

PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Oncology*

Manuscript NO: 66944

Title: Association of cancer with comorbid inflammatory conditions and treatment in patients with Lynch syndrome

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05464606

Position: Editorial Board

Academic degree: MD

Professional title: Professor, Surgeon, Surgical Oncologist

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: United States

Manuscript submission date: 2021-04-09

Reviewer chosen by: Sami Akbulut

Reviewer accepted review: 2021-06-30 16:52

Reviewer performed review: 2021-07-11 13:08

Review time: 10 Days and 20 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 Grade E: Do not publish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 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
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SPECIFIC COMMENTS TO AUTHORS

Chronic inflammation is one of the causative factors of inflammatory bowel disease (IBD)-associated colorectal cancer, which induces cyclooxygenase (COX)-2, inflammatory cytokines, and chemokines. Immunomodulators have anti-inflammatory properties and are used as maintenance therapy in IBD patients. There is limited evidence for the chemopreventive role for immunomodulators in IBD in most studies. However, one meta-analysis by Lu et al. revealed an antineoplastic effect of thiopurines on colorectal neoplasia in patients with IBD, particularly amongst the patients with ulcerative colitis (published in *Aliment Pharmacol Ther* 2018 Feb;47(3):318-331), Please add this in issue in the DISCUSSION part.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05261029

Position: Peer Reviewer

Academic degree: MD

Professional title: Chief Doctor, Professor, Surgeon

Reviewer's Country/Territory: China

Author's Country/Territory: United States

Manuscript submission date: 2021-04-09

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-07-09 11:51

Reviewer performed review: 2021-07-14 02:00

Review time: 4 Days and 14 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No

Peer-reviewer statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

This study is the first to evaluate the relation between HNPCC and CID, as well as, the impact of biologics and immunomodulators on cancer risk in HNPCC. Due to the small sample, no statistical differences were identified. But this theme was novel and deserved valuable molecular researches to detect the interaction between these two diseases. A small detects was the meaning of the abbreviation of TAH-BSO in the results part was not clear. Good job!

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05562085

Position: Peer Reviewer

Academic degree: FRCS (Gen Surg)

Professional title: Academic Fellow

Reviewer's Country/Territory: Canada

Author's Country/Territory: United States

Manuscript submission date: 2021-04-09

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-07-14 13:32

Reviewer performed review: 2021-07-14 15:28

Review time: 1 Hour

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 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 statements	Peer-Review: [<input checked="" type="radio"/>] Anonymous [<input type="radio"/>] Onymous Conflicts-of-Interest: [<input type="radio"/>] Yes [<input checked="" type="radio"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Thank you for this paper. This is a very important subject, as we gain more understanding of the interplay of the immune system and cancers, in particular MSI High tumors, this research will be increasingly relevant. This study is of course limited by the size of the cohort, so no definite conclusions can be made. I think the authors are cautious to avoid drawing any significant conclusions from the content. Although this is briefly mentioned, I think more focus needs to be given to the fact that disease severity is not known. In IBD patients, the risk of CRC is associated with duration of symptoms and likely severity of colitis. The use of immune modulating drugs can theoretically have a positive effect in that they can control the inflammation that is potentially acting as a stimulus for malignancy. Conversely, the drugs can decrease our immune surveillance in malignancy. There is too much confounding and missing information to understand the interplay between these. The number of patients exposed and unexposed will make it challenging to draw any definitive conclusions but I think this needs to be emphasized as a limitation. While IBD increases the risk of LS associated cancers, rheumatologic conditions don't and so there is limitation in grouping these together. Although the author tries to address the diseases separately, when it comes to comparing exposed and unexposed, the autoimmune diseases are generally grouped together. These should be evaluated separately. Additionally, there is no cancer specific survival for these patients. In some series, patients with IBD and those taking immunosuppressive medications present with later stage disease or have worse survival when controlling for stage. The impact of medical immunosuppression on survival in patients with LS who develop malignancy.