

**Author response to reviewer comments for Manuscript
Colonic Neoplasia and Celiac Disease: A Systematic Review.**

No:110210

Reviewer	Reviewer comment	Author response
1	<p>Abstract</p> <ol style="list-style-type: none"> 1. Focus on the most critical findings (Evidence linking CD with colorectal neoplasia) 2. Specify major challenges in diagnosing & screening for colorectal neoplasms in CD patients. 	<p>Dear, I have refined the Abstract to focus on association between CD and CRC in particular.</p> <p>Moreover, major diagnostic and screening challenges are specified. Kindly check page 3-4.</p>
	<p>Introduction</p> <ol style="list-style-type: none"> 1. More explicit clarification of focus on colorectal neoplasia 2. Focus should be specifically on colorectal neoplasia not small intestinal neoplasia 3. Brief mention of why colorectal neoplasms are less common than small bowel neoplasms in CD 	<p>Dear, The introduction section has been revised to clarify and emphasize the focus on CRC rather than small bowel neoplasm.</p> <p>Explanation for lower incidence of CRC in CR patients as compared to small lower neoplasia given in the introduction succinctly.</p> <p>Relevant studies added. Kindly have a look at page 6.</p>
	<p>GENE and Cell LEVEL MECHANISM - DISCUSSION</p> <ol style="list-style-type: none"> 1. Clearer explanation - complex interactions between GLIADIN PEPTIDES and IMMUNE CELLS strengthen by discussing " How various components of TME + including relevant studies on TME's role in immunotherapy" would add depth to discussion 2. Relationship between immune cells, 	<p>Thank you for raising the point.</p> <p>A relevant explanation is added in the Gene and cell level discussion.</p> <p>TME and its role in carcinogenesis (page 14) explained along with its role in immune therapy.</p> <p>Kindly check page 12,13</p>

	<p>tumor cells, and broader TME essential for predicting tumor response</p>	
	<p>Gene level changes - discussion</p> <ol style="list-style-type: none"> 1. More detail on How genetic changes specifically contribute to CRC in CD patients 2. How does mismatch repair deficiency in CD compare with that seen in other colorectal particularly those with Lynch syndrome 	<p>Thank you for highlighting this section.</p> <p>More details on Genetic level changes explained in the 'Gene Level' subheading within the introduction.</p> <p>Difference between the basis of mismatch repair deficiency between CRC and Lynch syndrome explained (page 12) . Relevant studies added. Kindly head to page 8 under the subheading "Oncogenic pathways in CD"</p>
	<ol style="list-style-type: none"> 1. Clarification needed for variable risk of Colon neoplasms in CD patients in more depth. Any patient specific factors?? (Age at diagnosis? Duration of untreated CD? Genetic background) that modify risk. 	<p>Dear, I have elaboration for heterogeneous presentation and individual variability in a dedicated 'Patient specific risk modifier' section (page 11) . Relevant studies added. Kindly head to page 7 under the heading "<i>Outcome of Long-term Gluten free Diet on Colorectal neoplasia.</i>"</p>
	<p>LIMITATIONS OF STUDIES REVIEWED NOT DISCUSSED</p> <p>Dedicate a section for Limitations of studies reviewed</p> <ol style="list-style-type: none"> 1. Majority of references from retrospective studies. What Potential bias??? What Gaps in data?? Could it affect interpretations of findings? 	<p>Dear, A dedicated section for limitations added highlighting the major gaps and how it could impact the findings in the Limitation section. Kindly check page 23 and page 32 .</p>

	<p>Management strategies not explained</p> <ol style="list-style-type: none"> 1. Particularly Integration of Genetic testing & Personalized treatment plans for pts at RISK OF NEOPLASIA 2. How might BIOMARKERS in clinical practice in addition to genetic tests be used to identify at risk patients? 3. Add Brief Discussion of potential interventions (immune / targeted therapies) For patients with neoplasia due to CD particularly in context of lymphoma and adenocarcinoma 	<p>A dedicated section for genetic testing and biomarkers has been added with relevant studies to support the personalized treatment strategies and a section for potential interventions added. Kindy check page 31-32.</p>
	<p>Restructure abstract as:</p> <ul style="list-style-type: none"> ● Background ● Aims ● Methods ● Results <p>Avoid conceptual definitions and focus on the core study and outcomes</p>	<p>Thank you for pointing this out. The abstract section has been restructured as per the standard.</p>

<p>2</p>	<p>Elucidation of bidirectional association between CD and CRC. A known CD patient has a risk of CA colon but converse epidemiological relationship?</p> <p>Whether the patient with CRC later exhibits an altered incidence of CD? Scientific literature on bidirectional causality and possibility of mutual pathogenic influence. Review and synthesize research on reciprocal association hypothesis.</p>	<p>There are limited studies available on reciprocal causality so far warranting further research.</p> <p>This has been explained under the subheading “Molecular level” first paragraph page 12-13.</p>
	<p>Comprehensive discussion on immunological mechanisms</p> <ol style="list-style-type: none"> 1. What the manuscript poses is the autoimmune nature of CD due to inducing generalized immune dysregulation facilitation of tumor immune escape mechanisms. <p>Other studies present that autoimmune disease in chronic inflammation states enhance immune surveillance and paradoxical reduction in overall cancer incidence by eliminating more effectively nascent malignant cells</p> <p>More detailed discussion on immunology that addresses dualistic nature of autoimmune responses in context of cancer development and progression</p>	<p>Dear, elaboration on immunological mechanisms has been added under the subheading <i>Chronic inflammation and carcinogenesis</i> page 18. Thank you.</p>

3

	<p>It is recommended that the authors supplement the review with more epidemiological data from different regions to enhance the universality and reliability of the conclusions</p>	<p>Dear, the search strategy and results yielded long term studies published in Europe, North and south Americas. No studies reported in the literature from Asia or Australia.</p>
	<p>delve deeper into the specific molecular mechanisms underlying the association between celiac disease and colorectal tumors, such as detailing the role of specific signaling pathways in tumorigenesis and analyzing them in conjunction with current cutting-edge research.</p>	<p>Dear, A dedicated section with a subheading “Molecular level” added in the introduction aiming to explore the signalling pathway that could potentially explain the association between CD and CRC. Kindly head to page 12-13 under the subheading “Oncogenic pathways in Celiac Disease”</p>
	<p>Discussions on the role of the gut microbiota should be expanded, as the gut microbiota is closely associated with gut immunity and inflammatory responses and may play a significant role in the association between celiac disease and colorectal tumors.</p>	<p>Agreeing with this note and the integral role, I prepared a full section titled Role of Microbiota that is within the oncogenic pathways following Tissue level. Kindly have a look at page 15-16. Thank you.</p>
	<p>It is recommended that the authors supplement their discussion of the impact of a gluten-free diet on colon cancer risk with more data from long-term follow-up studies to clarify the effectiveness of long-term adherence to a gluten-free diet in reducing colon cancer risk. to explore the impact of different follow-up periods on outcomes</p>	<p>A separate subheading “<i>Effects of a Long-term Gluten free Diet on Colorectal neoplasia</i>” has been added to emphasize and elaborate the impact of gluten free diet on colon cancer risk. Kindly check page 11.Thank you.</p>
	<p>Discussion on individualized risk assessment for CD. Consider the impact of genetic and environmental factors on tumor risk. Current research findings to include currently available risk. Assessment tools to</p>	<p>A relevant section “<i>Individualized risk assessment</i>” has been added on page 20. Moreover, genetic and environmental factors influencing tumor risk are discussed separately under the heading <i>effects of Long-term Gluten</i></p>

	<p>provide clinicians with more precise patient management strategies.</p>	<p><i>free Diet on Colorectal neoplasia</i> on page 16. Thank you.</p>
--	--	--

The authors have thoroughly addressed all previous review comments, and the revisions have significantly improved the manuscript. This in-depth review provides a comprehensive examination of the relationship between celiac disease (CD) and colorectal neoplasia, covering pathogenic mechanisms, clinical manifestations, and diagnostic approaches. The topic holds substantial clinical relevance, and the review is well-structured. The conclusions—highlighting the low incidence but poor prognosis of colonic lymphoma and adenocarcinoma in CD patients—offer valuable clinical insights.

Recommendation: Accept

Reply: Thanks for your comments.

The author has made comprehensive revisions to the manuscript in response to my review comments, particularly in refining the molecular mechanisms, supplementing long-term follow-up studies, and discussing individualized risk assessment. Although the author was unable to fully meet the requirement of supplementing epidemiological data from different regions, their explanation is reasonable. Given the author's positive response and revisions to most of the suggestions, I am inclined to accept the revised manuscript.

Reply: Thanks for your comments.