

Authors' Response:

Thank you for your thoughtful comments and review to strengthen our paper for publication. We have edited the paper as detailed below, with additions and changes highlighted. As the authors are native English speakers, we performed careful language review and correction of any grammatical errors.

Reviewer #1:

Dear Editor, thank you so much for inviting me to revise this manuscript about biliary tract cancer. This study addresses a current topic. The manuscript is quite well written and organized. English should be improved. Figures and tables are comprehensive and clear. The introduction explains in a clear and coherent manner the background of this study. We suggest the following modifications:

Introduction section: although the authors correctly included important papers in this setting, we believe the evolving systemic treatment scenario for BTC should be further discussed and some recently published papers added within the introduction (PMID: 33756174 ; PMID: 33571059; PMID: 35031442 ; PMID: 32806956), only for a matter of consistency. We think it might be useful to introduce the topic of this interesting study.

- The references mentioned have been added to the introduction as below with appropriate citations:

“Additionally, some evidence has suggested that sex differences not only impact survival but treatment response, with one meta-analysis reporting slightly higher overall survival in male patients receiving single-agent immunotherapy. This is an important finding as neoadjuvant therapies can improve the success of resection rates in certain subsets of biliary tract cancer patients and possibly reduce the rates of disease relapse.”

Methods and Statistical Analysis: nothing to add.

Discussion section: Very interesting and timely discussion. Of note, the authors should expand the Discussion section, including a more personal perspective to reflect on. For example, they could answer the following questions – in order to facilitate the understanding of this complex topic to readers: what potential does this study hold? What are the knowledge gaps and how do researchers tackle them? How do you see this area unfolding in the next 5 years? We think it would be extremely interesting for the readers.

- Thank you for your comments. The following has been added to expand the discussion and tie in the references added to the introduction:

“Recognizing patients at a higher risk for morbidity and mortality is important as we can consider the addition of neoadjuvant therapies and other treatment modalities to improve long term survival outcomes.

An understanding of the modifiable demographic and socioeconomic factors that affect survival is key to the development of healthcare policy. There are still significant knowledge gaps around why non-modifiable risk factors, such as sex or race / ethnicity may influence survival. The rise of precision medicine may be important to understanding the impact of genetics, of environmental and lifestyle influences, and of the microbiome on survival.”

One additional little flaw: the authors could better explain the limitations of their work, in the last part of the Discussion.

- The following sentence has been added to further expand and clarify:
“As this study occurred over an extended period, there have been advances in diagnostic tests and treatments available, which further impacts morbidity and mortality within certain populations.”

However, we think the authors should be acknowledged for their work. In fact, they correctly addressed an important topic, the methods sound good and their discussion is well balanced.

We believe this article is suitable for publication in the journal although major revisions are needed. The main strengths of this paper are that it addresses an interesting and very timely question and provides a clear answer, with some limitations. We suggest a linguistic revision and the addition of some references for a matter of consistency. Moreover, the authors should better clarify some points.