Thank you for your feedback. We have included additional comments in the discussion section.

(page 11, line 193-197, reference 23-26).

Line 178/196: First you mentioned, that this is the first study describing the relationship between nutritional indices and sarcopenia, however later you cite a study in diabetic patients, which researched the relationship between NRI and sarcopenia.

Reply: Although studies have been conducted on the correlation between NRI and sarcopenia in diabetic or hemodialysis patients, this current study is the first to investigate this relationship in adult cardiac surgery patients.

Also as a clinical implication, you could discuss preoperative optimization of nutrition as an intervention for sarcopenic patients and the possibility of monitoring this by the NRI

Reply: We appreciate your comments. We have included sentences regarding the clinical implications of our findings in the discussion section.

(page 12, line 216-223, reference 31, 32)

Study limitations: One of the main pitfalls of this study is, that all the results are data-driven since you chose cut-off values based on your own data set. You should discuss this and explain why you did not adapt cut-off values from the literature.

Reply: Currently, there are no validate cut-off values of the relationship between NRI and sarcopenia available for adult cardiac surgery patients. We utilized a quartile classification approach, commonly used. And we have included the limitation

(page 13, line 240-242)

Line 211: the prevalence of sarcopenia is driven by the fact, that you chose the lowest quartile of your cohort, therefore it has to be 25 %, as in other studies, who chose their cut-off by the lowest quartile of the cohort. Additionally, the incidence cannot be established, since this study does not include serial measurements.

Reply: 124/499 patients were sarcopenia (24.8%). We misunderstand the hazard ratio and amended it to the odds ratio.

(page 9, line 161, table 4)

Table 1:

Please check the stated values for body mass index: according to the indicated unit, they should be higher. Maybe, the decimal sign is misplaced?

Reply: Yes, we misplaced the decimal sign. We revised table 1.

(table 1)

Table 2:

Please check the significance of the difference according to the CONUT score. Regarding the stated median and interquartile range, a significant difference between the groups seem to be unlikely.

Reply: The median and IQ range of CONUT scores were identical across the groups, and it may appear that there is no statistical significance between them. However, the distributions were indeed statistically significantly different by Mann-Whitney U-test. Moreover, there were also differences in the means and standard deviations of the groups (1.89 ± 1.67 and 2.66 ± 2.31), which were included in table 2.

Percentile	5	10	25	50	75	90	95
Non-sarcopenic	0	0	1.0	2.0	3.0	6.0	7.25
Sarcopenic	0	0	1.0	2.0	3.0	4.0	5.0

As these were non-normally distributed continuous variables, we presented the median and IQ range. After performing the Mann-Whitney U-test, we found that p-value was < 0.001 .

Figure 3:

This figure is unclear for the outstanding reader and it costs a considerable amount of time to understand it. The combination of total and gender specific columns overloads the figure. Please consider at least color-coding total vs. gender groups (for example with different densities of the same color) or the more traditional Venn diagram to display your results. If you chose to keep this presentation, please label the y-axis. Figure 3c is mentioned in the figure legends, but not within the text. The results for the PNI/Figure 3c are not displayed in the graphical presentation.

Reply: Thank you for your suggestion. We have made the necessary changes to Figure 3, and now it only displays the data related to sarcopenia.

(figure 3)

Reviewer C

Comment 1: Using nutrition tool to screen for sarcopenia? Why not use sarcopenia-related tools (SARC-F, Handgrip)?

Reply 1: As this was a retrospective study, we were unable to utilize sarcopenia-related tools specifically designed for assessing sarcopenia. Instead, our aim was to explore the feasibility of using nutritional indices, which are faster, simpler, and more reproducible, as screening tools for sarcopenia in cardiac surgery patients.

Comment 2: The conclusion the authors draw is faulty – in this manuscript, nutrition screening tools are compared to muscle mass via CT scan. A more useful comparison

would be to compare a screening tool for nutrition with a screening tool for sarcopenia (e.g. SARC-F, handgrip-strength), or to compare a screening tool for sarcopenia with muscle mass obtained via CT-scan

Reply 2: Thank you for your suggestion. However, the main objective of this study was to evaluate the ability of nutritional indices to screen for sarcopenia, rather than comparing their usefulness with other screening tools. Nevertheless, we appreciate your suggestion and will consider conducting a comparative study between NRI and other screening tools in the future.

Comment 3: The here presented “nutrition”- scores are not the ones recommended by the international guidelines and they are mostly based on blood analyses which are uniformly not recommended for use. Especially the CONUT and PNI Score seem to consist only of labwork and such are in no way recommended to be used to detect either malnutrition or sarcopenia. It is therefore unsurprising that they yielded no results!

Reply 3: Yes, we agree that this study had an observational and retrospective design, which limited our ability to obtain extensive data and compare multiple nutritional indices. In future research, we plan to explore and compare various scoring and evaluation methods for nutrition and sarcopenia in a more robust study design.

Comment 4: I suggest using actually recommended tools (GLIM, NRS, NUTRIC, MUST, SGA)

Reply 4: Yes, we agree with your recommendation. In future research, we will design to incorporate the tools you have suggested.

Comment 5: Methods: The design is unclear. What were the defined inclusion criteria?

Reply 5: We outlined the inclusion criteria in the methods section. We collected a total of 655 patients aged > 18 years who underwent cardiac surgery using CPB. Among them, 499 patients who underwent preoperative abdominal CT and had their serum cholesterol levels checked were included in the study.

Comment 6: These are rather low sensitivity and specificities, even for the NRI, which was “best” to predict sarcopenia. Hence none of them are useful for the determination of sarcopenia- as is to be expected from lab-work-relying nutritional screening tools.

Reply 6: Yes, we agree that NRI is not the optimal tool for predicting sarcopenia, but our study demonstrated that NRI has potential as a screening tool for sarcopenia in cardiac surgery patients. This study was the first of its kind to focus on this specific patient population. In the future, we aim to conduct a prospective study to validate the sensitivity and specificity of NRI in screening for sarcopenia before cardiac surgery.

Minor points:

Introduction

P4, L 53: this is incorrect. Gait speed is a measure of physical function, not muscle mass.

Reply: Yes, gait speed is a measure of physical function not of muscle strength. We amended the sentence.

(page 5, line 56-57)

P4 L 56: there are tools for ICU patients, e.g. quadriceps ultrasound, anthropometry, BIA

Reply: Yes, we agree that there are existing tools to measure muscle mass for ICU patients, but these methods tend to be more time-consuming, less reproducible, and less straightforward. In this study, we aimed to identify a more rapid and simpler screening method for sarcopenia in cardiac surgery patients by examining nutritional indices based on previous research.