

## **Role of Interleukins Pathogenesis in Cholangiocarcinoma: A Literature Review**

**Manuscript NO:** 107341

**Dear Editor**

The reviewers raised the following queries which are explained below.

### **A point-by-point response to the reviewers' reports**

We would like to express our gratitude to the reviewers for dedicating their time to thoroughly evaluate the manuscript and providing us with insightful and constructive feedback.

### **Reviewers report**

This study represents a significant advancement in the field of cholangiocarcinoma, the article presents a novel and creative approach to the topic, demonstrating a comprehensive understanding of the relevant literature. The unique insights and methodologies employed contribute significantly to the field, making this work a valuable addition to the existing body of research. The manuscript is well-organized with a clear and logical flow of information. The title accurately and concisely reflects the core focus of the manuscript. The abstract provides a clear and concise overview of the study's objectives. The keywords are relevant to the research question and provide a useful index for potential readers. The introduction clearly states the research question and its significance, providing a strong rationale for the study. The explanation and interpretation of the data provides a clear and comprehensive analysis of the findings, focusing on the specific implications of the findings, presenting the key points in a clear and logical manner. The precise methodology employed in this study, strengthens the reliability and validity of the findings. The reference list is extensive and includes the most relevant and current literature in the subject area. The figure and table are presented in a clear and consistent manner also, effectively convey the key points of the paper. The conclusions are clear, concise, and accurately reflect the study's findings presented in the results section. The authors successfully achieved the research objectives, providing valuable insights into the role of interleukins Pathogenesis in Cholangiocarcinoma. The section for abbreviations is missing in the manuscript, it is necessary to be included in the manuscript to facilitate into the reader. Recommend exploring underlying biological mechanisms to strengthen the causal inference and to become more effective in solves this problem. Based on the previous comments, the

paper is of high quality, well-crafted and informative paper and strongly recommend acceptance for publication.

**Author response:** Thank you for your feedback. We have added the new information on these points in the revised manuscript which is highlighted in yellow color.

‘Multiple types of complex biological processes underlie CCA which contributes to its aggressive nature and resistance to treatment. At the molecular level, genetic changes like mutations are essential for encouraging unchecked cell proliferation and survival, especially in intrahepatic subtypes [5].

Epigenetic changes, such as DNA methylation and non-coding RNA dysregulation, further impair gene expression and aid in the development of tumors. A pro-tumorigenic microenvironment is fostered by chronic inflammation, which activates important signaling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and signal transducer and activator of transcription 3 (STAT3). While immune evasion mechanisms, such as programmed death ligand 1 (PD-L1) expression, enable CCA cells to evade immune monitoring, the epithelial-mesenchymal transition (EMT) pathway gives tumor cells invasive characteristics. The intricacy of cholangiocarcinoma is highlighted by these interrelated biological processes, which also offer potential problems for focused treatments [ 5].’