Re: Response for manuscript R1 "Prognostic Value of 11-factor Modified Frailty Index in Postoperative Adverse Outcomes of Elderly Gastric Cancer Patients: A Retrospective Cohort Study"

Dr. editor

Thanks for providing us with this great opportunity to submit a revised version of our manuscript. We appreciate the detailed and constructive comments provided by the reviewers. We have carefully revised the manuscript by incorporating all the suggestions by the review panel. We hope this revised manuscript has addressed your concerns, and look forward to hearing from you.

Responses to the comments from Reviewers.

Reply to Reviewer # 1

Dear Reviewer,

We also appreciate your clear and detailed feedback and hope that the explanation has fully addressed all of your concerns. In the remainder of this letter, we discuss each of your comments individually along with our corresponding responses. To facilitate this discussion, we first retype your comments in *italic font* and then present our responses to the comments. Changes to the manuscript are shown in red.

Comment 1: *Article title needs streamlining.*
Response 1: Thank you for your invaluable advice. After a strict abridgement of the vocabulary, we finally revised it to: Prognostic Value of 11-factor Modified Frailty Index in Postoperative Adverse Outcomes of Elderly Gastric Cancer Patients: A Retrospective Cohort Study.

Comment 2: *The study is well conceiving and analysed, but has some methodological flaws (secondary objective of comparing TNM with and thereby mFI-11) which are two dissimilar things.*

Response 2: We understand the reviewer's suggestion. Numerous studies have shown the predictive role of some indicators regarding postoperative complications, including TNM pathological stage. It is well known that the TNM system actually reflects the severity of the disease and provides clinicians and patients with information about cancer. The bad part is the information we get after surgery. The limit the use of preoperative screening to assess patient outcomes. Although the two indicators were obtained before and after surgery, they did not appear to be comparable. However, both indicators can provide useful information for patient prognosis. Therefore, our team conducted this study to investigate the impact of preoperative screening metrics on adverse outcome outcomes. By comparing our interesting findings on the prognostic value of mFI-11 better than other indicators, this provides new ideas for clinical screening.

Comment 3: *The discussion is repetitive at many places which I have commented alongside the article. Please consider correcting them.*

Response 3: Thank you for your invaluable advice. The following sentence appears several times and we have abridged it: After comparing the prognostic value of mFI-11, TNM and PNI for three postoperative adverse outcomes, we found that the mFI-11 had the best prognostic value. It is also proved that frailty condition is an independent risk factor in three kinds of postoperative adverse outcomes".

----------End of Reply to Reviewer#1----------

Reply to Reviewer #2

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript and your very encouraging comments on the merits. To facilitate this discussion, we first retype your comments in *italic font* and then present our responses to the comments. Changes to the manuscript are shown in red.

Comment 1: *The methodology of univariable and multivariable logistic regression analysis seems to be difficult to understand. I recommend that the authors explain it in the Methods section. Furthermore, the authors should describe the results of univariable logistic regression analysis, followed by multivariable one.*

Response 1: Thank you for your invaluable advice. We adjusted the description of univariable and multivariable logistic regression analysis: (P5-6-193-203) **sTable 3** showed univariate and multivariate logistic regression analysis of 1-year mortality. **sTable 4** showed univariate and multivariate logistic regression analysis of 6-month mortality. **sTable 5** showed univariate and multivariate logistic regression analysis of anastomotic fistula. **sTable 6** showed univariate and multivariate logistic regression analysis of admission to ICU. Univariate analysis revealed mFI-11 as a predictive indicator of postoperative outcome (1-year postoperative mortality: OR = 2.241, 95% CI [1.370 - 3.666], $P = 0.001$; 6-month mortality: OR =3.744, 95% CI [2.012 - 6.969], $P < 0.001$; anastomotic fistula: OR = 3.008, 95% CI [1.439 - 6.288], $P = 0.003$; admission to ICU: OR = 2.688, 95% CI [1.795 - 4.026], $P < 0.001$). **Table 2** multivariate logistic regression analysis of adverse outcomes in elderly patients with GC after radical treatment. Multivariate analysis revealed mFI-11 as an independent predictive indicator of postoperative outcome (1-year postoperative mortality: aOR = 4.432, 95% CI [2.599 - 6.343], $P = 0.003$; 6-month mortality: aOR = 2.438, 95% CI [1.075 - 5.484], $P = 0.033$; anastomotic fistula: aOR = 2.852, 95% CI [1.357 - 5.994], $P = 0.006$; admission to ICU: aOR = 2.058, 95% CI [1.188 - 3.563], $P = 0.010$). Multivariate analysis also revealed TNM and PNI as independent predictive indicators of 1-year postoperative mortality(TNM Ⅲ vs. Ⅰ: aOR = 1.423, 95% CI [1.004 - 3.453], $P = 0.005$; TNM Ⅳ vs. Ⅰ: aOR = 2.422, 95% CI [1.524 - 5.292], $P = 0.032$; PNI: aOR = 0.925, 95% CI [0.902 - 0.964], $P = 0.021$).

Comment 2: *Please provide an unabbreviated word of "PNI" and "ICU".*

Response 2: Thank you for your invaluable advice. When they first appeared we added amplification and acronyms : Intensive Care Unit (ICU) ;prognostic nutritional index (PNI); Tumor Node Metastasis (TNM) .

Comment 3: *"Gastric cancer" should be abbreviated to "GC" from the second appearance.*

Response 3: The manuscript has been revised accordingly. Changes to the manuscript are shown in red.

Comment 4: *The authors commented that identification of greater risks may lead to management changes. Readers would be interested in this point. Please describe it in detail, by showing some examples.*

Response 4: Our team responded to this suggestion by adding to the discussion the following: (P8-285-294) In contrast, identification of greater risks may lead to management changes, prompt consideration of close observation and/or reduce the threshold for intervention. Once the frailty diagnosis is identified, three perioperative domains of intervention could potentially improve the prognosis of frail patients: shared decision making, prehabilitation, and interdisciplinary geriatric co-management[]. During the shared decision making process, a careful discussion with frail patients about goals of care, with the advice of other specialists. Multimodal prehabilitation programs, including exercise, nutrition and psychological interventions, have the potential to improve the perioperative prognosis in frail patients, but should be further studied before they are incorporated as standard recommendations.

----------End of Reply to Reviewer#2----------

Reply to Reviewer #3

Dear Reviewer,

Thank you very much for your time involved in reviewing the manuscript. To facilitate this discussion, we first retype your comments in *italic font* and then present our responses to the comments. Changes to the manuscript are shown in red.

Comment 1: *Why is a cut-off value of 0.27 used ? only because it seemed best empirically ?*

Response 1: Thank you for your invaluable advice. High-risk frailty(mFI-11^{High}) was defined when the mFI-11 score ≥ 0.27 and low-risk frailty (mFI-11^{Low}) was defined when the score was less than 0.27. On the one hand, a wealth of previous research has confirmed that a score of 0.27 can be used to define high and low risk of frailty (PMID: 34669672; PMCID:PMC7858206; PMID: 31735257; PMID: 32540161). On the other hand, our pre-experiment found significant differences in results using a 0.27 score for grouping. We has thought about this cutoff and will further analyze whether specific scores, in different groupings, make a difference to outcomes. We plan to use the ROC curve to find the best cutoff for group analysis (Ongoing, unpublished articles).

Comment 2: *When the mFI-11 is tested for its superiority in multivariate analysis there are no arguments for why other variables are used in the model (was it because they tested significant in the univariate analysis? if this is the case: then why is PG vs TG used and not ?)*

Response 2: Thank you for your invaluable advice. We understand the reviewer's suggestion. "drinking" this covariant was statistically significant only in patients with low-risk versus high-risk frailty conditions (P = 0.002, Table 1). But we also did univariate and multivariate logistic regression analysis for the outcomes(**sTable 3** showed univariate and multivariate logistic regression analysis of 1-year mortality. **sTable 4** showed univariate and multivariate logistic regression analysis of 6-month mortality. **sTable 5** showed univariate and multivariate logistic regression analysis of anastomotic fistula. **sTable 6** showed univariate and multivariate logistic regression analysis of admission to ICU). We included the final model variable analysis for univariate logistic factor analysis that made sense(P < 0.05).

Comment 3: *Why is not used a dichotomosized cut-off value for serum albumin (that would be a stronger variable than the numeric value) AND this seems to be the same problem with PNI in the multivariate model.*

Response 3: Thank you for your invaluable advice. We can't agree with you more: dichotomosized cut-off value for serum albumin (that would be a stronger variable than the numeric value. In other articles, we've done the same. However, as the reviewers noted, the PNI index is calculated on the basis of serum albumin, making it less convenient to convert it into a binary variable. But that doesn't affect the process or the conclusion.

Comment 4: *It is not really clear how mFI-11 is calculated: congestive heart failure and myocardial infarction may be included in "cardiac problems" - same with cerebrovascular problems and history of stroke.*

Response 4: The 11 variables that were used to calculate the mFI-11 were functional status, history of diabetes, respiratory problems, congestive heart failure, myocardial infarction, cardiac problems, arterial hypertension, delirium, history of related to cognitive impairment or loss, cerebrovascular problems, and history of stroke/decreased peripheral pulses. Details of specific variables that match these factors are defined in **sTable 1**.

sTable 1. Detailed explanation of the 11 variables of the modified frailty index.

mFI-11	Explanation
1. Myocardial infarction	History of myocardial infarction
2. Cardiac problems	History of angina or percutaneous coronary intervention
3. Congestive heart failure	History of congestive heart failure
4. Cerebrovascular problems	History of transient ischemic attack or cerebrovascular accident without neurological deficit
5. History of stroke	History of cerebrovascular accident with neurological deficit
6. Decreased peripheral pulses	History of peripharal vascular disease or ischemic rest pain
7. Respiratory problems	History of COPD disease or pneumonia
8. History of diabetes mellitus	History of diabetes mellitus
9. Nonindependent functional status	Changes in everyday activity problems with bathing; problems with carrying; out personal grooming; problems getting dressed; problems cooking,

	problems going out alone
10. Clouding or delirium	History of impaired sensorium
11. Arterial hypertension	History of hypertension requiring medication

mFI-11: modified 11-item frailty index, COPD:chronic obstructive pulmonary disease

Comment 5: *The reference list is not correct (in example page 3 line 90 "Velanovich" for reference 9 and line 274 "Donald" for reference 24 and line 279 "Dayama" for ref 26). Ref 18 and 19 is the same.*

Response 5: Thank you very much for your advice. We are ashamed that such a basic mistake was made. Modified and marked red.

Comment 6: *In the grouping of 65-75 vs >75 years there is no big difference in mFI-11 distribution: That indicates that there may be some selection - especially as age seems to be important in multivariate analysis of admission to ICU - why is this parameter not shown for mortality ?*

Response 6: Thank you very much for your advice. Age, a covariable, was significantly different in baseline comparisons (P = 0.039). However, this covariant was not statistically significant for mortality outcomes in an univariate logistic regression analysis. Baseline comparisons were made between the debilitating groups, and logistics analysis explained the relationship between variables and outcomes, which did not conflict. Thus, why age is not statistically significant in one-year mortality and six-month mortality is explained as follows: there was no significant difference between the 65-75 age group in this study, which was actually concentrated at age 71, and the 75-plus age group, which was concentrated at age 73. The concentration of age trends may therefore be responsible for the absence of significant statistical differences in mortality. And we respect all objective statistical results.

Comment 7:*In fig 3 the E-diagram is not necessary, as it is included in F.*

Response 7: Thank you for your advice. We also considered whether Figure E was redundant, since one of our endings was a 6-month mortality rate, and the E graph was able to clearly magnify the information in Figure F. In keeping with the ending, we still plan to keep the E chart.

We would be glad to respond to any further questions and comments that you may have. We would like to take this opportunity to thank you for all your time involved and this great opportunity for us to improve the manuscript. Looking forward to hearing from you regarding our submission!

Sincerely,

Dr. Xin-xin Wang