Dear Editor-in-Chief and Reviewer, Artificial Intelligence in Gastroenterology:

Attached is our manuscript, "Application of Artificial Intelligence in Hepatology: Mini-review". The paper is submitted for consideration of publication in Artificial Intelligence in Gastroenterology as a mini-review article. Neither the entire paper nor any of its contents has been accepted by any other journal nor is the paper being submitted to any other journal.

All authors have participated sufficiently in the work and have given final approval of the submitted manuscript. There are no conflicts of interest.

Thank you for your letter and for the reviewers' comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made correction which we hope meet with approval.

The main corrections in the paper and the responds to the reviewer's comments are as following:

Response to reviewer's comments:

1. The logic flow and presentation of the results could be optimized if different AI methods (deep learning vs. conventional machine learning) and disease types (diffuse liver diseases vs. focal liver diseases) were organized in separate sections. Explicit subheadings might be helpful as well.

Response: Thank you very much for your valuable comment and advice.

We added subheadings and added a table to demonstrate different AI methods in different diseases.

Table 1. Clinical applications of artificial intelligence (AI)

	Samples	Diagnosis	AI technique	Accuracy (%)	AUROC	Ref.
Focal liver disease detection	US	Benign tumors	DL	97.2	-	[23]
	serum tests, clinical data	HCC	ML (gradient boosting)/DL	87.34/83.54	0.940/0.884	[25]
Diffuse liver disease staging	US	FLD	DL/SVM/ELM	100/82/92	1.0/0.79/0.92	[26]
	US	NAFLD	DL	-	0.9777	[27]
	Elastography	Cirrhosis	DL	-	0.97	[32]

Risk assessment	Clinical, pathohistological data	Poorer survival after HCC resection	2 DL models	-	0.78, 0.75 (c-index)	[35]
	Sequence data	Poorer survival after HCC resection	DL	-	0.68 (c-index)	[36]
	Clinical data	HCC development	ML	-	0.64 (c-index)	[37]
	Clinical, histological data	1-year and 3-year clinical outcomes	ML		0.78, 0.76	[38]

AUROC, area under the receiver operating characteristics; c-index, confidence interval; DL, deep learning; ELM, extreme learning machine; FLD, fatty liver disease; HCC, hepatocellular carcinoma; ML, machine learning; NAFLD, nonalcoholic fatty liver disease; Ref, reference; SVM, support vector machine; US, ultrasonography

2. Another major concern is about the strong conclusion and general impression given by the authors throughout the manuscript on the usefulness and accuracy of AI, without mentioning potential limitations of the current AI techniques. In my opinion the general message should be milder, these algorithms are promising but we need multi-center studies with a standardized workflow and strong external validation to test and improve generalizability and reproducibility. Thus, a paragraph discussing the limitations of AI in liver diseases is suggested.

Response: Thank you very much for your valuable comment. We have added "limitations of AI technology" as a following new section.

5. LIMITATIONS OF AI TECHNOLOGY

Although the algorithms mentioned above are promising, AI has several limitations[39]. First, it may not be possible to understand how and why the model is created. Second, AI does not conform to personal preferences and legal responsibility. If the AI makes a wrong decision, who will be held accountable for this result? Moreover, a biased AI could affect the outcome of several patients. Therefore, careful attention should be paid to the interpretation of AI's decision. Third, to avoid the overfitting problem, multicenter studies with high-quality datasets to validate the models are required. Fourth, the protection of privacy and security of data is crucial. The personal medical history should be protected and the hacking or manipulating the model should be strictly avoided.

3. The manuscript also lacks an important section which briefly describes the

methodologies of current AI methods.

Response: Thank you very much for your valuable comment. We have added current AI methodology as a following new section.

2. CURRENT AI METHODOLOGY

AI systems can be roughly divided into four categories: search algorithm, expert system, machine learning, and deep learning. Machine learning generates a mathematical algorithm from the training dataset and utilizes it to predict outcomes or make decisions[14]. Moreover, machine learning is divided into supervised and unsupervised learning. In a supervised learning model, the algorithm learns from a labeled dataset (individual parameters and outcomes). Conversely, deep learning is based on the neural network structure inspired by the human brain. There are different types of neural networks in deep learning, and representative types are artificial neural network (ANN), convolutional neural network (CNN), and recurrent neural network (RNN).

ANN is a computational analysis tool inspired by the biological nervous system[15]. It consists of three layers: input, hidden, and output. Each layer comprises several "neurons," and the hidden layer processes the input and the output layer produces the result. Through an appropriate training process, the weights among the neural connections are adjusted to optimize the result.

CNN is an image-based machine learning method, which is directly inspired by the visual cortex of the brain[16]. A basic CNN consists of convolution layers, non-linear layers, and pooling layers. CNNs are currently one of the most successful deep learning models because of their unique ability to process spatial information[17].

RNN is a type of neural network with feedback connections[18][19]. It exhibits great performance in labeling and predicting sequential data. A prominent example of sequential data is natural language. RNN maintains the history of input data within the network, and the output is produced from the past input. In the following sections, we discuss related studies from the literature. The content is summarized in Table 1.

Minor comments: 1. Introduction, third paragraph: the authors gave a very detailed and comprehensive description of NAFLD. However, NAFLD could not account for most diffuse liver diseases. It might be reasonable to shorten contents on NAFLD and give a line or two describing liver fibrosis.

Response: Thank you very much for your valuable comment. We have shorten contents on NAFLD and added a description about fibrosis as follows.

Chronic liver disease causes liver fibrosis and progresses through mild fibrosis to cirrhosis. Liver fibrosis is a well-known risk factor for hepatic decompensation and HCC development[12][13].

2. The authors are suggested to mention the specific imaging modalities used in all cited studies.

Response: Thank you very much for your comment. We have added imaging modality information.

3. Page 8, second paragraph: the study conducted by Sato et al. might better fit in the "diagnosis" (part 2) instead of the "risk assessment" (part 3) section.

Response: Thank you very much for your comment. We moved the study to diagnosis section.

We believe the paper may interest your readers in particular because the paper focuses on recent advances in artificial intelligence in hepatology field.

Once again, thank you very much for your comments and suggestions.
We look forward to hearing from you soon.

Sincerely yours,

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Reviewer's code: 03727233

SPECIFIC COMMENTS TO AUTHORS

If possible, I would very much like to read a section dedicated to successful applications of AI technologies in other specialties and how hepatologists can learn from them.

Response to Comment of Reviewer's code: 03727233:

Thank you for your valuable comments.

Although we did not add a new section, we added new references [40]-[50] and accordingly revised our manuscript as follows.

In CONCLUSION section, page 10, lines 16-22,

…The application of artificial intelligence in medical imaging has a good prospect and value. It has been reported that successful applications of AI technologies in endoscopic images for esophageal cancer[40], gastric cancer[41-43], small intestinal cancer[40], colorectal cancer[44,45], analysis of computed tomography for pancreatic cancer[46,47] and others[48-50]. Hepatologists should learn from other area.

AI will also be an essential element in the management of….

Reviewer's code: 03648840

SPECIFIC COMMENTS TO AUTHORS

I had a look through the manuscript. While the subject is very interesting, I could not find any specific methodology for conducting this minireview. As the methods section is quite important for any type of study, I suggest the authors to revise the whole manuscript by considering an appropriate methodology for writing a review paper and reporting the findings.

Response to Comment of Reviewer's code: 03648840:

Thank you for your valuable comments.

According to your suggestions, we revised our manuscript as follows.

In Abstract section, page 2, lines 5-6,

…In this review, we searched for the articles in PubMed and summarize recent developments of AI concerning hepatology…

In Introduction section, page 5, lines 6-8,

…and discuss their clinical implications. In this review, we searched for the literatures in PubMed and summarize recent developments of AI concerning hepatology….

Reviewer's code: 03009411

SPECIFIC COMMENTS TO AUTHORS

The application of artificial intelligence in medical imaging has a good prospect and value. The authors summarize recent developments of AI concerning hepatology while focusing on the diagnosis and risk assessment of liver disease in this review. After modification, the article comprehensively expounds the application value and limitations of AI technology in the diagnosis of liver diseases.

Response to Comment of Reviewer's code: 03009411:

Thank you for your encouraging comments.