

Dear Editors,

We are very pleased with the positive feedback to our study and we are delighted to provide you with the revised manuscript alongside annotated changes that were made in reply to the reviewers. We sincerely thank the reviewers for their kindness advices in upgrading the quality of this manuscript. We hope that it will similarly meet the interest of readers of World Journal of Gastroenterology and we wish it will spark enthusiasm for further research and discussion on the topic.

Please find, on the next pages, our replies to the reviewers and to the Editor's changes.

Sincerely,

The Authors

REVIEWER 01553680

In this manuscript, the authors tried to identify bio-markers which distinguish the prognosis of obstructive colorectal cancers (OCCs). They investigated 128 patients with OCCs who underwent emergent surgery (ES) or bridge to surgery (BTS) after insertion of self-expandable metal stent (SEMS). They found that lymphocyte-monocyte ratio (LMR) is associated with overall survival (OS) and disease-free survival (DFS) in patients with BTS. Based on these data, the authors propose that SEMS is recommended in patients bearing high LMR ratio. I have a few concerns. 1) Although they performed extensive analysis in clinical data, the authors analyzed data in a retrospective manner. Please tone down the conclusions. 2) Page 27 discussion; Is there any evidence that insertion of SEMS induces differentiation of TAM or impaired tumor detection by lymphocytes? I recommend to delete these sentences. 3) The authors just analyzed ratio of immune cell populations. They have not analyzed immune responses such as production of cytokines or expression of PD-1 or CTLA-4. Immune cell population ratio does not mean immune responses occurring in the systemic circulation or tumor. Please add these points in the discussion to avoid misunderstanding.

We sincerely thank the reviewer for the kind words of interest in our work, and we agree with the raised concerns and revise the manuscript according to the reviewer's comments.

1) Although they performed extensive analysis in clinical data, the authors analyzed data in a retrospective manner. Please tone down the conclusions.

We have tone done our conclusion followed the reviewer's suggestion and rephrased the conclusion as "For OCC, as potential benefit group, patients with a low LMR might be preferred for BTS via SEMS insertion".

2) Page 27 discussion; Is there any evidence that insertion of SEMS induces differentiation of TAM or impaired tumor detection by lymphocytes? I recommend to delete these sentences

Recently, very few studies focused on the impacts of the stent related mechanical stress on the surrounding immune response. As lack of strong evidences on the

change of TAM or impairment of tumor detection, we delete the sentence “from two aspects: 1. the increasing recruited monocytes would differentiate into tumor-associated monocytes (TAMs) that promote tumor metastasis and angiogenesis^[32]; 2. tumor-infiltrating lymphocytes play an essential role in the immune escape mechanism in the tumor microenvironment^[33]” in our **discussion part**.

3) The authors just analyzed ratio of immune cell populations. They have not analyzed immune responses such as production of cytokines or expression of PD-1 or CTLA-4. Immune cell population ratio does not mean immune responses occurring in the systemic circulation or tumor. Please add these points in the discussion to avoid misunderstanding.

We have added the sentence “3)Furthermore, this study just analyzed the ratio of immune cell populations in the peripheral blood, instead of systematic immune responses including the production of cytokines or expression of PD-1 or CTLA-4. More efforts should be spent on the investigation of immune responses occurring in the systemic circulation or tumor” in the last paragraph of the discussion. In order to avoid unnecessary misunderstanding.

REVIEWER 01557050

General comments Dr. Chen and Dr. Zhang, et al. investigated ‘The Lymphocyte-to-Monocyte Ratio is an optimal biomarker for Obstructive Colorectal Cancer’. The article is informative and well-presented. The reviewer has some comments. 1. It is difficult to understand the correlations between NLR, LMR or dNLR and ES or BTS in OCC. Because the authors did not divided into two groups strictly such as ES group and BTS group in this study. How did the authors select OCC patients for ES or BTS? The authors should describe the definitions that they divided in two groups. Then, the authors can describe your results. The reviewer cannot understand whether it is useful to compare these uncertain two groups.

We sincerely thank the reviewer for the kind words of interest in our work, and we agree with the raised concerns and revise the manuscript according to the reviewer’s comments.

1. It is difficult to understand the correlations between NLR, LMR or dNLR and ES or BTS in OCC. Because the authors did not divided into two groups strictly such as ES group and BTS group in this study. How did the authors select OCC patients for ES or BTS? The authors should describe the definitions that they divided in two groups. Then, the authors can describe your results. The reviewer cannot understand whether it is useful to compare these uncertain two groups.

Recently, the indication of SEMS insertion in the OCCs still be controversial. Only the European Society of Gastrointestinal Endoscopy (ESGE) recommended SEMS placement as the superior choice for patients in the ‘high risk’ group, which is defined as older patients and/or those with American Society of Anesthesiologists (ASA) scores greater than 3. Conversely, ES was deemed suitable for patients in the ‘low risk’ group. However, this indication seems ambiguous. That’s the reason why we initiated this study. We have added the sentence “Patients were divided into ES group and BTS group based on the grade of bowel obstruction and families’ choices. For incomplete obstruction, ES was preferred as first choice. For complete obstruction, once patients who refused to accept SEMS insertion or failed in SEMS insertion would accept ES with intraoperative decompression.” in the **patient population** paragraph.

Dear Editor,

We sincerely thank you for the advices in drafting the manuscript in agreement with your quality standards. We would apologize for any inconsistency that you might have previously found with respect to your instructions.

We have revised the manuscript following your suggestions, specifically:

1.Title

We have renamed the title as “The Lymphocyte-to-Monocyte Ratio effectively predicts the survival outcome of Obstructive Colorectal Cancer”, instead of previous one.

2.Running title

A short running title, as “Inflammation biomarkers of obstructive colorectal cancers”, was added in the manuscript.

3.Co-first author

We have deleted the mark for co-first author. Instead, we transfer this sentence, “Xian-qiang Chen and Chao-rong Xue both equally contributed to this work”, to Author contributions part.

4.Supported by

We have deleted the grant without grant application form, uploaded the remained grant (Qihang Project of Fujian Medical University (No.2017XQ1050)) application form in the attaching files.

5.Audio core tip

After following your instructions on the website, we have uploaded an Audio core tip.mp3 audio file. In this file, the first author described the final core tip, and the file size is 1.3 MB/10 MB.

6.The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author’s name, with no spaces.

All of the reference numbers in the manuscript have been transformed to superscripted in square brackets without spaces.

7.ARTICLE HIGHLIGHTS

We have added the followed words in this part:

Research background

Obstructive colorectal cancer (OCC) presenting with acute abdominal

symptoms always accompanied by severe complications, the optimal strategy for patients with OCCs remains undetermined. Emergency surgery (ES) and Self-expandable metal stents (SEMS) as a bridge to surgery (BTS) were the major treatments for OCCs, however, the indications still remain debated. According to different status of immunology and nutrition, predictive factors for prognosis might be different between the two groups. Preoperative inflammation indexes might favor patient selection in the prognosis of OCCs.

Research motivation

Weighing the waxes and wanes of ES and BTS, both acute and chronic inflammation response should be accounted for the selection of optimal patients.

Research objectives

This study was designed to build up an inflammatory model for the surgical indication of ES and BTS in OCCs.

Research methods

This was a retrospective study that 128 patients who underwent surgery for OCC in the Department of Emergency Surgery at Fujian Medical University Union Hospital from January 2008 to October 2015 were included in this study. Patients were divided into ES and BTS group according to the surgeon' advises and patients' selection. Inflammation indexes were fully evaluated in this study.

Research results

Comparable survival outcomes were observed between ES and BTS group. ROC curve showed dNLR as the optimal biomarker for the prediction of DFS in ES, by contrast, LMR was recommended for BTS on OS and DFS. dNLR was related to stoma construction, postoperative pneumonia, and DFS in ES group. LMR closely related to lymph nodes invasion, OS and DFS in BTS group. LMR could differ OS between ES and BTS group. A high LMR (≥ 1.67) was correlated with a low incidence of death and tumor recurrence in the BTS group.

Research conclusions

As a supplement for the latest ESGE guideline, the indication for the use of SEMSs in OLCCs might elaborate to patients with low preoperative LMR, would benefit from BTS via SEMS insertion.

8.Reference

Each reference item now lists all authors (first author in bold), with PMID and DOI for all available items. The volume number has been written in bold according to instructions. Moreover, all references are now written with 1.5 spacing. There are no repeated references.

However, the Following references cite websites, presentations or registries, and as such they do not have a DOI or PMID: 5, 8, 16, 19, 27, 28.

9. Table

All tables' titles do not contain abbreviations and all the abbreviations inside the table have been explained in the footnote of each table.

10.Figures

All figures have been transformed to ppt files, with editable version for all elements inside the figures. As figures have different directions, two for horizontal way and one for vertical way, we divided them into two ppt files.

CrossCheck

Dear Editor,

We sincerely thank you for the cross check on the similarity of our manuscript. We would apologize for any inconvenient that you might have previously encountered when dealing with this study. As this is a serial study, owe to our previous work recently published in journal of Gastroenterology Research and Practice, few similar words were found in the method paragraph. Now, we have rephrased the sentence to avoid unnecessary misunderstanding.

January 2008 to October 2015 were included in this study. Data from the patients' records were retrospectively collected and ¹evaluated. The study protocol was approved by the Institutional Review Board of our hospital, and all patients provided written informed consent for surgery.

We have changed the sentence structure into “The Institutional Review Board of Fujian Medical Union Hospital has approved this study’s protocol. All patients have signed the informed consent for surgery. Patients were divided into ES group and BTS group based on the grade of bowel obstruction and families’ choices. For incomplete obstruction, ES was preferred as first choice. For complete obstruction, once patients who refused to accept SEMS insertion or failed in SEMS insertion will accept ES with intraoperative decompression.”.

¹ Surgical procedures

Isoperistaltic lavage or manual decompression for intraoperative clearance was performed as described previously to avoid bacterial translocation and the interruption of bowel peristalsis in left-side OCC. For

We have changed the sentence structure into “For left-side OCC, we performed intraoperative lavage or manual decompression for better bowel preparation, these protocols have been previously depicted.”

SEMS with BTS

² Stent placement was performed by an endoscopist who had previously performed more than 400 endoscopic retrograde cholangiopancreatography (ERCP) procedures. ¹ If stent placement was successful and the intestinal obstruction was relieved, elective surgery was later performed. If the surgery was unsuccessful, ES with intraoperative irrigation or manual decompression was immediately performed.

We have changed the sentence structure into “Stent insertion was performed by an endoscopist who had experienced over 400 endoscopic retrograde cholangiopancreatography (ERCP). Bridge to elective surgery was performed, once the stent was so successfully inserted that the intestinal obstruction completely relieved. Otherwise, ES was immediately performed.”

² The pathological tumor stage was diagnosed according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition [21].

² Hypertension, diabetes mellitus, and single and multiple organ dysfunction were defined as comorbidities. The degree of obstructive symptoms was divided into 5 grades, termed as The ColoRectal Obstruction Scoring System (CROSS) [22]. ² Perioperative complications were subdivided into five grades according to the Clavien-Dindo classification system [23,24].

¹ Statistical analysis

Between-group differences in qualitative variables were compared using the chi-square test or Fisher's exact test, and quantitative variables were compared using t tests. ¹ The 3-year OS and 3-year DFS were calculated using

We have changed the sentence structure into “According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th edition)[²¹], we classified the tumor pathological stage. Comorbidities were defined as hypertension, diabetes mellitus, and single and multiple organ dysfunction. The degree of obstructive symptoms was divided into 5 grades, termed as The ColoRectal Obstruction Scoring System (CROSS)[²²]. According to the Clavien-Dindo classification system[^{23,24}], we classified the perioperative complications into five grades.

Statistical analysis

Qualitative variables were compared by the chi-square test or Fisher's exact test, and quantitative variables were compared via t tests. Through Kaplan-Meier analysis, the 3-year OS and 3-year DFS were calculated. A cox proportional hazards regression model has been built up to identify the independent risk factors for 3-year DFS and 3-year OS. Stratification analysis was used to compare the differences between subgroups.”.

This study was a retrospective analysis of one cohort at one center; thus, a prospective, multicenter study needs to be performed in the future to confirm our findings. In addition, the sample size was not large, and additional samples are required in future research.

We have changed the sentence structure into “There still some limits exist in this study.

1) This was a retrospective study with one single center; thus, we will initiate a prospective, multicenter study to confirm our findings. 2) The sample size was not so large that more patients needed in future research. 3) Furthermore, this study just analyzed the ratio of immune cell populations in the peripheral blood, instead of systematic immune responses including the production of cytokines or expression of PD-1 or CTLA-4. More efforts should be spent on the investigation of immune responses occurring in the systemic circulation or tumor”.