

Dear editors and reviewers:

Thanks for your kind help. The reviewers gave us many useful suggestions and comments for our article, and we have revised one by one accordingly. We have conducted the searching strategy again, and we included nine studies (than six studies in previous format) this time, in total, the results remained the same after pooling up all the data.

Furthermore, we have invited a native English speaker who was familiar with medical terminology to help us revise the expression of this article (the American Journal Experts has modified this article). We hope that the revised article could be better understanding and more rigorous. Thanks again for the help of all the editors and reviewers. Here are our answers.

Reviewer 1

This is a study for subjects for which prospective intervention studies are difficult, and I think this study is a very important study. I have some questions.

Q1. It is known that cardiovascular events such as myocardial infarction and cerebral infarction increases in dialysis patients. Is there any data of cardiovascular events?

A1: We are really appreciated with your suggestion. The cardiovascular complications were reported in four studies, we extracted these data in the four studies and found that the CKD group had higher rates of cardiovascular complications (OR=3.39, 95% CI=2.34 to 4.91, $P<0.01$) than the non-CKD group. (Line 38-39, Line 173-176, table 2)

Q2. Figure 4 shows that CKD patients have poorer OS. I think that CKD patients also have many non-cancer related deaths. Was there a distinction between cancer-related death and non-cancer-related death in each study?

A2: We are appreciated with your suggestion, and we think that it is very helpful. We have collected all the data from the nine studies, however, there were no non-cancer related deaths and cancer-related death available for meta-analysis. Therefore, we added the important information into the limitation: however, some information was lacking, such as postoperative hospital stay, cancer-related death, blood transfusion, reoperation rate, adjuvant chemotherapy, R0 resection rate, perioperative chemo-radiotherapy and completion of the schedule of chemo-radiotherapy. (Line 247-251)

Q3. Figure shows that CKD patients have poorer DFS. I think that adjuvant chemotherapy may be difficult for CKD patients. Did you have any data on adjuvant chemotherapy in each study?

A3: Thanks for your reminder. Unfortunately, there were not enough data available for meta-analysis in terms of adjuvant chemotherapy. Therefore, we added the important information into the limitation: however, some information was lacking, such as postoperative hospital stay, cancer-related death, blood transfusion, reoperation rate, adjuvant chemotherapy, R0 resection rate, perioperative chemo-radiotherapy and completion of the schedule of chemo-radiotherapy. (Line 247-251)

Q4. This study analyzes low eGFR levels and hemodialysis patients together, but the presence or absence of dialysis may make a big difference among CKD patients. I think it is better not to do the same analysis for non-dialysis and dialysis cases with low eGFR levels.

A4: Thanks for your reminder and we agree with it. We have conducted the searching strategy again, and we included nine studies (than six studies in previous format) this time, therefore, there were enough data conducting subgroup analysis of for non-dialysis and dialysis cases with low eGFR levels. In this meta-analysis, we firstly compare the difference between the CKD group and non-CKD group (Fig 2a, Fig 3a and Fig 4a); Then we did subgroup analysis of the non-dialysis groups (Fig 2b, Fig 3b and Fig 4b); Finally, subgroup analysis of the dialysis groups was conducted (Fig 2c, Fig 3c and Fig 4c). (Line 168-172, line 178-187).

Reviewer 2

The study hypothesis

Q1. CKD affects the post operative complications, is non controversial. The other hypothesis 2) CKD influences the prognosis of colorectal cancer has no published data and also the possible ways in which the oncological outcome of colorectal cancer can be influenced by CKD is not discussed. (There are only data to show that CKD may be associated with increased risk of Colon cancer).

A1: We are really appreciated with your suggestion. In this study, the primary outcome of the current meta-analysis was postoperative complications, and the second outcome was the long-term prognosis of OS and DFS. There two outcomes were in controversial the ORs and HRs of the included study were shown in Fig 2a, Fig 3a and Fig 4a. Therefore, the purpose of this study was to analyze whether CKD affected the complications and prognosis of patients with CRC after primary CRC surgery. The possible reason of CKD on oncological outcomes were as follows: The probable reason was that CKD was associated with endothelial dysfunction, malnutrition, volume overload or changes in calcium and phosphorus metabolism, and the dysfunction would cause higher rates of cardiovascular events.³⁶⁻³⁷ Higher rates of postoperative complications might result in a poor prognosis.³⁸⁻³⁹ Moreover, postoperative complications and perioperative blood loss can suppress immune function, which might be a factor for promoting cancer recurrence.⁴⁰⁻⁴¹ (Line 218-219)

Q2. In this study only age, sex, ASA score, TNM staging and co morbidities are the parameters, that are used to assess the homogeneity between the groups. It is said that the CKD group had higher proportion of patients with colon cancer. This analysis is performed for colon and rectal cancer combined. Operable rectal cancer patients receive perioperative Chemo radiotherapy and no data is analyzed with reference to this, thus rendering homogeneity between these groups questionable. Difference in chemo radiotherapy schedule, completion of the schedule etc., between the groups may alter the prognosis.

A2: Thanks for your carefully comments. Indeed, perioperative chemo-radiotherapy,

schedule, completion of the schedule and the site of CRC might also affect the prognosis. However, we have extracted all the data that could be analyzed in this study. We have added it in the limitation, therefore, multicenter, high-quality and well-controlled prospective studies including comprehensive baseline information comparing the complications, OS, DFS and CSS should be performed in the future. (Line 247-259)

Q3. There is no data about the different surgical procedures, like elective, emergency, re surgery, R0 R1 surgery, between the two groups. Blood transfusion, a factor that influences the prognosis, may have been more in the CKD group. The follow up details are missing.

A3: Thanks for your reminder and we agree with it. We have conducted the searching strategy again, and we included nine studies (than six studies in previous format) this time. There was no difference in emergent surgery between the CKD group and the non-CKD group (OR=1.31, 95% CI=0.84 to 2.05, P=0.23). (Table 2) However, other information were lacking in the included studies, therefore, we added it in the limitation: we extracted all of the data that could be analyzed in this study, however, some information was lacking, such as postoperative hospital stay, cancer-related death, blood transfusion, reoperation rate, adjuvant chemotherapy, R0 resection rate, perioperative chemo-radiotherapy and completion of the schedule of chemo-radiotherapy. (Line 247-251)

Q4. Though the methodology used appears appropriate in this meta-analysis, not considering the other factors that may influence the long term outcome, render the results less valuable. In this meta analysis, 679 patients with colorectal cancer and CKD (not all have eGFR as stated) were compared with 44203 patients with Colorectal cancer. Comparing this two groups may give misleading information. Comment: Major revision required.

A4: We are appreciated with your suggestions, and we think that it is very helpful. We have conducted the searching strategy again, and we included nine studies (than six studies in previous format) this time. A total of nine studies^{15-18, 25-29} including 47771 patients, were included in this meta-analysis. There were 952 patients in the CKD group and 46819 patients in the non-CKD group. (Table 2) This study focused on the CKD on the complications and prognosis, therefore, other parameters were not included. In this meta-analysis, pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for OS and DFS of CRC patients after CRC surgery, and HRs were extracted from multivariate analyses and/or univariate analyses or estimated from Kaplan-Meier survival curves.²² (Line 127-130) Some included HRs were from multivariate analyses which were considered for other parameters; some of the survival data were extracted from the Kaplan-Meier survival curves, which might result in inaccuracies. And we added it in the limitation section. (Line 251-252)

Reviewer 3

Q1. The authors should consider including outcomes from recent studies such by Shaan Dudani et al 2021 :The Impact of Chronic Kidney Disease in Patients With Locally Advanced Rectal Cancer Treated With Neoadjuvant Chemoradiation

A1: Thanks for your approval. Your kind suggestions help us a lot. According to your kind suggestions, we have conducted the searching strategy again, and we included nine studies (than six studies in previous format) this time, The three new studies included: Shaan Dudani et al 2021 :The Impact of Chronic Kidney Disease in Patients With Locally Advanced Rectal Cancer Treated With Neoadjuvant Chemoradiation. In total, the results remained the same after pooling up all the data. (Table 2, Ref: 27-29) Furthermore, we have revised some minor description in the abstract (Line 23-27), introduction (Line 59-62), methods (Line 110-113) and discussion section (Line 230-232) according to your suggestions.

Science editor:

Q1. This manuscript is a meta-analysis to analyze whether chronic kidney disease (CKD) affects complications and prognosis after primary CRC surgery in colorectal cancer (CRC) patients. Please check if there are any data on cardiovascular events; data on adjuvant chemotherapy; and data on different surgical procedures between the two groups, such as elective, urgent, reoperation, R0 R1 surgery.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

A1: We feel indebted for your reminder. We have extracted all the data that could be analyzed in this study. The cardiovascular complications were reported in four studies, we extracted these data in the four studies and found that the CKD group had higher rates of cardiovascular complications (OR=3.39, 95% CI=2.34 to 4.91, P<0.01) than the non-CKD group. (Line 38-39, Line 173-176, table 2) There was no difference in emergent surgery between the CKD group and the non-CKD group (OR=1.31, 95% CI=0.84 to 2.05, P=0.23). (Table 2) However, other information was lacking, and we added it in the limitation section: however, some information was lacking, such as postoperative hospital stay, cancer-related death, blood transfusion, reoperation rate, adjuvant chemotherapy, R0 resection rate, perioperative chemo-radiotherapy and completion of the schedule of chemo-radiotherapy. (Line 247-251)

Company editor-in-chief:

Q1. I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, 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. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. 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) 2022.

A1: Thanks for your reminder. The figures and tables were original. We have revised our tables and figures. Furthermore, we have invited a native English speaker who was familiar with medical terminology to help us revise the expression of this article (the American Journal Experts has modified this article).

Thanks for your kind help. According to your suggestions, we have revised one by one accordingly. We hope that the revised article is more attractive and clearly reading.

Answering reviewers for Re-Review:

Authors have reasonably indicated the limitations of the study, while replying to the comments. However to state that this study has analyzed 47771 patients in this meta-analysis, appears misleading. The total number of patients with colorectal cancer included in the ACS-NSQIP was taken into account, (wherein only 0.06% of them were receiving dialysis). Although they have indicated this in the limitations.

Response: It is our honor to your comments. And we feel really appreciated for your approval of our article which gave us hope and confidence. We hope that our article is interested for readers when published.