Peer Review File

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Reviewer A:

I appreciate to have the opportunity to review this manuscript.
This is a very interesting approach for the management of HCC with MVI, however, the lack of the optimal method for the diagnosis of MVI may result in undesirable outcomes.
The authors recommended anatomical resection to ensure a margin distance of more than 1cm. HCC recurrence usually occurs distant to the primary lesion. That may mean that MIV is a surrogate marker of the spread of HCC. Some retrospective studies showed the significance of the superiority of anatomic resection, however, in the case of narrow-margin resection, MVI cannot be evaluated preciously. There may be bias. And anatomic resection does not always promise adequate margins. Therefore, even with an adequate margin, the effect for the improvement of survival may be limited.
I have several questions.

Comment 1: Precision of MVI assessment may be the most important key in the clinical setting for the success of this consensus. In MVI prediction, the authors recommended the EHBH nomogram. The nomogram included HBV DNA level, but not HCV status. Recently, the incidence of HCC with non-alcoholic steatohepatitis has been increasing in the world. Do the authors consider that such etiologies affect the MVI?
Reply 1: Thanks for the reviewer's suggestion. In our country, the majority of HCC is caused by HBV and our method for predicting MVI is based on patients with HBV-HCC. So, the consensus only applies to HCC caused by HBV. We do agree with the reviewer’s opinion that non-alcoholic steatohepatitis and HCV could affect MVI, and we might go deeper into that later in other articles.

Comment 2: The AUC of the EHBH nomogram is about 0.80, therefore, the risk of false negative threatens HCC patients with MVI. What is the rationale of this paper? How do the authors intend for this consensus to improve the clinical outcome in patients with HCC in China?
Reply 2: We thank the reviewer for this critical issue. For now, at least, predicting MVI is an unsolved problem and there are no standards or guidelines for predicting MVI all over the world. Although the EHBH nonagram proposed by our team is not perfect, the literature shows that it has good prediction accuracy and application stability. We recommend diagnostic and therapeutic strategies for MVI in terms of definition, preoperative, intraoperative and postoperative management. We believe that standardized treatment can improve outcomes for HCC patients with MVI. In addition, our consensus also raises urgent clinical questions for MVI research, such as

more accurate prediction methods, and more effective neoadjuvant/adjuvant treatment strategies. If these can be well addressed, it can improve the overall survival of HCC patients in China.

Comment 3: In the first curative treatment, the authors recommended surgical resection or PRFA/PMCT as the first choice for patients with a diameter ≤3 cm who are predicted to be at low risk for MVI. How do the authors predict the MVI? Do they use the EHBH nomogram?
Reply 3: We thank the reviewer for this critical issue. We recommend EHBH nomogram to predict MVI before PRFA/PMCT.

Comment 4: In addition, how do the authors determine the size criteria of HCC (a diameter ≤3 cm)? It seems that 3cm HCC is too large for PRFA/PMCT. Is there any evidence?
Reply 4: We thank the reviewer for this critical issue. Much of the literature[1,2] on PRFA uses the criterion that the tumor diameter is less than or equal to 3cm. Our national liver cancer guidelines[3] also indicated that PMCTPRFA can be applied to HCC with a diameter ≤ 3cm, and adopted by our consensus.

1.Kim TH, Koh YH, Kim BH, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: A randomized phase III trial. J Hepatol. 2021;74(3):603-612.
2.Vogl TJ, Martin SS, Gruber-Rouh T, et al. Comparison of Microwave and Radiofrequency Ablation for the Treatment of Small- and Medium-Sized Hepatocellular Carcinomas in a Prospective Randomized Trial. Rofo. 2024;196(5):482-490.
3. Zhou J, Sun H, Wang Z, et al. Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 Edition). Liver Cancer. 2023;12(5):405-444.

Comment 5: In preoperative neoadjuvant therapy, the authors suggested the clinical efficacy of neoadjuvant TACE decreasing MVI. TACE should affect HCC itself. It may be difficult to distinguish the anticancer effect of TACE between the tumor itself and MVI. MVI affects the prognosis even in patients with HCC ≤3 cm. In addition, it may be difficult to diagnose the presence of MVI in patients with HCC ≤3 cm. Why do the authors recommend the neoadjuvant TACE as the first choice for curative treatment for patients without MVI?
Reply 5: We thank the reviewer for this critical issue. We do agree with the reviewer's opinion that it is not currently recommended to use TACE as neoadjuvant therapy for HCC patients who are predicted to be at high risk for MVI.

Comment 6: In treatment after recurrence, the authors recommended surgery if the time to recurrence is more than 1 year. What is the evidence?
Reply 6: We thank the reviewer for this critical issue. If the time to recurrence is more than 1 year, we consider it a late relapse. According to the "Multidisciplinary Management of Recurrence and Metastasis of Hepatocellular Carcinoma: International Expert Consensus"[1], if the recurrence focus is solitary, there is no portal

vein main trunk cancer thrombus, and if the time to recurrence (TTR) is ≥1 year, surgical resection may be considered.

1. Wen T, Jin C, Facciorusso A, et al; MDT of West China Hospital*. Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus. Hepatobiliary Surg Nutr. 2018;7(5):353-371.

Reviewer B:

I read with great interest this statement paper coming from the Chinese liver surgeons' community about how to manage patients with hepatocellular carcinoma with microvascular invasion. This is a topic of great interest, since the presence of microvascular invasion is the most important oncologic risk factor for such tumors, and few indications are provide in the literature, particularly in the Western countries. The methodology is clear, and the results are well presented. I have few concerns:

Comment 1:1- This expert statement came from a systematic review of the literature. However, I noted that most of the reported experiences are from Eastern countries, particularly from China. Checking on pubmed, I identified other papers that are related to the subject, but they were excluded, e.g.:

- Famularo S, Di Sandro S, Giani A, Lauterio A, Sandini M, De Carlis R, et al. Long-term oncologic results of anatomic vs. parenchyma-sparing resection for hepatocellular carcinoma. A propensity score-matching analysis. Eur J Surg Oncol 2018;44:1580–
- Zhao H, Chen C, Gu S, Yan X, Jia W, Mao L, et al. Anatomical versus non-anatomical resection for solitary hepatocellular carcinoma without macroscopic vascular invasion: A propensity score matching analysis. J Gastroenterol Hepatol 2017;32:870–8.
- Kaibori M, Kon M, Kitawaki T, Kawaura T, Hasegawa K, Kokudo N, et al. Comparison of anatomic and non-anatomic hepatic resection for hepatocellular carcinoma. J Hepatobiliary Pancreat Sci 2017;24:616–26.
- Hidaka M, Eguchi S. Impact of Anatomical Resection for Hepatocellular Carcinoma with Micro-portal Invasion (vp1): A Multi-institutional Study by the Kyushu Study Group of Liver Surgery. HPB 2018;20:S391. doi:https://doi.org/10.1016/j.hpb.2018.06.2692.
- Famularo S, Piardi T, Molfino S, Di Martino M, Ferrari C, Ielpo B, Diago MV, Giani A, Griseri G, Terés LB, Gianotti L, Baiocchi GL, Sommacale D, Romano F. Factors Affecting Local and Intra Hepatic Distant Recurrence After Surgery for Hcc: An Alternative Perspective on Microvascular Invasion and Satellitosis - A Western European Multicentre Study. J Gastrointest Surg. 2021 Jan;25(1):104-111. doi: 10.1007/s11605-019-04503-7. Epub 2020 Jan 21. PMID: 31965441.

Those are only examples. However, I guess the systematic review should be carefully re-evaluated, including all the relevant papers. On the opposite, the reason for exclusion should be clearly stated.

Reply 1: We thank the reviewer for this critical issue. The literature searching stratigies and literature selection process are as follows:

A literature search was done using following electronic databases: MEDLINE via Ovid, Embase.com, Web of Science Core Collection, and Cochrane CENTRAL via Wiley. Full search strategy is ("MVI"[All Fields] OR"microvascular invasion"[All Fields] "microvascular thrombus"[All Fields])And ("hepatocellular carcinoma"[All Fields] OR "hepatocarcinoma"[All Fields] OR "HCC"[All Fields])

Inclusion and exclusion criteria

Studies that met the following eligibility criteria were included: (1) they involved human patients diagnosed with HCC and MVI; (2) The content of the article should be related to the definition, diagnosis, prediction or treatment of MVI.

Studies that met the following exclusion criteria were removed during the study selection process: (1) they involved human patients without an HCC diagnosis; (2) they were reviews or similar articles; (3) their full-text was not available in English.

Study selection

Two authors independently performed the study selection process, and discrepancies were resolved by a third author based on a consensus. Duplicates among the original articles identified in the initial search of all databases were removed. Next, the articles were subjected to an initial screening by title and abstract based on exclusion criteria. Then, the remaining articles' full texts were screened against the eligibility criteria, and those meeting the inclusion criteria were identified. Then, we evaluated the including studies including the source, timeliness, study design, data quality and reliability of the results. Last, if there are too many literatures in one aspect, we will choose representative literatures to cite at last and if there is controversial in certain area, we will cite the results of high-quality meta-analysis if available or consider expert's opinions.

The literature you mentioned is about the importance of MVI and the therapeutic effect of surgical methods on MVI, and we have already discussed these aspects in the consensus (Please see 2.1.1-Paragraph 2; 2.3.2.2-Paragraph 1).

Comment 2: While the purpose of the paper is clinical, I would reccomend to add a session about the pathophysiology of microvascular invasion. In the last 30 years, many studies and speculations were made on this. For example, Sakon, Kobayashi and Nagano proposed that microvascular invasion could be a sort of indirect sign of the presence of circulating tumor cells, which could exaplain the high risk of recurrence even in case of radical resection.

Reply 2: We thank for the reviewer's kind reminding and we do agree with the reviewer's opinion. The pathophysiology of MVI has been mentioned in another Guideline in China called "Guidelines for the Pathological Diagnosis of Primary Liver Cancer[1]". So, our consensus focuses on the clinical diagnosis and treatment of MVI.

1. Cong WM, Bu H, Chen J, Dong H, Zhu YY, Feng LH, Chen J; Guideline Committee. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update. World J Gastroenterol. 2016 Nov 14;22(42):9279-9287.

Comment 3:- In the last few years, some artificial intelligence and machine learning algorithms have been proposed to detect microvascular invasion before treatments. I think these new instruments should be better considered and reported.
Reply 3: We thank for the reviewer's kind reminding. In the section of MVI prediction in our consensus, we have mentioned the effects of AI or deep-learning methods (Please see 2.2.2-Paragraph 2). Although these new technologies are very promising, but they have yet to be applied or proven on a large scale. So, we do not currently recommend such methods for predicting MVI, but we encourage further research.

Comment 4:- Regarding the surgical approach for these patients: the authors recommend anatomic resection rather than non-anatomic, particularly for small HCC. However, the literature is full of papers describing that in case of MVi, anatomic resection didn't provide the same success rate as in case of no MVi. There are also few meta-analyses on this.
Reply 4: We thank the reviewer for this critical issue. It is indeed controversial at present whether MVI patients would benefit from anatomic resection. The recommendation is based on the results of meta-analysis and experts opinion. And if there is more evidence of a higher level in the future, we may change our recommendation.

Comment 5:- Adjuvant strategies for patients with MVI have been reported, but no prospective or randomized trials are available. Most of the data come from single centre single country (China) retrospective studies, which are clearly biased by definition. I think these should be clearly stated by the authors, because that data cannot be considered as a strong evidence. I think that also the level of evidence should be lowered.
Reply 5: We thank the reviewer for this critical issue. We have revised down the strength of the recommendation of adjuvant radiotherapy, HAIC, lenvatinib and sorafenib. (Please see Recommendation 7)

Reviewer C:

The Chinese Expert Consensus on HCC microvascular invasion is well organized. Authors evaluated it using the GRADE system, but it gave evidence B even though there were no prospective studies. Please evaluate the data again and apply the GRADE system.
Comment 1. The 5-year recurrence after HCC hepatectomy was 70%, but it cited too old papers. Recently, it has been lowered to around 50% due to accurate preoperative evaluation and use of antiviral agents.
Reply 1: We thank for the reviewer's kind reminding. We have modified this data and cited new references[1]. (Please see Reference 2)

1.Huang G, Lau WY, Wang ZG, et al. Antiviral therapy improves postoperative survival in patients with hepatocellular carcinoma: a randomized controlled trial. Ann Surg. 2015 Jan;261(1):56-66.

Comment 2. Please properly apply the GRADE system to evaluate the recommendation for the key question. If there is no prospective study at all, a large-scale retrospective study is evidence C.
Reply 2: We thank the reviewer for this critical issue. We have re-evaluated the evidence and made changes to the level of evidence as requested. (Please see Recommendation 1-8)

Comment 3. Many MRI-related papers predicting microvascular invasion before HCC surgery have been published recently. Please organize it using more imaging papers.
Reply 3: We thank the reviewer for this critical issue. We do agree with the reviewer's opinion that MRI has its own advantages and characteristics in predicting MVI. In our manuscript, we also cited a lot of literature on the use of MRI to predict MVI(Please see reference 22,24,65,69,78,92,110,140,143-146,148,153-162), but at present the accuracy of MRI alone in predicting MVI varies greatly in different studies and needs to be improved in the future.

Comment 3. What is EHBH?
Reply 4: We thank the reviewer for this critical issue. EHBH is the abbreviation of Eastern Hepatobiliary Surgery Hospital.

Comment 5. Do you really think that Recommendation 3 is evidence B, strength strong?
Reply 5: We thank the reviewer for this critical issue. We have adjusted the evidence level and recommendation strength of Recommendation 3. (Please see Recommendation 3)

Comment 6. I agree with Recommendation 4, but there is no difference in OS in 3 RCT studies. Please recommend with sufficient evidence. Evidence C, strength weak is C2. C2 cannot be recommended.
Reply 6: We thank for the reviewer's kind reminding. There is no prospective studies comparing the efficacy of surgery and PMCT in HCC patients who are predicted to be at high risk for MVI. In our manuscript, we cited well-designed retrospective studies that for patients with small HCC (diameter ⩽3 cm) predicted preoperatively to be at high risk for MVI, liver resection, especially anatomical liver resection, has significantly better 5-year DFS and OS than percutaneous radiofrequency ablation (PRFA)/percutaneous microwave coagulation therapy (PMCT); for low-risk patients, the efficacy of liver resection is similar to that of PRFA/PMCT.[16,26,189,191]

Comment 7. You mentioned antiviral therapy, but only mentioned HBV. Please add a part about HCV.
Reply 7: We thank for the reviewer's kind reminding. We have added relevant content to the recommendation.

Comment 8. Please add more studies on adjuvant therapy with immune-check point inhibitors. Please delete Sintilimab.
Reply 8: We thank for the reviewer's kind reminding. Although many clinical trials have been conducted at present on adjuvant therapy with immune-check point inhibitors, positive results have been obtained only in T+A and Sintilimab at present. If there are more positive results in the future, we will update our consensus

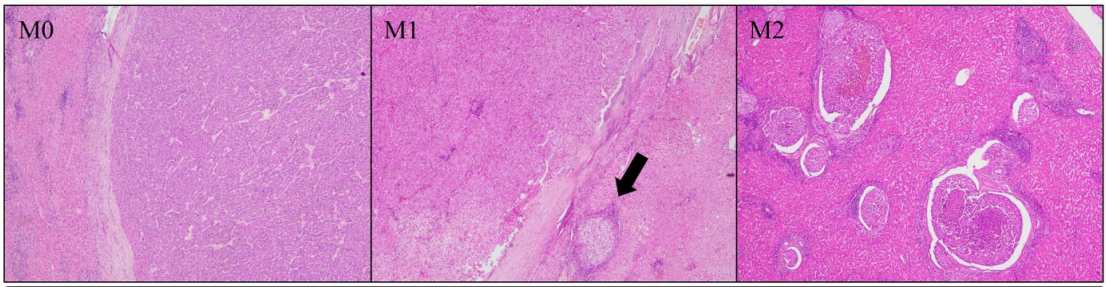
Comment 9. In Recommendation 8, the treatment direction should be determined based on tumor location, liver function, and remnant liver volume. Please add more parts to these.
Reply 9: We thank the reviewer for this critical issue. Treatment after recurrence has always been a difficulty in the treatment of HCC, and there is also a great controversy. We have previously introduced another consensus[1] which has systematically described the management of such patients.
1.Wen T, Jin C, Facciorusso A, et al; MDT of West China Hospital*. Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus. Hepatobiliary Surg Nutr. 2018;7(5):353-371.

Reviewer D:

The paper provides comprehensive summary for Chinese expert consensus for managing HCC with MVI, developed through systematic literature reviews and the Delphi method. It covers the incidence, diagnosis, and classification of MVI, recommending specific pathological grading standards and sampling methods. The paper emphasizes the importance of preoperative prediction of MVI using clinical features and imaging techniques, with the EHBH nomogram being highly recommended. Treatment strategies include surgical resection, postoperative adjuvant therapies like antiviral therapy, TACE, radiotherapy, HAIC, and targeted therapies. The guidelines advocate for a multidisciplinary approach to optimize patient outcomes and highlight the need for ongoing research and updates.

This paper is carefully reported by the experienced group, but raises several minor concerns:

Comment 1: The diagnosis and classification of MVIs and the criteria for classification are well explained, but it can be helpful to have visual aids. It is recommended to supplement the text with diagrams or images showing examples of MVI classifications.
Reply 1: We thank the reviewer for this critical issue. We refer to the previously published guidelines for the pathological diagnosis of liver cancer[1], which have a more detailed description.



MVI grading	Criteria
M0	No MVI
M1	1-5 MVIs and at ≤1 cm away from adjacent liver tissue
M2	>5 MVIs, or any MVI at >1 cm away from adjacent liver tissue

1. Cong WM, Bu H, Chen J, Dong H, Zhu YY, Feng LH, Chen J; Guideline Committee. Practice guidelines for the pathological diagnosis of primary liver cancer: 2015 update. World J Gastroenterol. 2016 Nov 14;22(42):9279-9287.

Comment 2: It is recommended that the Expert Consensus in this paper are summarized in a single table. This paper is very comprehensive and detailed, but there are too descriptive, which makes it difficult for the reader to easily grasp the conclusions.

Reply 2: We thank the reviewer for this critical issue. All the 8 recommendations are listed in Supplementary Table 1.

Supplementary Table 1 Consensus on statements in third Delphi survey

No.	Statement	Strength of recommendation (n = 76); No. (%)					
		Recommend			Do not Recommend		
		Strong	Weak	GPS*	Strong	Weak	GPS*
1	It is recommended to use the MVI pathological grading criteria as outlined in the "Guidelines for Pathological Diagnosis of Primary Liver Cancer": M0: No MVI found; M1: ≤5 MVI and occurring in the peri-tumoral liver tissue area (≤1 cm); M2: >5 MVI or MVI occurring in the distant peri-tumoral liver	76(100)	0	0			

	tissue area (>1 cm)						
2	It is recommended to use the "7-point method" for sampling liver cancer specimens (Evidence level: B; Recommendation level: Strong), and IDS may be used where feasible	76(100)	0	0			
3	It is recommended that hepatocellular carcinoma patients undergo preoperative MVI prediction, and using the EHBH nomogram for predicting MVI is highly recommended	61(80.2)	5(6.6)	10(13.2)			
4	For patients with resectable HCC, surgical resection is recommended as the first choice; for patients with a diameter ≤3 cm who are predicted to be at low risk for MVI, either surgery or PRFA/PMCT can be chosen.	70(92.1)	4(5.3)	2(2.6)			
5	It is not currently recommended to use TACE or radiotherapy alone as neoadjuvant therapy for HCC patients who are				0	71(93.4)	5(6.6)

	predicted to be at high risk for MVI;						
	to reduce postoperative recurrence rates, it is encouraged to conduct clinical trials of neoadjuvant therapy in these patients.	0	0	76(100)			
6	It is recommended to perform anatomic liver resection or ensure a margin distance ≥1 cm for HCC patients predicted to be at high risk for MVI;	76(100)	0	0			
	if anatomic liver resection is not possible or a margin distance ≥1 cm cannot be ensured, intraoperative radiotherapy may be used in equipped centers.	0	66(86.8)	10(13.2)			
7	Postoperative antiviral therapy is recommended for hepatitis B-related HCC patients,	76(100)	0	0			
	and for patients diagnosed with MVI postoperatively, at least one of the following adjuvant treatments are	76(100)	0	0			

	recommended: T+A,						
	Sintilimab	76(100)	0	0			
	TACE	76(100)	0	0			
	radiotherapy	76(100)	0	0			
	HAIC	76(100)	0	0			
	lenvatinib or sorafenib	0	62(81.6)	14(18.4)			
8	It is recommended to decide on the prevention and treatment plan for MVI-positive HCC recurrence after MDT discussion: if there are ⩽3 recurrences and the maximum diameter is ⩽3 cm, PRFA/PMCT is preferred; if the recurrence focus is solitary, there is no portal vein main trunk cancer thrombus, and TTR ≥1 year, surgical resection may be considered; for unresectable recurrence foci or early recurrence (TTR ≤1 year) and PMCT/PRFA cannot be performed, TACE is recommended.	0	66(86.8)	10(13.2)			

*GPS: good practice statement.

Comment 3: “Systematic literature review” should include literature searching stratigies and flow chart (PRISMA) including literature selection process. (by PRISMA 2020 guideline). The authors are required to provide searching information for 251 selected articles.

Reply 3: We thank the reviewer for this critical issue. The literature searching stratigies and literature selection process are as follows:

A literature search was done using following electronic databases: MEDLINE via Ovid, Embase.com, Web of Science Core Collection, and Cochrane CENTRAL via Wiley. Full search strategy is (“MVI”[All Fields] OR“microvascular invasion”[All Fields] “microvascular thrombus”[All Fields])And (“hepatocellular carcinoma”[All Fields] OR “hepatocarcinoma”[All Fields] OR “HCC”[All Fields])

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Studies that met the following eligibility criteria were included: (1) they involved human patients diagnosed with HCC and MVI; (2) The content of the article should be related to the definition, diagnosis, prediction or treatment of MVI.

Studies that met the following exclusion criteria were removed during the study selection process: (1) they involved human patients without an HCC diagnosis; (2) they were reviews or similar articles; (3) their full-text was not available in English.

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Two authors independently performed the study selection process, and discrepancies were resolved by a third author based on a consensus. Duplicates among the original articles identified in the initial search of all databases were removed. Next, the articles were subjected to an initial screening by title and abstract based on exclusion criteria. Then, the remaining articles’ full texts were screened against the eligibility criteria, and those meeting the inclusion criteria were identified. Then, we evaluated the including studies including the source, timeliness, study design, data quality and reliability of the results. Last, if there are too many literatures in one aspect, we will choose representative literatures to cite at last and if there is controversial in certain area, we will cite the results of high-quality meta-analysis if available or consider expert’s opinions.

Comment 4: In the section of comprehensive prediction method (2.3.3), the EHBH nomogram was recommended. The EHBH nomogram considered seven factors (tumor diameter, number of tumors, tumor capsule, AFP levels, 287 PLT count, HBV DNA levels, and typical imaging enhancement features). Although external validation has been demonstrated and the AUC level is reliable, important factors are missing, including preoperative anticancer treatment including various locoregional treatment, which should be mentioned as limitations.

Reply 4: We thank the reviewer for this critical issue. We have listed it in our manuscript as limitations (Please see Foresight, Paragraph 1-Line 4-6).