Jan 8th, 2022
Respected Dr. Jin-Lei Wang, Company Editor-in-Chief, and editorial team,

We are sincerely thankful to the editorial office for considering our manuscript and providing us the opportunity for revising and improving our manuscript. We have made relevant changes as highlighted by the reviewers and editorial office and are supplying the files. We now provide a point-by-point responses to the comments by the reviewers and editorial office. Our responses are in red font:

Reviewer #1:
**Scientific Quality:** Grade C (Good)
**Language Quality:** Grade B (Minor language polishing)
**Conclusion:** Minor revision
**Specific Comments to Authors:** I think it's a well written review that summarized multiple AI-based models or algorithms in the diagnosis and treatment of CCA mostly in the last three years. As the authors mentioned, CCA is an aggressive tumor diagnosed sporadically in advanced stages with high mortality. Therefore, it is urgent to evaluate AI's power concerning CCA in prospective cohort study. But considering the generality of AI, I think it is also necessary to highlight its unique aspects (if there is any) in CCA application.?

Response: Thank you for the beneficial suggestions. We highlighted the unique aspects of AI in CCA application as follows:

"AI is particularly helpful in CCA diagnosis as the condition is not common and there is heterogeneity in anatomical location of the tumor and risk factors of the tumor (16). This makes the traditional algorithms inferior compared to AI."

(Page 4, paragraph 2, lines 6-9).

Reviewer #2:
**Scientific Quality:** Grade C (Good)
**Language Quality:** Grade B (Minor language polishing)
**Conclusion:** Accept (General priority)
**Specific Comments to Authors:** This paper reviews the application of artificial intelligence in cholangiocarcinoma, with clear logic and certain value. It is recommended that the abstract and introduction reflect the timeliness of AI, not the oldest.

Response: The authors greatly appreciate your great comment. The following revisions are made based on the useful comment:

"Artificial intelligence (AI) is the timeliest field of computer science and attempts to…"

(Page 2, paragraph 1, line 1).

"…histologic, radiologic that can be assimilated together by modern AI tools for diagnosis,…"
(Page 2, paragraph 1, line 8).

"…the infinite potential of Big data in medical field. AI, the timeliest field of computer…"
(Page 3, paragraph 1, line 3).

"…The presence of the vast array of serum markers has led to utilization of the markers in novel AI tools in combination with imaging."
(Page 4, paragraph 1, lines 4-6).

"Novel AI tools have been able to help in individualizing candidates for each treatment modality."
(Page 4, paragraph 1, lines 15-16).

"AI is particularly helpful in CCA diagnosis as the condition is not common and there is heterogeneity in anatomical location of the tumor and risk factors of the tumor (16). This makes the traditional algorithms inferior compared to AI."
(Page 4, paragraph 2, lines 6-9).

Reviewer #3:
**Scientific Quality:** Grade C (Good)
**Language Quality:** Grade B (Minor language polishing)
**Conclusion:** Minor revision
**Specific Comments to Authors:** 1. In the third paragraph of the INTRODUCTIOND section: "Although liver function tests remain the initial lab tests, a combination of tumor markers like carbohydrate antigen (CA) 19-9 and carcinoembryonic antigen (CEA) are also utilized to diagnose the disease especially in patients with primary sclerosing cholangitis (PSC)[8]. "I don't know what this expression is meant to explain? In addition, the content of the third paragraph should be related to AI.

Response: Thank you so much for the great comment. The following revision has been made.

"A combination of serum markers like liver function tests, carbohydrate antigen (CA) 19-9, and carcinoembryonic antigen (CEA) are utilized to diagnose the disease (8). The presence of the vast array of serum markers has led to utilization of the markers in novel AI tools in combination with imaging."
(Page 4, paragraph 1, lines 2-6).

"(MRCP) are valuable tools harnessed by AI to assess the extent of tumor and staging of"
(Page 4, paragraph 1, line 8).

"Novel AI tools have been able to help in individualizing candidates for each treatment modality."
(Page 4, paragraph 1, lines 15-16).

2. In the AI IN THE DIAGNOSIS OF CCA section: "LR is a linear regression model used for binary classification of problems. SVM is an appropriate model for small samples, high-dimensional, and non-linear patterns assigning labels to objects and has advantage of avoiding "over learning" problem. ANN or multilayer perceptron is an attempt to simulate the biologic nervous system with neurons interconnected able to do parallel processing. Developed by Huang et al., Extreme Learning Machines (ELM) are a type of feedforward neural network models that have shown superiority over SVMs and traditional feedforward neural networks. Convoluted neural network (CNN), a type of DL consists of multilayer of ANN that results in a superior learning ability of complex tasks and has been used in radiology and imaging of the malignancy and associating the radiological data to the clinicopathologic data. Every method has their advantages and drawbacks illustrated in table 1. ", can be considered to be added to INTRODUCTIOND.

Response: Thank you very much for the great observation. The above paragraph has been added to the introduction as suggested.
(Page 4, paragraph 2, lines 10- Page 5, paragraph 1, lines 7).

3. In the AI IN THE DIAGNOSIS OF CCA section, the research mentioned in "Histology, CT, MRI and MRCP", it is recommended that the researches with similar methods should be appropriately combined and then expressed. For example: "Xu et al. studied 106 patients with CCA and developed a SVM model that showed superior results when used in combination with lymph node involvement in MRI and CA 19-9 level compared to SVM model alone (validation group AUC 87.0% vs. 78.7%)[32]. " and " Yao et al. validated a radiomics based particle swarm optimization and SVM model based on 110 MRI images of the CCA patients attempting to diagnose the extent of lymph node metastasis with an average accuracy AUC of 90% and 88%[35]. " These two studies can be combined.

Response: Thank you very much for the fantastic comment. The two studies are combined as below:

"Xu et al. and Yu et al. each studied MRI of more than 100 patients with CCA and developed SVM models that showed superiority (validation group AUC 87.0% and 90%, respectively (33, 34)"

(Page 7, paragraph 2, lines 3-5).

CA 19-9 as a tumor marker has shown promise in prognosis of CCA. Li *et al* and Muller et al. each validated an AI model to prognosticate the CCA tumors based on clinical, tumor markers such as CA 19-9, serologic like albumin level, and clinical data like nodal metastasis. Li et al. model retrospectively studied a total of 1,390 patients and achieved a Concordance Index (C-index) superior to the staging system proposed by the 8th edition of the American Joint Committee on Cancer (C-index: 0.693, 95% CI: 0.663- 0.723) (41). Muller et al. model was able to predict the 1-year survival of patients with an AUC of 89% and 80% for the training and validation sets, respectively (42).
(Page 8, paragraph 3, lines 1-8).

4. In the "TREATMENT AND PROGNOSIS OF CCA" section, you can summarize the studies using the same or similar evaluation criteria "CA 19-9, tumor size, CT images, nodal metastasis, etc." instead of listing individual studies.

Response: Thank you very much for the useful comment. The following headings are added, and studies added under them:
***CT imagining, CA 19-9, and palliative measures***
(Pages 8 and 9)

***(1) Science editor:***
Artificial intelligence (AI) is the oldest field of computer science and attempts to mimic cognitive function of humans to solve problems. Cholangiocarcinoma (CCA) is the second most common primary malignancy of liver that has shown an increase in incidence in the last years. This reviews contribute to the application of artificial intelligence in cholangiocarcinoma. This article is useful has guiding value.
Language Quality: Grade B (Minor language polishing)
Scientific Quality: Grade C (Good)

Thank you very much for the excellent comment.

***(2) Company editor-in-chief:***
I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Oncology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing

specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Thank you very much for the beneficial comment. The PowerPoint files containing figures are provided. In addition, the tables are revised to standard three-line tables conforming to editing specifications.

Please let us know if anything else is required for this manuscript. We are hopeful for a successful submission.

Sincerely,
Muhammad Aziz, MD
University of Toledo Medical Center