Round-1

May 3, 2021

Monjur Ahmed, Florin Burada, Rosa M Jimenez Rodriguez, and Pashtoon Kasi
Editors-in-Chief World Journal of Gastrointestinal Oncology

Dear Drs. Monjur Ahmed, Florin Burada, Rosa M Jimenez Rodriguez, and Pashtoon Kasi:

I wish to resubmit our manuscript for World Journal of Gastrointestinal Oncology, which is titled "**Neutrophil-to-lymphocyte ratio and CA19-9 as prognostic markers for advanced pancreatic cancer patients receiving first-line chemotherapy.**" (manuscript NO ; 59880)

The paper was coauthored by Eun-Kyo Jung, Se Jun Park, Sangyun Jung, In-Ho Kim and Myung-ah Lee.

The manuscript has been rechecked, and the issues raised by the science editor and reviewers were addressed. We hope that this revised version of the manuscript is now suitable for publication

Thank you for your efforts in reviewing our manuscript. We look forward to hearing from you.

Sincerely,

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Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors:

It should be said that research on NLR and CA19-9 in the field of advanced pancreatic cancer is not uncommon.

As a retrospective study, this article is a certain supplement to other similar studies. The article summarizes and analyzes the case characteristics of the author's medical center. There are some questions that need to be answered.

1. The exact definition of advanced pancreatic cancer needs to be explained. Is the locally advanced cancer truly advanced? Is there any literature support? Of course, I have also seen many literatures that local advanced pancreatic cancer was included as advanced pancreatic cancer for statistical analysis.

In this article the definition of 'advanced pancreatic cancer' is locally advanced PC(LAPC) and metastatic PC(mPC). Locally advanced pancreatic cancer is defined as followed (NCCN guideline Version: 2.2021)

-solid tumor contact with SMA and/or CA >180 degrees

-solid tumor contact with CA and aortic involvement

-Unreconstructable SMV and/or PV due to tumor involvement or occlusion

And many studies showed that the patients with locally advanced pancreatic cancer had better survival than metastatic pancreatic cancer. That is the reason we distinguished LAPC from mPC. In a multivariate analysis in this article also showed that LAPC showed better prognosis than mPC. (table 2)

The proportion of LAPC is quite less than other centers in this article. (about 8%) The reason is many mPC patients are referred to our center from local hospital for chemotherapy.

2. First-line chemotherapy is therapeutic chemotherapy for pancreatic cancer, not first-line palliative chemotherapy. The manuscript mentioned palliative chemotherapy in the part of method (line 40), why?

As you mentioned the term 'palliative' is not appropriate. I should change the term with 'first-line chemotherapy' uniformly as you recommended

3. There are several modes of first-line chemotherapy. In this article, the first-line chemotherapy based on gemcitabine and other chemotherapy programs are not described in detail. It is recommended that the chemotherapy be clearly

stated.

Gemcitabine single (n=86), Gemcitabine/elotinib(n=117), Gemcitabine/Nab-paclitaxel(n=39), Gemcitabine/capecitabine (n=14), Gemcitabine/5-Fluorouracil (n=9), FOLFIRINOX(Folic acid, 5-fluorouracil, Oxaliplatin, Irinotecan) (n=6)

We added chemotherapy regimen in detail as you recommended. We revised the baseline characteristics and re-categorized patients into Gemcitabine single group and other regimen group. Other regimens are doublet or triplet(FOLFIRINOX) and they are considered to have better efficacy than gemcitabine single. Univariate analysis and multivariate analysis were also revised due to the revised variable.

4. The article mentioned that chemotherapy was performed at least one cycle, but the evaluations were completed after two cycles of chemotherapy. Why?

Some of patients had progressive disease before completion of two cycles of chemotherapy. They were also included in the study population if they had response evaluation and other clinical information including complete blood count. We added additional description in detail in the manuscript.

5. The time for obtaining blood test specimens is too vague, and it is recommended to specify clearly.

Blood sampling timing

We added additional description in detail in the manuscript.

'NLR and CA19-9 data were collected within one week before treatment and within one week after response evaluation was performed.'

6. Although most patients had a overall survival time of less than 12 months, but some patients had a survival time more than 3 years (according to the data in the article) was it reasonable to use a 1-year survival period as an ROC curve? Explanation is needed.

To define a cut-off value of NLR and CA 19-9 decline, we applied time-dependent ROC method with 1-year survival as a set point.

1) There are many studies that showed 1-year survival of advanced pancreatic cancer. Landmark studies like phase 3 PRODIGE study and the phase 3 MPACT trial, the primary end point was overall survival and one-year survival is also time of interest in their analysis. 1-year survival rate for PRODIGE study was about 35% and 28% for MPACT trial. In our study 1-year survival rate of the entire cohort is 26.9%.[1, 2]

2) Golan at el. divided patients into surviving ≥12 months vs. <2 months in their survival analysis of metastatic pancreatic cancer patients in the SEER database. Surviving more than 12 months was defined as long-term survivors in their article.[3]

3) There is an article evaluating prognostic significance of NLR with the similar method as we did. Chen et al. applied 1-year survival as the time point to generate the receiver operating characteristic (ROC) curve and determined the optimal cut-off value of NLR. They had area under the curve (AUC) of 0.634 in their analysis. In our study, we applied

1-year survival as the time point and AUC was 0.73 with NLR cut-off 2.62.[4]

7. Some flaws about data, icons, grouping and others are annotated in the text, please read it.

We agreed with most of your correction and they were revised as you recommended.

[Reference]

1 Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M, Groupe Tumeurs Digestives of U, Intergroup P. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**(19): 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

2 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**(18): 1691-1703 [PMID: 24131140 PMCID: PMC4631139 DOI: 10.1056/NEJMoa1304369]

3 Golan T, Sella T, Margalit O, Amit U, Halpern N, Aderka D, Shacham-Shmueli E, Urban D, Lawrence YR. Short- and Long-Term Survival in Metastatic Pancreatic Adenocarcinoma, 1993-2013. *J Natl Compr Canc Netw* 2017; **15**(8): 1022-1027 [PMID: 28784864 DOI: 10.6004/jnccn.2017.0138]

4 Chen Y, Yan H, Wang Y, Shi Y, Dai G. Significance of baseline and change in neutrophil-to-lymphocyte ratio in predicting prognosis: a retrospective analysis in advanced pancreatic ductal adenocarcinoma. *Sci Rep* 2017; **7**(1): 753 [PMID: 28392554 PMCID: PMC5429710 DOI: 10.1038/s41598-017-00859-5]

Science editor:
Issues raised:
(1) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and

We prepare the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

(2) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text.

As requested, we added the "Article Highlights" section at the end of the main text

Round-2

July 5, 2021

Monjur Ahmed, Florin Burada, Rosa M Jimenez Rodriguez, and Pashtoon Kasi

Editors-in-Chief World Journal of Gastrointestinal Oncology

Dear Drs. Monjur Ahmed, Florin Burada, Rosa M Jimenez Rodriguez, and Pashtoon Kasi:

First, thank you for giving us one more opportunity to resubmitting. I wish to resubmit our manuscript for World Journal of Gastrointestinal Oncology, which is titled "**Neutrophil-to-lymphocyte ratio and CA19-9 as prognostic markers for advanced pancreatic cancer patients receiving first-line chemotherapy.**" (manuscript NO ; 59880)

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The manuscript has been rechecked, and the issues raised by the reviewers were addressed. We hope that this revised version of the manuscript is now suitable for publication

Thank you again for your efforts in reviewing our manuscript and giving us opportunity.

Sincerely,

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SPECIFIC COMMENTS TO AUTHORS

1. In the section of "patients", the chemotherapy is still called first-line palliativechemotherapy 2. No "table 4" was found in the manuscript. 3. In "table 1", the number of patients "721" should be "271". This kind of mistake is ridiculous. 4. The groups were labeled as "A, B, C" in the text but "a, b, c" in the figures. It should be consistant.

point-by-point responses to the comments

1. In the section of "patients", the chemotherapy is still called first-line palliativechemotherapy

It has been revised as suggested.

(Page5 line 137) the first-line palliative chemotherapy → the first-line chemotherapy

2. No "table 4" was found in the manuscript.

We added Table 4 in the manuscript. (Page 30)

We found that a mistake in the sentence that describes Table 4. P-value was not properly described. It has been revised.

(Page 11 line 315) p=0.046 → p= 0.032

3. In "table 1", the number of patients "721" should be "271". This kind of mistake is ridiculous.

It has been revised as suggested. (page 25, table 1) 721 → 271

4. The groups were labeled as "A, B, C" in the text but "a, b, c" in the figures. It should be consistant.

We agree with your recommendation.

1) First, we took out 'a, b, c' in the Figure 1 and Figure 3 for simplicity.
By this, Figure 1,3 and their legend became simpler and more understandable.

2) Second, we changed the "Group A, B, C" to "Group 1, 2, 3" in the (page 10 line 277) because the Figure 3 already has (A) and (B) and "Group A, B, C" was already defined in the previous paragraph.

Figure 2 and its legend have been revised according to the change.

We are sorry for making it complicated, but we did our best to make it better. Thank you.