

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 80013

Title: Increased CD4/CD8 Lymphocyte ratio predicts favourable neoadjuvant treatment response in gastric cancer: A prospective pilot study

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04427657

Position: Editorial Board

Academic degree: MD

Professional title: Chief Physician, Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

Manuscript submission date: 2022-10-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-10-04 02:45

Reviewer performed review: 2022-10-05 10:52

Review time: 1 Day and 8 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous
	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

The study aimed to investigate the utility of CD4, CD8, Galectin-3 and E-cadherin in predicting neoadjuvant FLOT chemotherapy tumour response in gastric adenocarcinoma. And the authors conclude that an elevated CD4+/CD8+ Ratio is a promising immunohistochemistry (IHC)-based biomarker to predict favourable treatment response to FLOT neoadjuvant chemotherapy in locally advanced gastric cancer. It was interesting. However, I have some comments. 1. Core tip section should be reorganized. 2. Some relevant contents should be added in the too simple INTRODUCTION. 3. A flow chart should be used in this study. 4. How to define and obtain the normal specimens should be mentioned in the METHODS. 5. The observers and magnifications should be addressed in the histological analysis. 6. Disadvantages of neoadjuvant chemotherapy in this present study should be involved. 7. The DISCUSSION was too redundant. Please deleted some irrelevant contents and added some relevant mechanisms in the section. 8. Some images (25th Percentile) in Figure 1A were not correct. Please added some arrows in the images.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00505755

Position: Editorial Board

Academic degree: PhD

Professional title: Senior Research Fellow

Reviewer's Country/Territory: Japan

Author's Country/Territory: Canada

Manuscript submission date: 2022-10-03

Reviewer chosen by: AI Technique

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Review time: 8 Days and 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous
	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

This study demonstrates that CD4/CD8 ratio distinguish the treatment responsivity to neoadjuvant FLOT chemotherapy. The legend for Figure 2C may be revised to describe models more in detail and the meaning of the solid and dotted lines. The texts citing the Figure 1A, B, and C may be revised to be in order.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02842791

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: Canada

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Review time: 8 Days

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection

Re-review	[<input checked="" type="checkbox"/>] Yes [<input type="checkbox"/>] No
Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous
	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

This study evaluate some potential biomarkers provide predictive value in evaluating treatment response following neoadjuvant FLOT chemotherapy. They demonstrate that an elevated ratio between CD4+ and CD8+lymphocytes is a promising biomarker to predict treatment response to neoadjuvant chemotherapy in locally advanced gastric cancer. However, the small sample size may limit the significance of research findings.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 06344948

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Serbia

Author's Country/Territory: Canada

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection

Re-review	[<input checked="" type="checkbox"/>] Yes [<input type="checkbox"/>] No
Peer-reviewer	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous
statements	Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No

SPECIFIC COMMENTS TO AUTHORS

This is an interesting pilot study in which the authors investigated the utility of CD4, CD8, Galectin-3 and E-cadherin in predicting neoadjuvant FLOT chemotherapy tumour response in gastric adenocarcinoma. They have convincingly demonstrated that the elevated CD4 + /CD8 + ratio is a promising IHC-based biomarker to predict favourable treatment response to FLOT neoadjuvant chemotherapy. This is a widely investigated and researched topic, as the CD4 + /CD8 + ratio is recognized as a nonspecific immune biomarker for a number of pathological states. This study builds well on the existing clinical trials and available literature and presents new insight into mechanisms related to neoadjuvant FLOT chemotherapy action. A comprehensive statistical analysis supports the main conclusions although with somewhat high error expectations. Although the prognostic significance of CD4 + /CD8 + ratio is confirmed in this study, the small sample size limits the adequate interpretation of the acquired data. I believe that this study is worthy of further investigation and that it can be published after the minor changes. I have minor suggestions: 1. In the Background part the sentence: Predictive biomarkers using immunohistochemistry is one method to inform treatment response should be reformulated: Predictive biomarkers detected by immunohistochemistry method may provide useful data regarding treatment response. 2. The Introduction part (page 4) is a little bit scarce with data and should begin with more general data, instead with the method that authors have been used in this research. Clinical and epidemiological data demonstrate that gastric cancer (GC) is a highly heterogeneous cancer with a poor prognosis. Patients with the same TNM staging can

exhibit quite different clinical outcomes. Regardless of the innovations of modern screening methods, emerging new drugs, and multidisciplinary management, the prognosis of GC patients still remains poor. I believe these were the main motives for authors to search for new information to guide treatment strategies in clinical practice and to convey this research, and the implementation of these data are needed at the beginning of the text. The purposes of neoadjuvant chemotherapy in gastric cancer also deserve to be discussed in a couple of sentences (the authors may rely on the reference G. Knight, C. C. Earle, R. Cosby et al., "Neoadjuvant or adjuvant therapy for resectable gastric cancer: a systematic review and practice guideline for North America," *Gastric Cancer*, vol. 16, no. 1, pp. 28–40, 2013). So, these data should be incorporated on the very beginning of the Introduction section, followed by the paragraph regarding the FLOT treatment and afterword paragraph regarding the IHC method the authors have applied in this study. Also, more data are needed regarding the role of the tumor microenvironment where the host immune response occurs with the special emphasis on the role of main immunocompetent cells (CD4 and CD8), and clinical significance and interpretation of their ratio. 3. In the Introduction section (page 4) the sentence: In breast cancer, E-cadherin expression has been associated with chemotherapy response, the authors should provide the additional explanation regarding the expression pattern of E-cadherin related to chemotherapy response, so that readers can get insight into the role of this adhesion molecule (in the text adhesion molecular should be changed to adhesion molecule). 4. In the Key words: CD4; CD8; Galectin-3; Neoadjuvant; Response; Gastric Cancer, the term Chemotherapy should be added beside Neoadjuvant, and the term Treatment before Response. 5. In the Introduction part (page 4) the sentence Neoadjuvant chemotherapy is known to cause adverse events, including hospitalization in approximately 25% of patients requires a reference. 6. In Statistical analysis (page 8) in the second paragraph in the sentence The NIR is defined as defined as the largest one

term defined should be erased. 7. In the Discussion section (page 12) in the sentence Irrespective of efficacy, cytotoxic chemotherapy is also associated with....the phrase cytotoxic chemotherapy should be reformulated to cytotoxicity of chemotherapy is also associated....