Dear editor and reviewers:

Thank you very much for reviewing our manuscript entitled "Radiomics in hepatocellular carcinoma: a state-of-the-art review" (ID: 64706). Those comments are exceptionally inspiring and constructive for our work, as well as of great guiding significance to our further research. We have studied all comments carefully and have made correction which we hope meet with approval. Below, I will detail how we revised our manuscript in order to address each of the comment in the original decision letter.

Response to editor:

Many thanks for your professional advices and giving us the precious opportunity of revision. We have followed the helpful comments and revised the paper carefully. The major changes are explained as below.

1. The Figure 2 has been enhanced to be more comprehensive and intuitive.
2. The Table 1 has been condensed to be more representative and organized.
3. New references have been added appropriately in the related part of the manuscript.
4. Some grammatical errors have been revised, and the manuscript has been rechecked.

We would like to express our most sincere gratitude for all the warm words and the constructive comments. They are extremely helpful for our work. We have made point-to-point revisions according to these comments. We hope the above responses can address your questions properly. If you have any further questions, please do not hesitate to contact us.

Response to comments of Reviewer # 1

I am very grateful to your meaningful and professional comments for the manuscript. According with your comments, we have revised the relevant part in manuscript. All the questions were answered below:

Comment-1

The authors extensively reviewed the topic of "radiomics in hepatocellular carcinoma", and provides new insight for the future management of HCC in the radiomic perspective. thus, it will be of interest to the readership of our journal.

Author's response: Thank you so much for your professional comments and profound insights. We would like to express our most sincere gratitude for all the warm words and the constructive comments. They are extremely helpful for our work, and greatly encourage us. Express our sincere thanks to you again.

If you have any further questions, please do not hesitate to contact us.

Response to comments of Reviewer # 2

I am very grateful to your meaningful and professional comments for the manuscript. According with your comments, we have revised the relevant part in manuscript. All the questions were answered below:

Comment-1

Some of the areas of the manuscript have grammatical errors which need corrections. For e.g., histopathological is written as histopathogical, diagnosis is written as dignosiss etc. These need to be worked on.

Author's response: Thank you so much for the careful check of grammatical errors in this manuscript. We have revised the grammatical errors and the manuscript has been rechecked. Thank you again for your careful scrutiny.

Comment-2

Role of deep learning in the treatment of GI cancers needs a mention (e.g. PMID: 33076511, PMID: 33644756).

Author's response: Thank you so much for your professional comments. We have read the studies that focus on artificial intelligence (AI) in GI cancers you mentioned above and cited them appropriately in the related

part of the manuscript (reference 11 and 12). Thank you again for your kind recommendation.

Comment-3

Figure 2 is not clear. This needs to be enhanced. Please provide a flowsheet of the topics of discussion (for the deep learning and radiomics)

Author's response: Thank you so much for your professional comments and profound insights. The flowsheet of the topics of discussion for radiomics and deep learning has been provided. Besides, a set of illustrations has been added to show the clinical application scenario intuitively. The Figure 2 has been enhanced and is presented below. Express our sincere thanks to you for helping to make the figure comprehensive again.

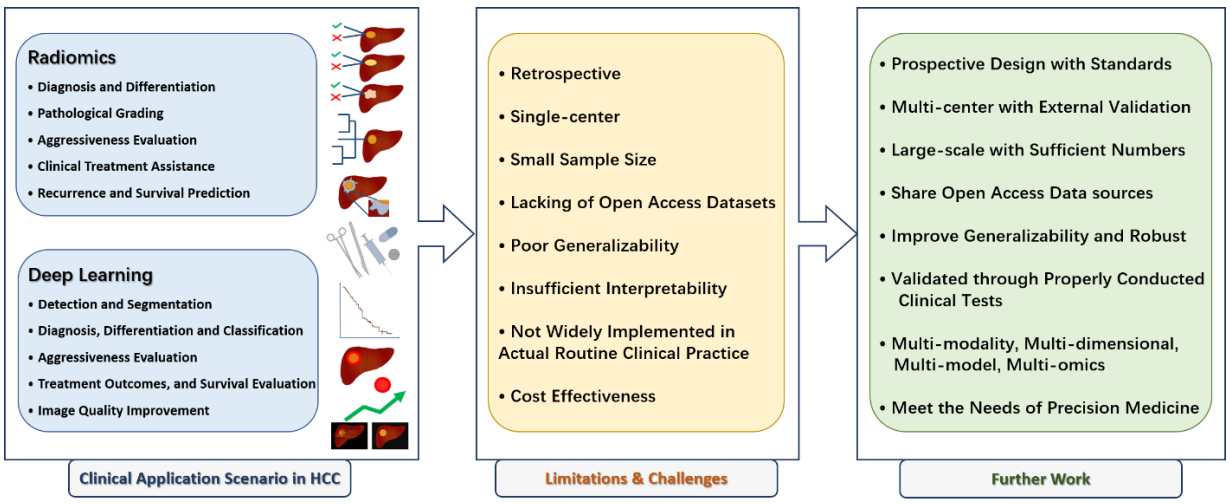

Figure 2. The summary of the clinical application scenario, limitations, challenges and further

work of state-of-the-art radiomics and deep learning in HCC.

Comment-4

Table 1 needs to be condensed.

Author's response: Thank you so much for your professional advice for helping to make the table organized and clean. We feel sorry to ignore such detail as which may cause mess to the manuscript. After careful reading and consideration, we have removed some studies with similar tasks or using in-house developed software, and retained the latest and the most representative studies for each clinical application scenario. In addition, the expression of content in the table is refined. The Table 1 has been condensed as below. Thank you so much sincerely again.

Table 1. Some representative studies of radiomics in HCC.

References	Application Task	Study Design	Imaging Modality	Radiomics Features	Algorithm	Sample Size	Training Set	Test/Validation Set	Performance
Liu et al. 2021	Differentiation of cHCC-CC from HCC and CC	Retrospective, single-center	CT, MRI	1419	SVM	85 patients with HCC (37), cHCC-CC (24) and CC (24)	85	N/A	Excellent performance for differentiation of HCC from non-HCC (AUC=0.79-0.81 in MRI, AUC=0.71-0.81 in CT).
Nie et al. 2020	Differentiation of HCA from HCC	Retrospective, two-institutes	CT	3768	mRMR, LASSO	131 patients with HCC (85) and HCA (46)	93	38	Favorable performance (AUC=0.96 in training set, AUC=0.94 in test set).
Wu et al. 2019	Pathological grade of HCC	Retrospective, single-center	MRI	656	LASSO	170 patients with HCCs	125	45	Radiomics signature model outperformed the clinical factors-based model; the combined model achieved the best performance (AUC=0.80).
Mao et al. 2020	Pathological grade of HCC	Retrospective, single-center	CT	3376	RFE, XGBoost	297 patients with HCCs	237	60	The combining radiomics signatures with clinical factors significantly achieved the best performance (AUC=0.8014).
Xu et al. 2019	Preoperative prediction of MVI in HCC	Retrospective, single-center	CT	7260	Ref-SVM, Multivariable logistic regression	495 patients with HCC	300	145 (test); 50 (validation)	Good performance (AUC=0.909 in the training/validation set, AUC=0.889 in the test set).

Table 1. (Continue) Some representative studies of radiomics in HCC.

References	Application Task	Study Design	Imaging Modality	Radiomics Features	Algorithm	Sample Size	Training Set	Test/Validation Set	Performance
Chong et al. 2021	Preoperative prediction of MVI in HCC	Retrospective, single-center	MRI	854	LASSO, RF, logistic regression	356 patients with HCCs ≤5 cm	250	106	AUC=0.920 using RF; AUC=0.879 using logistic regression (in validation set).
Fu et al. 2019	Assistant in optimal treatment choices of HCC between LR and TACE	Retrospective, multi-center (5 institutions)	MRI	708	LASSO, Akaike information criterion	520 patients with HCC	302	218	Good discrimination and calibrations for 3-year PFS (AUC=0.80 in training set, AUC=0.75 in validation set); Threshold≤-5.00: suggesting LR, threshold >-5.00: suggesting TACE.
Sun et al. 2020	Predicting the outcome of TACE for unresectable HCC	Retrospective, single-center	MRI	3376	LASSO, multivariable logistic regression	84 patients with BCLC B stage HCC	67	17	The combining radiomics signatures with clinical factors significantly achieved the best performance (AUC=0.8014).
Ji et al. 2020	Predicting early recurrence after LR	Retrospective, multi-center (3 institutions)	CT	846	LASSO-Cox regression	295 patients with HCC	177 (Institution 1)	118 (Institution 2 and 3, external validation)	Better prognostic ability (C-index=0.77, P<0.05), lower prediction error (integrated Brier score=0.14), and better clinical usefulness than rival models and staging systems.

Table 1. (Continue) Some representative studies of radiomics in HCC.

References	Application Task	Study Design	Imaging Modality	Radiomics Features	Algorithm	Sample Size	Training Set	Test/Validation Set	Performance
Zhao et al. 2020	Predicting early recurrence after LR	Retrospective, single-center	MRI	1146	LASSO, stepwise and multivariable logistic regression	113 patients with HCC	78	35	The combined nomogram integrating the rad-score and clinicopathologic-radiologic risk factors showed better discrimination and clinical utility (AUC=0.873).
Wang et al. 2020	Predicting 5-year survival after LR	Retrospective, multi-center (2 institutions)	MRI	3144	RF, multivariate logistic regression	201 patients with HCC	160	51 (five-fold cross-validation)	The combined model incorporating the radiomics signature and clinical risk factors obtained good calibration and satisfactory discrimination (AUC=0.9804 in training set, AUC=0.7578 in validation set).
Song et al. 2020	Predicting RFS after TACE	Retrospective, single-center	MRI	396	LASSO-Cox regression, multivariate Cox regression	184 patients with HCC	110	74	The combined model using the radiomics signature with the clinical-radiological risk factors showed the best performance (C-index=0.802).

Note: cHCC-CC: combined hepatocellular cholangiocarcinoma; HCC: hepatocellular carcinoma; CC: cholangiocarcinoma; CT: computed tomography; MRI: magnetic resonance imaging; GLCM: gray-level co-occurrence matrix; SVM: support vector machine; AUC: area under the receiver operating characteristic curve; HCA: hepatic adenoma; mRMR: maximal relevance and minimum redundancy; LASSO: least absolute shrinkage and the selection operator; RFE: recursive feature elimination; XGBoost: eXtreme Gradient Boosting; MVI: microvascular invasion; Ref-SVM: recursive feature selection support vector machine; RF: random forest; LR: liver resection; TACE: transarterial chemoembolization; PFS: progression-free survival; BCLC: Barcelona Clinic Liver Cancer; C-index: concordance index; RFS: recurrence free survival.

We would like to express our most sincere gratitude for all the warm words and the constructive comments. They are extremely helpful for our work. We have made point-to-point revisions according to these comments. We hope the above responses can address your questions properly. If you have any further questions, please do not hesitate to contact us.