

Peer Review

Review of: "Histopathologic Evaluation and Single-Cell Spatial Transcriptomics of the Colon Reveal Cellular and Molecular Abnormalities Linked to J-Pouch Failure in Patients with Inflammatory Bowel Disease"

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Olivas et al. make a significant contribution to the field of IBD and pouch surgery by identifying high-risk histologic features and molecular pathways associated with pouch failure. The integration of histopathology and spatial transcriptomics is innovative and provides valuable insights into the cellular and molecular mechanisms underlying pouch failure. However, the study's retrospective design, small sample size for spatial transcriptomics, and lack of functional validation are notable limitations.

Major concerns:

- To strengthen the molecular findings, the authors should consider expanding the spatial transcriptomics analysis to a larger cohort of patients. This would provide more robust evidence for the identified pathways and cellular interactions.
- The study would benefit from functional validation of the identified molecular pathways. For example, in vitro experiments using organoids or animal models could help confirm the role of IL-10, IL-1 β , and interferons in pouch failure.
- The authors should consider adjusting for potential confounding factors, such as medication use and postoperative complications, in their statistical analysis. This would provide a more comprehensive understanding of the risk factors for pouch failure.

- The methods section for spatial transcriptomics could be expanded to make the techniques more accessible to readers without a bioinformatics background. Including a more detailed explanation of the data processing and analysis pipeline would improve clarity.
- The authors should include a more detailed discussion of the study's limitations, particularly the retrospective design and the potential for selection bias. Acknowledging these limitations would provide a more balanced interpretation of the results.

The study has strong potential, but it would benefit from addressing the weaknesses outlined above, particularly expanding the spatial transcriptomics cohort, including functional validation, and addressing confounding factors. With these revisions, the study could make an even more impactful contribution to the field.

Declarations

Potential competing interests: No potential competing interests to declare.