



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 71260

Title: Postoperative Morbidity Adversely Impacts Oncological Prognosis after Curative Resection for Hilar Cholangiocarcinoma

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05430262

Position: Peer Reviewer

Academic degree: BSc

Professional title: Academic Fellow

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2021-09-01

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-01 17:31

Reviewer performed review: 2021-09-02 15:57

Review time: 22 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The authors present a work entitled "Morbidity after curative resection for hilar cholangiocarcinoma adversely impacts oncological prognosis". In their work they highlight the incidence of postoperative morbidity (major and minor) following HCCA resection, and identify risk factors for the development of postoperative morbidity. They also show that postoperative morbidity adversely affects the oncologic prognosis from the perspective of recurrence-free and overall survival. First, please be sure to re-read for grammatical accuracy with respect to the English language. There are small grammatical errors throughout that need to be addressed. Second, the statistical analyses are well done, and the conclusions from these data are well-made. HCCA resection is a very morbid procedure and the authors found that pre-existing conditions such as cirrhosis, diabetes, and obesity increase the risk of morbidity. The authors correctly note that preoperative medical optimization may lessen this risk, but what about the increased operative blood loss as an independent risk? Perhaps one solution could be the use of a different type of electrocautery - either bipolar as opposed to traditional monopolar? Or plasma, which has been shown to have some anticancer efficacy? Or water sealed bipolar? I think this merits exploration. Third, I would caution the authors on drawing conclusions on the influence of various non-biological factors on RFS. Tumor recurrence is due to inherently biological characteristics. The authors are correct in saying that tumor histological properties such as microscopic invasion and degree of differentiation can increase the risk of a poor RFS, but I doubt age and ASA score (non-tumor intrinsic properties) have a reliable association with recurrence. These variables should likely have been defined a priori. Does the final Cox



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model change when you omit clinical characteristics and use only pathological tumor traits for RFS? Last, I think the authors adequately detail the current literature with respect to morbidity and HCCA resection. As mentioned this is a morbid procedure, and certainly larger studies may be necessary to help establish new treatment algorithms for these patients, which was a limitation mentioned.



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05419473

Position: Peer Reviewer

Academic degree: MD

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Reviewer's Country/Territory: United States

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-20 01:24

Reviewer performed review: 2021-09-20 03:15

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Well-conducted and well-written study on a topic that has not been extensively investigated to date. Some specific comments are shown below: -Please provide IRB and Biostatistics Certificate in English. -Figure 1 is not properly cited in the text. The authors have confused Figure 1 with Figure 2. -There seems to be a problem with the data. How is the number at risk higher for RFS compared to OS in Figure 2 at 60 months? Didn't this last patient die on the first figure panel? Then, why isn't that patient having an event in the second figure panel? Please review all your survival data. -Were all cases performed open? -How many cases required vascular reconstruction and how many had a Pringle maneuver? Please include in Table 2 and further analyses separately for arterial and venous reconstruction. -How many patients underwent lymph node dissection and how many lymph nodes were resected? Please include in Table 2 and further analyses. -In Tables 5 and 6, please provide exact values for HR (95%CI) and p-value instead of the abbreviation "NS". -I agree with the authors' Discussion that propensity score matching is not required.



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00077376

Position: Editorial Board

Academic degree: MD, PhD

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Reviewer's Country/Territory: Japan

Author's Country/Territory: China

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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Although postoperative morbidity after curative resection for hilar cholangiocarcinoma (HCCA) is common, there have been few reports whether postoperative morbidity has an impact on oncological prognosis. Therefore, the authors aimed to evaluate the influence of postoperative morbidity on tumor recurrence and mortality after curative resection for HCCA. Postoperative morbidity (especially major morbidity) is revealed to be an independent risk factor for unfavorable prognosis. This is an interesting study; however, I have the following comments and questions. (1) In the abstract, “postoperative morbidity” and “major morbidity” should be defined objectively, using such as Clavian Dindo classification. (2) In the abstract, the following sentence, “the median OS and RFS of patients with morbidity were less favorable”, shows weak meaning, because the difference between the two groups was statistically significant. (3) In core tip, you mention, “It was the first study to investigate the oncological prognosis of hilar cholangiocarcinoma with postoperative morbidity”, however, the previous study like yours had been already reported, as “.Post-operative morbidity results in decreased long-term survival after resection for hilar cholangiocarcinoma (HPB 2011, 13, 139-147)” (4) There is no explanation on Figure 1 in the text, and Figure 1 A and B appearing in the text (survival curves) should be Figure 2A and B. (5) In the text, you describe, “with minor morbidity occurring in 91 (38.1%) and major morbidity in 55 (23.0%) of patients”, however, In Table 1, minor morbidity in 78 patients (32.6%) and 68 patients (28.5%). Which is correct? (6) Some types of postoperative complications overlap, such as biliary infection, bile leak, and cholangitis. For example, biliary infections, bile leaks, cholangitis, etc. are overlapping, as are SSIs, abdominal infections,



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and wound dehiscence. There should be clearer definitions on this matter. (7) In the patient characteristics, the following sentence, "Postoperative morbidity was experienced by 146 (61.1%) of the total 239 patients.", is not required because it has been already mentioned in peroperative outcomes. Instead, "Table 2 shows comparisons of patients' clinicopathologic and operative variables between patients with and without postoperative morbidity.", should be mentioned. (8) In the text, you describe like "obesity, diabetes mellitus, cirrhosis, preoperative CA19-9 > 150 U/L, and intraoperative blood loss > 500 ml were more common in patients with morbidity ($P < 0.05$)", however, In table 2, preoperative CA19-9 doesn't show any significant difference ($p=0.099$) (9) You describe, "based on the severity of postoperative morbidity, major morbidity was associated with both lower OS", however, there is no exact survival data. If you add the data of OS and RFS according to major and minor morbidity in Figure 2, it will be more impressive. For example, Figures 2 A and B should have three survival curves of the patients without postoperative morbidity, those with minor morbidity and those with major morbidity. Table 4 already shows OS and RFS data according to with and without postoperative morbidity. Therefore, Figure 2 should have three survival curves.



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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

This is a well-organized paper, but I have some suggestions. Please describe figure 1 explanation in the main text. Please clarify minor and major morbidity rate in the text and Table 1. The authors described preoperative CA 19-9 were more common in patients with morbidity, but there is no difference between two groups as shown in Table 2. In this study, patients who received adjuvant chemotherapy were excluded, but I think the role of adjuvant chemotherapy is important for cholangiocarcinoma patient after curative resection. Because adjuvant chemotherapy cannot be administered immediately when complications occur after surgery, so what do you think will affect the prognosis. It would be better put these in the discussion section.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

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Author's Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

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

SPECIFIC COMMENTS TO AUTHORS

The revised manuscript has been corrected well according to the reviewers' comments.