

April 15, 2021

Subrata Ghosh, AGAF, FCAHS, FRCP (C), FRCPC, FRCPE, MD

Andrzej S Tarnawski, DSc, MD, PhD

Editors-in-Chief

World Journal of Gastroenterology

Dear Editors:

Thank you for your comments and efforts concerning our manuscript entitled: “**Application of Artificial Intelligence in the Preoperative Imaging of Hepatocellular Carcinoma: Current and Future Perspectives**” (No. 63445)

The comments are all valuable and helpful for revising and improving our paper. We have studied the comments carefully and have made the following point-by-point modifications to the manuscript (our responses are shown in blue):

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The authors reviewed current data on the role of artificial intelligence (AI) in preoperative imaging diagnosis of hepatocellular carcinoma (HCC) focused on some promising results in the field of segmentation, differential diagnosis, prediction of histopathology, early recurrence after curative treatment, and treatment response. They also pointed out several limitations in applying AI on preoperative evaluation for HCC currently such as low reproducibility, heterogeneity of imaging acquisition, and lack of external multicenter validation. This manuscript was well written

with adequate language overall, only minor revision was recommended.

1. More data regarding immunotherapy (IO) for HCC has been published recently, please update reference 56.

Response: Thank you for your valuable advice. We have checked the literature carefully and reviewed results of recent clinical trials about immunotherapy for HCC, such as CheckMate 040, GO30140 and IMbrave150 [reference 1-3]. In these clinical trials, the objective response rates were relatively low and not more than 36%. We updated reference 56 and added 2 references into the *Immunotherapy* part in the revised manuscript.

Reference:

1. Yau, T, et al. Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Advanced Hepatocellular Carcinoma Previously Treated with Sorafenib: The CheckMate 040 Randomized Clinical Trial. JAMA oncology 2020; 6(11).
- 2.Finn RS, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. The New England journal of medicine 2020; 382(20): 1894-1905.
- 3.Lee MS, et al. Atezolizumab with or without bevacizumab in unresectable hepatocellular carcinoma (GO30140): an open-label, multicentre, phase 1b study. The Lancet Oncology 2020; 21(6): 808-820.

2. Revise 'machining learning' to 'machine learning' in figure 2.

Response: Thank you for your revision. We have modified this expression in figure 2.

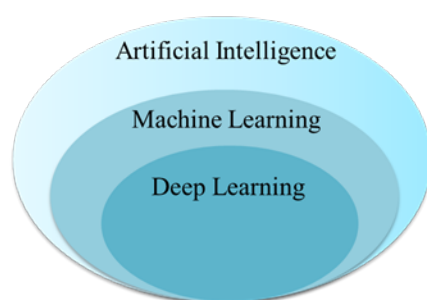


Figure 2 described the relationship of artificial intelligence, machine learning

and deep learning.

Science editor:

Scientific quality: The manuscript describes a review of the application of artificial intelligence in the preoperative imaging of hepatocellular carcinoma. The topic is within the scope of the WJG.

1. Classification: Grade B;

Response: Thank you for your comment.

2. Summary of the Peer-Review Report: The authors reviewed current data on the role of artificial intelligence in preoperative imaging diagnosis of hepatocellular carcinoma focused on some promising results in the field of segmentation, differential diagnosis, prediction of histopathology, early recurrence after curative treatment, and treatment response. However, the manuscript was based on a descriptive analysis. The causal relationship was not further explored. The questions raised by the reviewer should be answered;

Response: Thank you for your valuable suggestion. In this manuscript, we described the promising results of AI in preoperative imaging, as well as the limitations and potential research directions. We barely mentioned causal relationship in each aspect and this really needs to improve. Although AI and radiomics has been proved useful in various aspects of HCC, the underlying mechanisms have not been clearly stated, such as pathological correlation, the relationship between radiomics and genomics. Therefore, we added this key point in the limitations. We will pay more attention to those fields and follow up recently published articles to explore the causal relationship among imaging, pathophysiology and prognosis of HCC.

We have answered the questions raised by Reviewer #1 in our first part of this response.

3. Format: There are 2 figures.

Response: Thank you for your comment. There are 2 figures in this manuscript. We added one table according to the advice of company editor-in-chief.

4. References: A total of 60 references are cited, including 45 references published in the last 3 years;

Response: Thank you for your comment. We updated reference 56, and added 2 references in the revised manuscript, which were published in 2020. Therefore, 48 of our 62 references were published in the last 3 years.

5. Self-cited references: There is 1 self-cited reference. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations that are closely related to the topic of the manuscript, and remove other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated;

Response: Thank you for your comment. Reference 27 was published by our research group. In this article, we constructed a radiomics signature from CT and developed a machine learning model to predict MVI preoperatively. It is closely related to the topic of this study, therefore we cited it in this review.

6 References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the

editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

Response: Thank you for your reminder. According to the comments of Reviewer #1, we reviewed the results of recent clinical trials about immunotherapy for HCC and updated the references in the revised manuscript. Also, we didn't receive any request from any peer reviewer to cite their references.

2 Language evaluation: Classification: Grade B. A language editing certificate issued by Editage was provided.

Response: Thank you for your comment. We tried our best to improve the manuscript and made some changes to the manuscript. These changes will not influence the content and framework of our manuscript. And we have sent the revised manuscript to Editage [www.editage.cn] again for English language editing. We will update the language editing certificate when submitting our revised manuscript.

Academic norms and rules: No academic misconduct was found in the Bing search.

Thank you for your comment. We abide by the academic norms and rules in our research.

4 Supplementary comments: This is an invited manuscript. The study was supported by 5 grants. The topic has not previously been published in the WJG.

Response: Thank you for your comments. We will upload all the 5 approved grant application forms when submitting our revised manuscript.

5 Issues raised:

(1) The “Author Contributions” section is missing. Please provide the author contributions;

Response: Thank you for your reminder. We have added the “Author Contributions” section in the revised manuscript.

Author contributions: Feng B performed literature review and drafted the manuscript; Cai W contributed to data collection of the study; Wang S, Liu XB and Zhao XM reviewed the manuscript; Ma XH contributed to conception and design of the study, and critically revised this manuscript; all authors have read and approved the final manuscript.

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: Thank you for your comment. We will upload all the approved grant application forms when submitting the revised manuscript.

(3) The authors did not provide original pictures. 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;

Response: Thank you for your reminder. We will upload the original figure documents when submitting the revised manuscript.

(4) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For

example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable;

Response: Thank you for your comment. Figure 1 and Figure 2 were drawn by ourselves and they were not published elsewhere.

(5) The column should be minireviews.

Response: Thank you for your comment. We have modified the column to minireview.

6 Recommendation: Conditional acceptance.

Response: Thank you for your comment and generous help. We have revised all the suggestions carefully.

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 Gastroenterology, 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. Before final acceptance, the author(s) must add a table/figure to the manuscript.

Response: Thank you for your valuable advice. We have added Table 1 to the manuscript. As follows:

Table 1 Summary of studies on the differential diagnosis of hepatocellular carcinoma

Study	Aim of the study	Modality	Patients	Method	AUC of the final model
Nie P et al [7]	Differentiation between HCC and HCA	CT	131	ML	T:0.96 V:0.94
Nie P et al [8]	Differentiation between HCC and FNH	CT	156	ML	T:0.979 V:0.917
Mokrane FZ et al [9]	differentiation between HCC and non-HCC nodules	CT	178	ML	T:0.70 V:0.66
Ponnoprat D et al [10]	Differentiation between HCC and ICC	CT	257	ML	N/A
Shi W et al [11]	Differentiation HCC from other FLLs	CT	449	DL	0.925
Yasaka K et al [12]	Liver masses classification	CT	560	DL	T:0.95 V:0.84
Cao SE et	FLLs	CT	517	DL	V:0.88-0.99

al [13]	classification					
Jiang H et al [14]	Comparing the MRI diagnostic accuracies of EASL (v2018), LI-RADS criteria and radiomics models for HCC	211	ML	T:0.861 V:0.810		
Zhen SH et al [15]	Classify liver tumors	1411	DL	0.960-0.998		
Liu X et al [16]	Differential diagnosis of HCC subtypes	85	ML	0.79-0.81		
Huang X et al [17]	Diagnosis of DPHCC	100	ML	0.731-0.784		
Jian W et al [18]	Characterization of HCC	112	DL	N/A		
Wu J et al [19]	Classification of HCC and hepatic hemangioma	369	ML	T:0.86 V:0.89		

Note: T: training cohort, V: validation cohort, N/A: not available, AUC: the area under the receiver operating characteristic curve, ML: machine learning, DL: deep learning, HCC: hepatocellular carcinoma, HCA: hepatocellular adenoma, FNH: focal nodular hyperplasia, ICC: intrahepatic cholangiocarcinoma, DPHCC: dual-phenotype hepatocellular carcinoma, FLLs: focal liver lesions