Peer Review File

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Reviewer A's comment:

1. Methods, 'statistical analysis' section - you describe how RDW was categorised into 3 groups. It would be good to know why RDW was categorised and not analysed as a continuous variable. I also wonder why data-driven methods were used to categorise RDW. I notice that the limitations do already describe that there is no standardised cut-off, but would something like the reference range limits be suitable alternatives to categorise RDW? I'm not suggesting you re-do the analysis using different cut-offs, but I am wondering why data-driven approaches were used.

Response:

Thank you for the question. The cut-off value of RDW's categorization in our study took as the study "Olafsson HB, Sigurdarson GA, Christopher KB, et al. A retrospective cohort study on the association between elevated preoperative red cell distribution width and all-cause mortality after noncardiac surgery. Br J Anaesth. 2020; 124(6):718-725." as reference (1). And according to our RDW distribution, the mean and median RDW values were exactly 14.0% and 13.3% respectively, in accordance with other study's cut-off value. This is why we used the cut-off. As for why we don't analyse RDW as a continuous variable, we consider although long-term survival would be affected by the RDW, the trend may not be linear, the result of categorized data would be easier to be explained if RDW and survival were not linearly associated.

2. Results, `High preoperative RDW is related to poor OS and DFS` section - the first sentence describes the mean follow-up period. Follow-up is usually summarised using the median. Therefore, could the authors please add the median follow-up time too?

Response:

We've re-checked the analysis and found the median follow-up time was exactly 56.0 months (95% CI 55.2–56.9). This could be an error in manuscript drafting, thank you for pointing out. We've revised the error in the revised version. **(Results: page 8, line 141)**

3. Results, `High preoperative RDW is related to poor OS and DFS` section - the sentence "The 5-year OS rates for patients in the three RDW groups were as follows:" is the first mention of 5-years. The survival time-point of interest should be specified

in the outcome definition in the Methods section.

Response:

Thanks for the reviewer's kind suggestion. The 5-year OS rates and the 5-year DFS rates have been specified in the outcome definition in the Methods section. (**Methods: page 5, line 83 - 85**)

4. Tables 2 and 3 - could you make it clearer, e.g. add a footnote, to explain that the category after the "/" is the reference category please.

Response:

The category after the "/" is the reference category, which has been added as a footnote of Tables 2 and 3. (**page 23-26, Table 2-3**)

5. Table 2 - your OS univariable HR and p-value for right colon disagree - the p-value suggests significant but the CI contains 1. Is this possible or is this just a typo?

Response:

Thank you for pointing out the problem. It was indeed an error in copying the statistical results to the table. We've also found several other typos and have corrected the result in red in the revised manuscript. **(page 22, Table 2)**

Reviewer B's comment:

1. You set the cutoff values for RDW at 13.3 and 14.0. Isn't there a more appropriate cutoff value? Did you perform statistical studies such as ROC analysis?

Response:

Thank you for the question. The cut-off value of RDW's categorization in our study took as the study "Olafsson HB, Sigurdarson GA, Christopher KB, et al. A retrospective cohort study on the association between elevated preoperative red cell distribution width and all-cause mortality after noncardiac surgery. Br J Anaesth. 2020; 124(6):718-725." as reference (1). And according to our RDW distribution, the mean and median RDW values were exactly 14.0% and 13.3% respectively, in accordance with other study's cut-off value. This is why we used the cut-off.

ROC analysis was not performed in this study. We used all the patients to perform the univariate and multivariate analysis to find the risk factors affecting the long term OS and DFS of CRC patients after radical resection. We didn't separate the patients into training group and validation group in our study since the objective of this study was not to build a prediction model to predict the survival of CRC patients who underwent radical resection. We'll include more in detailed independent risk factors to

predict the survival of these patients with larger sample size in the future.

2. You exclude Inflammatory disorders, but please provide more specific criteria (e.g., test values for CRP, Cr, etc.).

Response:

In recent years, a growing body of evidence has suggested that RDW is a reliable indicator of inflammatory disorders, such as active renal dysfunction, cardiovascular and pulmonary diseases. Thus, we excluded patients with active renal dysfunction, cardiovascular or pulmonary diseases to avoid any possible interference. The exclusion criteria depends on preoperative creatinine, cardiac ultrasound, and lung function results. (**Methods: page 5, line 80 - 81**)

As tumor tissue would cause inflammation and increase serum level of CRP, tumor cells could produce various cytokines and chemokines that stimulate CRP production in the liver, CRP does not serve as an exclusion indicator in our study (2).

3. How many patients have been treated with neoadjuvant or adjuvant chemotherapy?

Response:

Thank you for the question. In our study, 665 (10.7%) patients were treated with neoadjuvant therapy.

In our database the adjuvant chemotherapy data was not collected since most patients (around 70%) were not native Shanghai patients, after operation, their adjuvant therapy could be treated in local hospitals. The database couldn't track whether they used chemotherapy after operation based on our drug management system. So the adjuvant chemotherapy information was incomplete thus not included in this analysis. However, as for the Stage III and Stage II patients with high risk, standard adjuvant treatment plan were prescribed to each patient according to NCCN guideline.

4. Isn't it necessary to include CRP and erythrocyte sedimentation rate as indices of chronic inflammation?

Response:

Thanks for the reviewer's kind advice. However, it is not necessary to use C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) as indicators of chronic inflammation.

Both CRP and ESR are non-specific inflammatory markers, which are superior for monitoring the existence of acute infectious inflammation than chronic non-infectious inflammation (3). In addition, the CRP and ESR might be affected by certain medications, including hormones, non-steroidal anti-inflammatory drugs,

immuno-suppressants, biological agents, etc. (4). Therefore, CRP and ESR are not routinely measured for colorectal cancer patients in clinical practice.

5. The third paragraph of the discussion part is redundant. Please summarize a little more.

Response:

We appreciate the reviewer for the suggestions to improve the quality of our manuscript. The third paragraph of the discussion part has been summarized from 298 words to 225 words in the revised manuscript.