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Editorial Office Director, Company Editor-in-Chief

World Journal of Gastroenterology

Dear Editor:

We wish to re-submit the manuscript titled "**Clinical Online Nomogram for Predicting Prognosis in Recurrent Hepatolithiasis After Surgery: A Multicenter, Retrospective Study**". The manuscript was originally titled "**Clinical Online Nomogram for Predicting Prognosis in Secondary Hepatolithiasis: A Multicenter, Retrospective Study**". The manuscript number is 71569.

We thank you and the reviewers for your thoughtful suggestions and insights. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *World Journal of Gastroenterology*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers' suggestions. The responses to all comments have been prepared and attached herewith.

Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: 1 Title. YES, 2 Abstract. YES. But ıt could be better if adds some information about the materials and research results to the results section. 3 Key words. YES 4 Background. YES 5 Methods. YES 6 Results. Well documented. I think that the results will some contribution the the medical literature 7 Discussion. Well. Enough. 8 Illustrations and tables. OK 9 Biostatistics. YES, GOOD 10 Units. YES 11 References. YES, References are current and sufficient 12 Well documented. Well writen, discussed, and presented. There is no need linguistic revision. 13 They have prepared a large clinical series. I believe that it meets the required criteria and standards regarding the spelling rules. 14 Ethics statements. No problem

Response: Thank you for your positive evaluation and appreciation. We have attempted to improve the Abstract based on your sugegstion.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors:

1. The definition of "secondary hepatolithiasis" is the stones both mainly in the extra-hepatic duct and accumulated into the intra-hepatic duct, and "primary hepatolithiasis" is the stones mainly in the intra-hepatic duct (Ref. 6 and 7). The definition of Secondary hepatolithiasis is defined as hepatolithiasis with a history of biliary tract surgery for different reasons in your article. Therefore, I suggested that it is better to use the term "recurrent hepatolithiasis after operation" instead of secondary hepatolithiasis.

Response: Thank you for your valuable insights. We have now revised "secondary" to "recurrent" throughout the manuscript.

2. Concerning the study design, there were two cohort groups; training and validation cohort and two cohort patients come from the different hospitals. If we used the training and validation cohort is to prove the training group is accuracy or not by validation group. Therefore, how about supply used the group A and B? Please take a consideration

Response: Thank you for your helpful comments. This is indeed a good proposal, but after referring to the relevant literature, we find that in most nomogram studies[1,2,3,4], researchers tend to name the group used to build the model as the training cohort, and the group of external verification as the validation cohort. Therefore, we would prefer to retain the use of the terms "training cohort" and "validation cohort" in our manuscript.

References
1. *Lei Z, Li J, Wu D, Xia Y, Wang Q, Si A, Wang K, Wan X, Lau WY, Wu M, Shen F. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the Milan criteria. JAMA Surg 2016;**151**(4):356–63 [doi:10.1001/jamasurg.2015.4257]*
2. *Yang T, Xing H, Wang G, Wang N, Liu M, Yan C, Li H, Wei L, Li S, Fan Z, Shi M, Chen W, Cai S, Pawlik TM, Soh A, Beshiri A, Lau WY, Wu M, Zheng Y, Shen F. A novel online*

*calculator based on serum biomarkers to detect hepatocellular carcinoma among patients with hepatitis B. Clin Chem 2019;**65**(12):1543–53 [doi:10.1373/clinchem.2019.308965]*

3.   Wu J, Zhang H, Li L, Hu M, Chen L, Xu B, Song Q. A nomogram for predicting overall survival in patients with low-grade endometrial stromal sarcoma: a population-based analysis. Cancer Commun (Lond) 2020;40(7):301–12 [DOI: 10.1002/cac2.12067]

*4.   Zuo Z, Zhang G, Song P, Yang J, Li S, Zhong Z, Tan Q, Wang L, Xue Q, Gao S, Sun N, He J. Survival nomogram for stage IB non-small-cell lung cancer patients, based on the SEER database and an external validation cohort. Ann Surg Oncol 2021;**28**(7):3941–50 [doi:10.1245/s10434-020-09362-0]*

3. The topic is concerning the prognosis of the treatment, but we can't understand what's the content of the prognosis. It is better to tell us the independent facts which will affect the prognosis such as operative mortality, clearance rate of stone or life quality or malignant change etc

Response: Thank you for your recommendations. In our study, we evaluated the prognosis of patients based on the Terblanche classification for cholangitis. The specific criteria have been described in detail in the "Follow-up" section under "Materials and Methods", as follows: Grade I, no bile duct-related symptoms; Grade II, occasional bile duct-related symptoms requiring no treatment; Grade III, obvious bile duct-related symptoms requiring treatment; or Grade IV, presence of anastomotic stricture or formation of bile duct stones requiring surgical intervention and causing disease-related cancer or death. We considered Terblanche grades III and IV to indicate a poor prognosis, which was the study endpoint. These patients generally have poor quality of life. Residual or recurrent stones will undoubtedly increase the likelihood of the endpoint, but simple residual or recurrent stones do not necessarily lead to the endpoint.

4. In the section of "post-operative management" before discharge, all patients underwent abdominal CT examination again to confirm whether the stone was removed immediately during the operation". Are sure to perform CT? Why not post-operative T-tube cholangiography which will be more accuracy and easy to perform.

Response: Thank you for the pertinent question. All patients in the present study underwent CT after surgery per the clinical protocols followed at the four large medical centers. The main goals were to observe the postoperative abdominal condition, determine the time of removal of the abdominal drainage tube, and further observe the residual stones.

In addition, for patients with immediate stone residue, we usually performed choledochoscopy through the sinus of the T tube at 6–8 weeks after the surgery; this was performed several times until the stone was removed or could not be removed by any means. For patients with immediate clearance, we performed T-tube cholangiography at 2 weeks after surgery. In case a residual stone was observed, we performed choledochoscopy as described above.

Response: Thank you for your valuable comments. For patients with immediate stone residue, we usually performed choledochoscopy through the sinus of the T tube at 6–8 weeks after the surgery; this was performed several times until the stone was removed or could not be removed by any means. For patients with immediate clearance, we performed T-tube cholangiography at 2 weeks after surgery. In case a residual stone was observed, we performed choledochoscopy as described above. We have added the relevant text in the "Postoperative management" section under "Materials and methods".

Response: Thank you for you comments. This research was based on use of the R programming language to establish a nomogram for prediction, with further development of an online calculator of the score through *shinyapps.io*, so that it can be used by all surgeons. Individual prognostic scores can be generated for all patients with recurrent hepatolithiasis, and the probability of a good prognosis can be determined on the basis of the five risk factors in the model. We agree that Artificial Intelligence is a good research breakthrough point, and we believe that further study based on AI will play an important role in our team's future research endeavours.

Response: Thank you for your recommendation. We have provided details regarding the initial surgeries in the second paragraph of the "Results" section.

identified predictors were multiple previous operations, bilateral hepatolithiasis, lack of immediate clearance, preoperative NLR (neutrophil-to-lymphocyte ratio)>2.462, and preoperative AGR (albumin-to-globulin ratio) <1.5. Subsequently, the nomogram was constructed to demonstrate the risk for poor prognosis after secondary hepatolithiasis that showed good predictive performance both in the internal and external cohorts. The nomogram was further tested using decision curve analysis that confirmed sufficient predictive power. The strength of this study was that the created nomogram was validated through multiple calculation models and the use of online nomogram is quite easy. There are some limitations in this study and the greatest of which is the inclusion of only patients with secondary hepatolithiasis who underwent surgically treatment: however, the authors have clearly stated this in the discussion. Specific comments:

Minor points:

1. Abstract: The number of analyzed patients and the study design (multicenter, retrospective should be included in the methods.

Response: Thank you for pointing this out. We have modified the Abstract per your recommendations.

2. Introduction: The prevalence of hepatolithiasis is derived from the citation no. 5 (Ozturk A et al. Turk J Urol 2017). However, the original number of this was published by the Feng X et al. Intractable Rare Dis Res. 2012;1:151–6. Please consider substituting the citation.

Response: Thank you for pointing this out. We have replaced the reference.

3. Discussion: On page 13, the abbreviation "ICC" should be defined as firstly appeared in the row 5.

Response: Thank you for your careful review. We have defined the abbreviation ICC at the first instance of mention.

Company editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable),

Response: Thank you for your positive feedback and helpful suggestions. We have adjusted the figures and tables according to the requirements and provided the figures as decomposable images in a single PowerPoint file.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
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