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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 82030

Title: Real-world 10-year retrospective study of the guidelines for diagnosis and treatment of primary liver cancer in China

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05130811
Position: Peer Reviewer
Academic degree: MD
Professional title: Chief Doctor
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2022-12-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-12-06 01:59

Reviewer performed review: 2022-12-07 07:26

Review time: 1 Day and 5 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

COMMENTS TO AUTHORS: Manuscript NO: 82030 Title: Real-world 10-year retrospective study of Chinese guidelines for the diagnosis and treatment of hepatocellular carcinoma REVIEW: This report is a large, retrospective study evaluating the Chinese HCC Guidelines (CNLC), conducted at a representative single center in China. The Chinese HCC guideline (CNLC) are still relatively new, and this study evaluating it may be useful. The authors attempted to clarify the reality of HCC practice in China by presenting a large body of data from a representative Chinese institution. Practicing HCC according to the CNLC showed the possibility of prolonging recurrence-free survival after hepatic resection, although it could not be shown to prolong overall HCC survival compared to noncompliant cases. The study also demonstrated the utility of screening to detect early-stage HCC and suggested independent factors that may influence overall survival. However, this was a single-center retrospective study, so the authors concluded that future prospective studies are needed to confirm the results. However, there are several items that need to be improved. There is no definition of primary outcome and hence overinterpretation of the results is scattered (e.g. the superiority of progressive free survival in LR patients = overstating the sub-analysis). Also, some items that should be included in the methods section are not mentioned. In addition, matters not indicated by data in the 'Results' must not be stated in the 'Discussion' as the conclusion of the study. I think setting a primary outcome would make for a stylish paper. <Major> Abstract 1. How is the remaining 34% diagnosed ? (on page 2, line 30-31) 2. The data that screening reduces the risk of death was presented with COX model in the result of abstract, but data on the

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'effectiveness in HCC high risk' was not provided in the result of abstract. (on page 4, line 5) Core tip 3. "The findings suggest that the guidelines are well-consistent with long-term clinical practice in China" (on page 4 line13-14): Delete this sentence as the research design is not representative of the whole of China. Alternatively, specify that it is a single-centre study, e.g. "70% of HCC treatment at the First Affiliated Hospital of Zhengzhou University was performed according to guidelines". Introduction 4. " Patients from all over China often visit this hospital for continuous treatment after the diagnosis of HCC; therefore, we believe that the targeted participants in this study are representative of the general population of China." (on page 5 line 29-31): Single-center university hospitals are likely to be biased towards patients. For example, there will be bias for economic reasons and location, and patients with too light or too many underlying diseases and poor patient backgrounds may be excluded. Furthermore, HBV accounted for the majority of patients in the study and alcohol, NASH and HCV were less prevalent, which may not be an accurate reflection of HCC as a whole. Consider deleting or changing this sentence. Method 5. Primary and secondary outcomes should be clearly stated. 6. Study Design and Target Population (on page 6 line14): Please provide a definition of a definitive diagnosis of HCC and ICC. If diagnostic criteria for HCC and ICC is inaccurate, a significant number of HCCs may be removed as ICCs, or ICCs may be included as HCCs. 7."(5) Survival of the patients: Patients with no clinical outcome in the hospital were followed up." (on page 7 line 26-27): Describe follow-up method. 8. "Data analysis" (on page 7 line 30): Please describe the criteria for the choice of treatment method. If there are no criteria and the decision is made by the attending physician, please state that. 9. Screening analysis (on page 8 line 21): What is the definition of screening methods? Please describe it on Method section. Result 10. General characteristics of patients with HCC (on page 9 line 27): Please state patient's smoking and drinking history. The drinking history is particularly

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important. If this data is not available, it should be stated in limitation. 11. We collected data of 1128 clinical outcomes on page 12 line 17-18: The characteristics of those who were able to be followed should be described and a table should be created. As survival is an important outcome, the characteristics of the population for which it was analysed are also important. For example, PS, alcohol consumption, drinking, Child-pugh, stage, etc. 12."The results were verified by the multivariate analysis showing that AFP > 400 ng/ml (HR = 1.612, 95% CI = 1.256-2.070), Child-Pugh B (HR = 1.771, 95% CI = 1.243-2.524), middle stage (HR = 2.556, 95% CI = 2.032-3.215), and late stage (HR = 3.312, 95% CI = 2.113-5.192) were independent factors affecting postoperative recurrence of HCC. (Table 6)." (from page 13 line 32 to page 14 line 5): AFP and stage can be understood as an risk of postoperative recurrence in patients undergoing LR as tumor vigour, but what does it mean that Child-Pugh B is a risk of postoperative recurrence in patients undergoing LR ? Describe that in discussion section.

Discussion 13. "The guidelines recommend that imaging and pathological diagnosis can be used in the HCC diagnosis. In this study, the diagnosis methods of CNLC Ⅰa, Ⅰb, and Ⅱa stage patients were mainly pathology-based, with 70.3%, 60.4%, and 63.3% frequencies, respectively. The diagnosis methods of CNLC Ⅱb, Ⅲa, Ⅲb, and Ⅳ stage patients were mainly based on imaging examination combined with clinical features, with 67.3%, 58.6%, 69.3%, and 81.9% frequencies, respectively." (from page 14 line 30 to page 5 line 4): This sentence only repeated the results and does not describe the considerations. Please describe why approximately 30-40% of people were not diagnosed according to the guidelines. 14. "In this study, 304 patients were screened prior to the diagnosis of HCC." (on page 15 line 11): If the usefulness of screening is used in the conclusion, please describe in the Limitation the selection bias and confounding bias of cases undergoing screening. Items other than those identified as HCC high-risk in CNLC, such as wealth or urban area, may be factors that make people

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more likely to be screened. 15. "and improving the quality of life." (on page 15 line 26): Data on quality of life are not presented in the result section, so it is not possible to conclude this way. 16. "while some patients received more active treatment, which made these patients obtain certain survival advantages." (on page 18 line 25-27): Can you present data showing this in the Result section? 17. "which indicated that the results of this study were well representative of the HCC patient population." (on page 19 line 9-10): Although the present study is large, it is single-center, and retrospective study. So it difficult to conclude that it is representative of HCC as a whole. 18. Limitations on page 19 line 20: Is the exclusion of ICCs certain in this study? If not certain, the statement should be listed under limitation. Conclusion 19. "which indicates that the guidelines have a good effect on the treatment of patients with HCC in China." (on page 20 line 7-8): This sentence is unnecessary. "Despite the limited survival benefit for patients receiving the treatment recommended by the guidelines, patients who underwent LR in accordance with the guidelines had a significant survival advantage." is enough as conclusion. Redundant statements should be avoided. 20. "limited survival benefit" (on page 20 line 9): Survival benefits in the whole patients of HCC were not proven in the result section. Only patients who underwent LR in accordance with the guidelines had a significant progressive free survival advantage. Please consider changing "limited benefit in HCC patients as a whole" to "No benefit was demonstrated in HCC patients as a whole". The data described in the Result section should refrain from being overstated. I think that the lack of definition of primary outcome and secondary outcomes led to an over-interpretation of results. <Minor> Abstract 1. This sentence should be stated in the CONCLUSION. (from page 3 line 31 to page 4 line 3) Introduction 2. CNLC on page 5 line 10 is first appearance in main text. Spelling out. Method 3. "(4) The treatment information collected included" (on page 7 line23): There appears to be no mention of TACE or RFA. Please add it. Result 4.

"significantly elevated AFP levels (> 400 ng/ml)" (on page 10 line 7): Please describe the rationale for the "significantly elevated AFP levels defined as > 400 ng/ml" in Method section. 5. "clinical features" (on page 10 line 21): Please describe in detail.

Discussion 6. "Staging of liver cancer is very important for the selection of treatment options and the evaluation of prognosis. There are many staging systems, such as the BCLC, EASL, APASL, JSH, HKLC[3-7]. Among them, the most widely used staging is the BCLC. CNLC staging was established according to the patients' PS, liver tumor, and liver function by the National Health Commission in combination with China's specific national conditions and practice accumulation, including CNLC Ⅰa, Ⅰb, Ⅱa, Ⅱb, Ⅲa, Ⅲb, and Ⅳ stages[9-10]." (on page 14 line 8-15): This statement is duplicated in the intro. Please summarize in the intro. 7. "The method of CNLC staging was first published in 2017[9]. Due to the short period since the publication, there are currently no real-world studies on the diagnosis and treatment of patients based on CNLC staging, and only a few studies have been performed on specific treatment methods in different CNLC staging[11-13]." (on page 14 line 16-20): Moving to the intro would help readers understand the strengths of the paper earlier. 8. "As China is the country with the largest number of liver cancer cases in the world," (on page 14 line 20-21): A supporting citation is needed. 9. "The strength of this study is that we collected data of a large sample of patients with HCC from the real world and conducted CNLC staging for the patients to evaluate the compliance between CNLC staging and real clinical diagnosis and treatment in China. We also performed a systematic review and an analysis of the diagnosis and treatment choices of Chinese patients with HCC in the real world." (on page 14 line 24-29): This should also be mentioned in the intro. 10. "The guidelines have identified high-risk groups for HCC: people with HBV and/or HCV infection, excessive alcohol consumption, non-alcoholic steatohepatitis, cirrhosis caused by other causes, and a family history of

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liver cancer, especially men older than 40 years of age[10]. Regular screening of high-risk groups for HCC is recommended by the guidelines to detect more patients in the early-stage HCC." (on page 15 line 5-10): These sentence should be included in the Introduction or Method section. In the discussion section, you should in principle write a discussion of the data based on your own research. 11. "Taiwan of China" (on page 15 line 31): This sentence may be politically misleading. This is a scientific paper, so I recommend just stating 'Taiwan' so that any interpretation is acceptable. However, I am not a politician, so I cannot judge how this paper could be criticized because of this statement. The editorial board should decide whether to allow this wording or require a correction.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 82030

Title: Real-world 10-year retrospective study of the guidelines for diagnosis and treatment of primary liver cancer in China

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03252959
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Assistant Professor, Doctor, Surgeon, Surgical Oncologist
Reviewer's Country/Territory: Italy
Author's Country/Territory: China

Manuscript submission date: 2022-12-05

Reviewer chosen by: Dong-Mei Wang

Reviewer accepted review: 2023-01-30 20:33

Reviewer performed review: 2023-02-11 07:55

Review time: 11 Days and 11 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[Y] Grade A: Excellent [ ] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a real-world study based on the medical records of 3022 HCC patients with HCC admitted to the First Affiliated Hospital of Zhengzhou University from January 2011 to December 31, 2019 and recorded up to December 31, 2020. Patients were stratified according to the CNLC staging system with the aim of analyzing the current situation and existing issues of the guidelines for the diagnosis and treatment of HCC in China.

The authors conclude that: 1) the guidelines are well consistent with long-term clinical practice in China 2) patients who underwent liver resection according to the CNLC guidelines had a significant survival advantage 3) screening for high-risk groups of HCC according to guidelines can achieve earlier diagnosis and treatment 4) however compliance with the CNLC guidelines in the real world is still poor. These findings are relevant primarily because similar studies evaluating the impact of CNLC guidelines in the real world are lacking. The study was suitably designed and built. The final results are interesting and mainly suggest that screening for high-risk groups of HCC according to the guidelines of CNLC can achieve early diagnosis and treatment, and that patients undergoing therapeutic strategies, especially liver resection, in accordance with the

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guidelines had a substantial survival advantage. I find the manuscript excellent and suggest that it be published without significant changes.

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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 82030

Title: Real-world 10-year retrospective study of the guidelines for diagnosis and treatment of primary liver cancer in China

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03737141
Position: Editorial Board
Academic degree: PhD

Professional title: Professor

Reviewer's Country/Territory: Egypt

Author's Country/Territory: China

Manuscript submission date: 2022-12-05

Reviewer chosen by: Yu-Lu Chen

Reviewer accepted review: 2023-02-08 13:55

Reviewer performed review: 2023-02-18 18:41

Review time: 10 Days and 4 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

None

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 82030

Title: Real-world 10-year retrospective study of the guidelines for diagnosis and treatment of primary liver cancer in China

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05130811

Position: Peer Reviewer

Academic degree: MD

Professional title: Chief Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2022-12-05

Reviewer chosen by: Jia-Ru Fan

Reviewer accepted review: 2023-03-11 15:17

Reviewer performed review: 2023-03-12 04:49

Review time: 13 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer	Peer-Review: [Y] Anonymous [ ] Onymous

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statements	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

RESPONSE to Authors I think it is well corrected. However, there are still a few areas of concern. (Previous Point of View) The data that screening reduces the risk of death was presented with COX model in the result of abstract, but data on the 'effectiveness in HCC high risk' was not provided in the result of abstract. (on page 4, line 5). Author's Response: Thank you for highlighting this. We have added the following relevant results and data on the "effectiveness in hepatocellular carcinoma (HCC) high risk" at the end of the abstract following your suggestion: "Based on the Cox model survival analysis, HCC patients identified via screening had significant advantages in overall survival and tumor-free survival after hepatectomy ($P < 0.01$)." Comment to Authors：Is this analysis focused on the HCC high-risk group? If so, it should be stated as such. (Previous Point of View) Primary and secondary outcomes should be clearly stated. Author's Response: We created a subheading tagged "Primary and secondary outcomes" in the methods section with the following description: "The main research results of this paper show that the Chinese guidelines for HCC in China's real clinical practice of diagnosis and treatment compliance are good, and screening compliance is poor. According to the guidelines, screening and treatment can give patients certain survival benefits. This study found that patients who underwent hepatectomy according to the guidelines had a significant advantage in tumor-free survival compared with those who did not receive such treatment." Comment to Authors：This describes it as if it were an outcome; it should be changed to say that, for example, the PFS extension was set as the PRIMARY OUTCOME. (Previous Point of View) "The results were verified by the multivariate analysis showing that AFP > 400 ng/ml (HR = 1.612, 95% CI = 1.256-2.070), Child-Pugh B (HR = 1.771, 95% CI = 1.243-2.524), middle stage (HR = 2.556, 95% CI =

2.032-3.215), and late stage (HR = 3.312, 95% CI = 2.113-5.192) were independent factors affecting postoperative recurrence of HCC. (Table 6)." (from page 13 line 32 to page 14 line 5): AFP and stage can be understood as an risk of postoperative recurrence in patients undergoing LR as tumor vigour, but what does it mean that Child-Pugh B is a risk of postoperative recurrence in patients undergoing LR ? Describe that in discussion section. Author's Response: Thank you for this suggestion. We have now added the following to the third last paragraph of the "DISCUSSION" section: "When analyzing influencing factors for recurrence after hepatectomy, the patients with Child–Pugh grade A liver function were considered the reference because none of the patients with Child–Pugh grade C liver function received hepatectomy. Patients with Child–Pugh grade B liver function had more recurrences after hepatectomy ($P < 0.01$), indicating that the status of patients' liver function was an important risk factor for patients with recurrence after liver resection (LR)." Comment to Authors: Are there any previous reports that support the statement of higher postoperative recurrence rates in Child-pugh B? Please cite refferences. (Previous Point of View) Limitations on page 19 line 20: Is the exclusion of ICCs certain in this study? If not certain, the statement should be listed under limitation. Author's Response: Patients with ICC have definitely been excluded from this study. Comment to Authors: Pathological examinations have not been performed in all cases. Although the attending physician followed the guidelines to distinguish between HCC and ICC, it is impossible to rule out ICC or HCC-ICC perfectly because the guidelines are not 100% accurate. It would be better to state in the Limitation that a certain number of ICCs may have been mixed or some HCCs may have been excluded, to gain the reader's confidence.