Response Letter

Dear Editors and Reviewers:

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "**Early Warning Management of Pain in Patients with Hepatocellular Carcinoma after Transcatheter Arterial Chemoembolization: a retrospective study of integrated modeling based on machine learning algorithm"(ID: 82520)**. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. The revised portion is marked in red in the paper. The main corrections in the paper and the responds to the Editor's and reviewer's comments are as following:

Comments to Science editor:

The manuscript has been peer-reviewed, and it' s ready for the first decision.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade B (Very good)

Response: Thank you for your suggestions. We have revised and confirmed the language of the full text again according to the professional mother tongue polishing team of the reviewer.

Comments to Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastrointestinal Surgery, 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. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). 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. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating

figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. 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. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the RCA. RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response: We are deeply gratified and encouraged by the recognition of our research by the editor in chief. Here, we also agree with the suggestions put forward by the editor in chief and revise the requirements of manuscripts and magazines according to the suggestions of the editor in chief. The specific contents are as follows:

1. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words).

Response:

Original title: Early Warning Management of Pain in Patients with Hepatocellular Carcinoma after Transcatheter Arterial Chemoembolization: a retrospective study of

integrated modeling based on machine learning algorithm(25words)

Revised title:

Pain Management in Patients with Hepatocellular Carcinoma after Transcatheter Arterial Chemoembolisation: A Retrospective Study (14words)

2. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Response: We have revised the charts in the full text according to the publication requirements of the magazine, and put the original pictures in PowerPoint for the convenience of later magazine editors. Please refer to the uploaded attachment for details.

3. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision.

Response: Thank you very much for your valuable suggestions. In this study, we tried to use RCA software, which can guide us to use references more conveniently and efficiently. With the help of this software, we also modified and corrected the references cited in the full text to facilitate the smooth reception and publication of the articles (if possible).

Comments to Reviewer #1:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: I read this paper about the prediction of post-operative pain in TACE with interest. The Authors used an artificial intelligence application to develop a model able to predict the occurence of severe pain after TACE. Despite the use

of IA, the topic is not entirely novel. On the other hand, the authors provided a validation cohort, which is a strenght of this study. I have some concerns: 1) General comment: Even if the authors provided an Eglish language certificate, many obvious errors are still fount throghout the text (for instance "mid-term" HCC instead of "intermediate, "TACE surgery", etc). I suggest to perform a further language revision; 2) Study population: I fail to see how a prospective population from the same hospital which enorlled the patients in a the retrospective phase can be considered an "external time-space validation". Time maybe, but not space. 3) Study population: it is not clear how the January 2020 deadline was chosen. Was this a prospective/retrospective study which was approved by the IRB on that date? Please clarify. How could the patients enrolled in the retrospective cohort provide an informed consent, considering that many of the were probaby dead at the time of the study? Finally, please provide an Eglish translation of the IRB approval. 4) Methods: please integrate your information by creating a paragraph titled "Pain mangement", in which the pain-management protocol is described (please report whether the patients received corticosteorids as part of the protocol and whether the pain-management protocols changed between 2016 and 2022) 5) Discussion, Line 282: embolization of nodules close to the gallbladder might also be an alternative cuase of pain, especially if cystic artery vessels provided bllod to the nodules and had to be embolized. 6) Discussion, Line 324: the whole discussion about coagulation is not convincing nor supported by referenced literature. Plesase find some reference to support these statement or tone down this hypothesis.

Response: Thank you for your useful suggestions. We have adopted them and revised the relevant contents of the manuscript according to your suggestions.

1) General comment: Even if the authors provided an Eglish language certificate, many obvious errors are still fount throghout the text (for instance "mid-term" HCC instead of "intermediate, "TACE surgery", etc). I suggest to perform a further language revision; Response: Thanks for your advice, we have submitted to our paper, the Charlesworth Author Services (CAS) team (https://www.cwauthors.com.cn/) had helped us improve our language and correct grammatical errors existed in our manuscript. The CAS team confirmed that their proofreader had done a very good job of improving language and

correcting grammatical errors. We also checked the manuscript again and again, and we couldn't find grammatical errors.

Besides, we also extensively revise English in the text with the help of Bullet Edits. As follows:

2) Study population: I fail to see how a prospective population from the same hospital which enorlled the patients in a the retrospective phase can be considered an "external

time-space validation". Time maybe, but not space.

Response: Thank you for your suggestions. We agree with you that "Time maybe, but not space". Therefore, we have modified relevant contents in the methods part, as follows:

We retrospectively included 857 patients with HCC who received TACE in the Hepatic Surgery Center of Tongji Hospital from January 2016 to January 2020 through the electronic record system of the hospital. Additionally, we prospectively included 368 patients with HCC who underwent TACE in the hospital from February 2020 to October 2022 as the external verification cohort.

3) Study population: it is not clear how the January 2020 deadline was chosen. Was this a prospective/retrospective study which was approved by the IRB on that date? Please clarify. How could the patients enrolled in the retrospective cohort provide an informed consent, considering that many of the were probaby dead at the time of the study? Finally, please provide an Eglish translation of the IRB approval.

Response: Thank you very much for your question about the cut-off point of this study.

"it is not clear how the January 2020 deadline was chosen"---- In this study, we mainly carried out a retrospective study on the patient's case data, so we imported the patient data from 2016 to 2022 from the hospital's medical record system, and set the cut-off point of this study as January 2022. Since the patient's medical record data since 2022 has not entered the medical record system, we have not extracted it.

"Was this a prospective/retrospective study which was approved by the IRB on that date? Please clarify. How could the patients enrolled in the retrospective cohort provide an informed consent, considering that many of the were probaby dead at the time of the study?"--- This study is a retrospective study, because all patients will sign an informed consent when they enter the liver surgery center of Tongji Hospital for treatment. This informed consent means that all patients are willing to accept and participate in the retrospective study such as the extraction of medical record data and follow-up of patients that may be involved in the future. During this period, patients can also choose to give up their participation in the study, which is their own right. In addition, during the follow-up of patients, some patients may have died during the follow-up, so the patient's family members can be fully responsible for the signing of the informed consent form.

Finally, please provide an Eglish translation of the IRB approval--- We have translated the Chinese version of the Ethical Approval into English version. Please check the uploaded attachment of the English Ethical Approval.

4) Methods: please integrate your information by creating a paragraph titled "Pain mangement", in which the pain-management protocol is described (please report whether the patients received corticosteorids as part of the protocol and whether the pain-management protocols changed between 2016 and 2022).

Response: Thank you very much for your reminder. As for integrating information by creating as paragraph titled"Pain management", we have modied the title as follows:

Pain Management in Patients with Hepatocellular Carcinoma after Transcatheter Arterial Chemoembolisation: A Retrospective Study.

We also added relevant report as for "whether the patients received corticosteorids as part of the protocol and whether the pain-management protocols changed between 2016 and 2022" in the methods part.

5) Discussion, Line 282: embolization of nodules close to the gallbladder might also be an alternative cuase of pain, especially if cystic artery vessels provided bllod to the nodules and had to be embolized.

Response: Thank you for your suggestions. We have added relevant content in the discussion, as follows:

Consequently, the patient is more likely to feel pain and discomfort. Moreover, if more tumours are embolised, more iodised oil is required, and a larger embolised area may increase the pain caused by tumour necrosis. we speculated that embolization of nodules close to the gallbladder might also be an alternative cuase of pain, especially if cystic artery vessels provided bllod to the nodules and had to be embolized.(Please see line 277 to 282).

6) Discussion, Line 324: the whole discussion about coagulation is not convincing nor supported by referenced literature. Plesase find some reference to support these statement or tone down this hypothesis.

Response: Thank you for your suggestions. After carefully checking, we have modified the whole discussion, that is, we have added some reference to support these statement or tone down this hypothesis.(Please see references 30 to references 33).

Comments to Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is a very interesting paper, using ML to predict an outcome, with consistent results. I recommend aceeptance.

Response: Dear reviewer, we sincerely thank you for your high recognition and affirmation of this study. In the future research implementation, we will strive to do a good job in the transformation of relevant results, with a view to early clinical application and benefit patients.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.Once again, thank you very much for your comments and suggestions.