

Response to the Reviewers' Comments for the manuscript entitled: "The role of the prognostic nutritional index in the survival of patients with gastric and gastroesophageal junction adenocarcinoma: a systematic review."

Reviewer 1

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This review focuses on the review of prognostic related nutritional index (PNI) after gastric cancer surgery. The higher the PNI, the better the prognosis. The conclusions are scientific and accurate, and the main information is clear. However, the following issues need to be further modified:

1. "only" in the sentence "Surgery with or without chemotherapy is the only approach with curative intent" in the abstract is inaccurate, except for surgery and surgery plus chemotherapy, there are also immune therapy, targeting and other forms of treatments.

Response: The sentence "Surgery with or without chemotherapy is the only approach with curative intent" was changed to "Surgery **is the most common approach** with curative intent"

2. Tumor stage is very important for the classification of tumor prognosis. There is a large gap in the nutritional status of patients with early, advanced and advanced gastric cancer. However, the presentation of the literature conclusions in this review is somewhat chaotic, and it is recommended to start with gastric cancer of different stages and make clear classification.

Response: In our study we included patients with stage I-III gastric adenocarcinoma. Studies with stage IV gastric cancer patients were excluded since metastatic disease is in our exclusion criteria.

Tumor stage is undoubtedly very important for the prognosis. In the third column of Table 3 we state the number of patients (and the percentage) in each stage of disease of the studies that we included.

In the "Results" section of our study we have a separate paragraph in which we report the results of studies that performed a stage stratified analysis or that included only patients of one cancer stage (such as Wu et al. and Tokoyawa et al. that included stage III patients only etc.)

The paragraph that we are referring to is the following

“Wu et al, Liu et al and Toyokawa et al. also showed that PNI was significantly associated with OS.^{23,26,28} Of note, Wu et al. included only patients with stage III adenocarcinoma in their study.²⁸ Toyokawa et al., who also included only stage III patients, demonstrated that PNI was not significantly associated with OS in those patients.²⁷ In another study, which included stage II only gastric cancer patients Toyokawa et al. showed that PNI was an independent prognostic factor for OS.²⁶ Takechi et al. confirmed a significant association of PNI and OS only for stage I patients but not for stage II or III patients.¹⁷ Finally, Lee et al. and Kudou et al. showed that PNI was significantly associated with OS in stage-stratified analysis for stage I, stage II and stage III gastric adenocarcinoma patients.^{13,14}”

3. The conclusion does not merely summarize the key findings of the study, so in the conclusion, in addition to summarizing the results of the existing literature, the insight and applicability of the author's findings/results to further work should be highlighted.

Response: In the Conclusion section of our study it is stated that: “Future studies should focus on stratifying patients based on tumor stage, as well as on standardizing the PNI cut-offs. Whatsmore, more research needs to be done in terms of preoperative nutritional support as it could increase PNI and therefore improve short and long term outcomes.”. We also added the following: “Moreover, more studies should be performed in Western countries in order to examine whether the association between PNI and survival persists in those patients who undoubtedly present different genetic factors.”

4. This review has not yet summarized the correlation between PNI and the degree of tumor differentiation, Siewert subtype, tumor size, tumor depth and other important pathological characteristics, so it is recommended to further summarize.

Response:

The tumor location and TNM stage are mentioned in detail in Table 4. Siewert type and other characteristics, such as tumor depth or exact size, were not reported in the original cohort studies, therefore an analysis was not possible. The aim of our study is to address a trend between PNI and overall survival of patients with non-metastatic gastroesophageal cancer. Future research should further examine whether the prognostic significance of PNI differs depending on the multiple pathological characteristics of the tumor, therefore the following was added in the final paragraph of the Discussion section: “Whatsmore, patients were not divided according to specific tumor characteristics, such as the TNM stage, the size or depth or the tumor, the Siewert type or the tumor differentiation, therefore a correlation between the PNI and the survival depending on the multiple tumor characteristics could not be established.

It would be of interest if future studies would stratify patients and assess the prognostic significance of the PNI based on those characteristics"

5. "Albumin levels are a key indicator of a patient's nutritional status. Several scores based on albumin" in the Introduction "levels have been developed, such as the Nutritional Index, Glasgow Prognostic Score, Nutrient Profiling System (NPS), and Controlling Nutritional Status score (CONUT). "And controlling nutritional status score (Conut)." is an example of sodium levels, but it doesn't fit right in here, Recommendation placed after "Recent studies have demonstrated that perioperative inflammation-based prognostic scores can predict overall survival in patients with diverse forms of cancer. ".

Response: The CONUT score is comprised of the serum values of albumin (ALB), total lymphocyte count (TLC), and total cholesterol.

According to your recommendation, the revised paragraph is the following: "Historically, TNM classification has been the most prevalent and reliable indicator for patient prognosis.

However, there is an increasing number of cases where patients classified at the same stage exhibit significantly different prognoses. Recent studies have demonstrated that perioperative inflammation-based prognostic scores can predict overall survival in patients with diverse forms of cancer. Albumin levels are a key indicator of a patient's nutritional status. Several scores based on albumin levels have been developed, such as the Nutritional Index, Glasgow Prognostic Score, Nutrient Profiling System (NPS), and Controlling Nutritional Status score (CONUT). The Prognostic Nutritional Index..."

6. The overall literature time is not new, accounting for about half of the literature within 5 years. It is recommended to search and summarize the updated literature.

Response: The last literature search was performed on October 2023 and all of the most recent papers were assessed for eligibility and were included in our review. A new literature search was performed on December 2023 for the revision of the article, but no new studies that met the inclusion criteria were retrieved.

7. It is recommended to avoid bunching quotes. "Hirahara et al., Ishiguro et al, Lin et al, Murakami et al, Saito et al, Kudou et al and Xu et al reported 5-year OS rates between 41.7% and 70% for the low PNI groups and between 71.3% and 95.8% for the high PNI groups in their studies and in all of their studies PNI was significantly associated with Os.1,12,13,22,24,29,30 "cited several papers, this part is important to prove that PNI is significantly related to OS, it is recommended to cite separately and explain how these studies differ from each other.

Response: We revised the “Results” section and in order to explain how these studies differ from each other performed corrections and added the following :

- PNI was significantly associated with the Overall Survival (OS) in all of the studies included except for Toyokawa et al. study which enrolled 225 patients with stage III only gastric adenocarcinoma.²⁷ 184 of them were submitted to adjuvant chemotherapy and PNI was not associated with OS. Hirahara et al. included 368 patients that were submitted to laparoscopic or laparoscopy assisted gastrectomy and 100 of them were also submitted to adjuvant chemotherapy. The authors demonstrated in univariate analysis that PNI was significantly associated with OS, however the same result was not reached in multivariate analysis which showed that only CEA was significantly associated with OS.²¹
- 258 patients who underwent curative resection for gastric cancer were included in Ishiguro et al. study and adjuvant chemotherapy was not administered to patients with stage I of gastric cancer but only to patients with stage II or III and the authors demonstrated that PNI was independently associated with OS.²²
- Lin et al. included 632 patients with stage I gastric cancer, 526 with stage II and 1024 with stage III who underwent curative gastrectomy. 56% of them received adjuvant chemotherapy and the authors showed that PNI was independently associated with OS.¹² Saito et al. included 111 gastric cancer patients with and 343 without lymphatic invasion. 64 patients received adjuvant chemotherapy and 5 neoadjuvant and the authors demonstrated that high PNI was significantly associated with better OS.²⁴
- Hashimoto et al. included only elderly patients between 80 and 94 years of age. Fifty four of them were submitted to open surgery and fifty five to laparoscopic surgery, however it was not stated whether neoadjuvant chemotherapy was administered. The authors demonstrated that PNI was an independent prognostic factor for OS and reported a cumulative 3-year OS rate of 74.7%.²⁰ Whereas Xu et al. included younger patients (mean age 43.68±4.62) and they also showed that low PNI was significantly associated with lower OS.²⁹
- Shen et al. included 525 patients with stage I-III gastric cancer in their study who were submitted to robotic gastrectomy, 116 of them to neoadjuvant chemotherapy and 267 of them to adjuvant chemotherapy and they randomly divided them to a training and a validation set. The authors showed that PNI was significantly associated with OS in both sets and that PNI was an independent prognostic factor for OS.²⁵

8. There are some spelling mistakes in the text, which need to be corrected.

Response: The manuscript was thoroughly revised and spelling mistakes were corrected.

9. In the reference section, some are indented with the first letter and some are not indented with the first letter. It is recommended to unify the format.

Response: Citations in the reference section were reformatted accordingly.

Reviewer 2

Specific Comments to Authors:

1. This study cannot be called a systematic review study, because it does not follow the operation steps of systematic review. For example, the author did not conduct a complete literature search, and did not show any search methods and search processes.

Response: Thank you for your comments. In our review we followed the PRISMA checklist, which was submitted along with the manuscript and the PRISMA flow diagram is included in the Figures of our paper.

2. The inclusion and exclusion criteria for the study were not clear. For example, does "adult patients" mean patients aged more than 18 years old? "Studies published over the past 10 years" means 2013 to 2023?

Response: In the "Inclusion and exclusion criteria" Table we added "(2013 to 2023)" in order to clarify the publication dates of the included studies and "(over 18 years old)" for the adult age limit.

3. For cohort studies, we prefer to use the NOS(Newcastle-Ottawa Scale) to assess the quality. STROBE checklist was a reporting checklist, but it was not a risk of bias and quality assessment tool.

Response: We used the NOS scale and added Table 2 with the scores of each included cohort. The number in the name of the rest of the manuscript tables was changed accordingly.

In the "Risk of bias and Quality assessment" paragraph of the Materials and Methods section we changed: "... the STROBE checklist respectively..." to "...the Newcastle-Ottawa quality assessment scale (NOS) respectively..." and "The STROBE checklist consists of 22 items that each cohort study should include to be characterized as of high quality" to "The NOS consists of 3 categories (Selection, Comparability and Outcome) and 8 items. A maximum of one star can be awarded for each item within the selection and outcome categories and a

maximum of 2 stars for the comparability (Table 2). A study with a score of over 6 stars is considered to be of high quality.”

4. For the results, author just list the results but not pool them by meta-analysis, which was inadequate and biased.

Response: We conducted a systematic review of the literature following the PRISMA checklist. A meta-analysis could not be performed due to heterogeneity of data. Future research should focus on standardizing the patient selection and management in order to detect the confounding variables, stratify accordingly and be able to conduct a high quality meta-analysis. In the last paragraph of the Discussion, the following sentence was added: “Due to high heterogeneity of the recorded data, a meta-analysis could not be performed.” In the Conclusion section it is mentioned that “Future studies should focus on stratifying patients based on tumor stage, as well as on standardizing the PNI cut-offs.”

Reviewer 3

The authors may consider several suggestions listed below.

1. To give a background introduction for general readers, it is better to mention how PNI (prognostic nutritional index) is calculated in detail.

Response: Thank you for your detailed suggestions.

- We added to introduction : PNI is calculated by multiplying 10 times the serum albumin value (g/dl) plus 0.005 times the lymphocytes count (/mm³).
- Added to results : PNI was calculated by $10 \times \text{albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$

2. For the data and references mentioned and compared in this manuscript, are those PNI values calculated in the same way? Are the factor values for PNI calculation measured in the same way for different studies (groups)?

Response:

PNI was calculated in the same way in all of the studies included in our systematic review ($10 \times \text{albumin (g/dL)} + 0.005 \times \text{total lymphocyte count (/mm}^3\text{)}$)

3. In table 2, it is better to mention country additionally. It seems that most studies, if not all, are done in Asian countries. Are there any data from western countries? Will human genetic factor affect the association analysis?

Response:

- We added the country in the institute column in table 3
- There were no studies performed in Western countries that fit the inclusion criteria that we have set whilst designing our study
- The studies that we included were all performed in Eastern Asia (South Korea, Japan and east China). This could be attributed to the fact that Eastern Asia has the highest prevalence of gastric cancer (20-25 patients per 100.000) whereas the prevalence in Europe is lower (5-10 patients per 100.000) and in Northern America even lower (less than 5 patients per 100.000). The higher prevalence in East Asia is associated with higher H. Pylori infection rates, dietary habits and tobacco smoking. (Shin WS, Xie F, Chen B, Yu P, Yu J, To KF, Kang W. Updated Epidemiology of Gastric Cancer in Asia: Decreased Incidence but Still a Big Challenge. Cancers (Basel). 2023 May 6;15(9):2639. doi: 10.3390/cancers15092639. PMID: 37174105; PMCID: PMC10177574.)
- We added the following in the final paragraph of the Discussion section of our study: "Furthermore, the studies that we included in our study were all performed in Eastern Asia countries and there were no studies performed in Western countries that matched our inclusion criteria. This could be attributed to the fact that East Asia has the highest prevalence of gastric cancer (20-25 patients per 100.000, less than 5 patients per 100.000 in Northern America)."
- We added the following in the Conclusion section of our study: "Moreover, more studies should be performed in Western countries in order to examine whether the association between PNI and survival persists in those patients who undoubtedly present different genetic factors"

4. In table 4, the column "PNI cut-off value", some data just show low or high PNI, but without informative values.

Response:

→ After revision, Table 4 was changed to Table 5. More information regarding the study groups and the number of population were added to the “PNI cut-off value” column.

5. In the discussion section, the authors mentioned that PNI cut-off values ranged between 44.2 and 47. How did those studies determine the PNI cut-off value? What are the ranges for PNI in these studies? Are there any suggestions to standardize the PNI cut-off values?

Response:

We added the “PNI determination” column to Table 5, which states the method used to determine the PNI cut-off value in each study, and the “PNI range” column.

In the third paragraph of the Discussion section: “The studies included in this systematic review had variable PNI cut-off values that were calculated independently based on statistical analyses and ranged between 44.2 and 47. An optimal cut-off value for predicting long-term outcomes, however, has not been established in the literature.³⁶ Future research should focus on standardizing the PNI thresholds, as they may have significant clinical impact...” was changed to “The PNI cut-off values varied between the studies that were included in this systematic review and the methods that were used to calculate the PNI cut-off value are mentioned in Table 4. An optimal cut-off value for predicting long-term outcomes has not been established in the literature.³⁶ Future research should focus on standardizing the PNI thresholds by performing ROC curve analysis in prospective studies that include patients with minimum clinicopathological characteristics heterogeneity in order to identify the PNI cut-off value with the maximum sensitivity and specificity, as a standardized PNI cut-off value may have significant impact in daily clinical practice and decision-making”

Company editor-in-chief:

I have reviewed the Peer-Review Report and the full text of the manuscript, all of which have met the basic publishing requirements of the World Journal of

Gastrointestinal Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

1) The quality of the English language of the manuscript does not meet the requirements of the journal. Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

2) Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

3) Uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2023.

Response :

- 1) As we state in the "Non-Native Speakers of English Editing Certificate", Dr. Giakoustidis is One of our authors (Alexandros Giakoustidis) is a native English speaker. Documents are available upon request. The same situation was resolved in

the past for our articles “Neutrophil-to-lymphocyte ratio as a prognostic factor for survival in patients with colorectal liver metastases: A systematic review” and “Comparison between upfront surgery and neoadjuvant chemotherapy in patients with locally advanced gastric cancer: A systematic review” which were published in World Journal of Clinical Oncology and World Journal of Gastrointestinal Surgery, respectively, as Dr. Giakoustidis was also one of the authors.

Thank you for your understanding.

Moreover, spelling mistakes were corrected while revising the manuscript.

- 2) We searched the “RCA” database using our search algorithm that was applied in our initial database search, with the following keywords “Prognostic nutritional index”, “gastric cancer”, “survival”.

Prognostic nutritional index and gastric cancer : 0 results

Prognostic nutritional index and survival : 0 results

Prognostic nutritional index : 827 results

After 827 titles and 8 abstracts screening there were no articles that matched our inclusion criteria and that could further improve our systematic review.

- 3) We provide decomposable Figures in a single Powerpoint file.