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PEER-REVIEW REPORT

Name of journal: *World Journal of Hepatology*

Manuscript NO: 77505

Title: Heredity Hemochromatosis: Temporal trends, sociodemographic characteristics, and independent risk factor of Hepatocellular cancer – Nationwide Population-Based Study

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03538879
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Chief Doctor, Professor
Reviewer's Country/Territory: China
Author's Country/Territory: United States

Manuscript submission date: 2022-05-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-06 03:58

Reviewer performed review: 2022-05-09 14:05

Review time: 3 Days and 10 Hours

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish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	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection

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

SPECIFIC COMMENTS TO AUTHORS

This is an interesting case registration study. Hereditary metabolic disorder HH is an important risk factor for HCC, but lack of direct clinical evidence. It is generally believed that iron overload plays a crucial role in the progression of HH to HCC. Excessive iron storage in hepatocytes is the cause of liver fibrosis, cirrhosis and HCC. Due to the low prevalence of HH, there are only a few studies to evaluate the impact of HH on the development of HCC. Although this is a retrospective study, it is the first large sample case registration study. The conclusion" HH without cirrhosis is an independent risk factor for HCC" is also important to recognize the progress of HH and HCC, and will be of great value if it can make up for the gap of prospective cohort research in the future.

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Peer-review model: Single blind

Reviewer's code: 03022180
Position: Editorial Board
Academic degree: FAASLD, MD, PhD
Professional title: Associate Professor, Professor
Reviewer's Country/Territory: Brazil
Author's Country/Territory: United States

Manuscript submission date: 2022-05-05

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-05-06 02:55

Reviewer performed review: 2022-05-20 01:37

Review time: 13 Days and 22 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] 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
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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 an interesting study that evaluates the risk of HCC in patients with HH without cirrhosis and also the characteristics of this population using a large database (NIS). The study has some drawbacks that might be considered. The first is the definition of hemochromatosis. How can the authors confirm this diagnosis? We know that IDC is prone to many diagnostic errors. How did the authors overcome the misdiagnosis? I suggest the authors rewrite the following paragraph in discussion session, not in introduction: "Current literature lacks enough studies that have assessed admitted HH patients' characteristics, which makes our case-control study unique, especially with its large sample size. Whether or not hepatic iron overload in HH patients is an independent risk factor for HCC without cirrhosis remains relatively unclear, rare, and a topic of mainly few case reports and minimal previous studies regarding this question which we have involved some of them in our discussion part". "Our study performed HCC risk factor analysis and found that HH without cirrhosis is 28 times more likely to develop HCC. Thus, HH without cirrhosis is an independent risk factor for HCC. Previous studies showed that it could be from iron deposition and its carcinogenic effects or the HFE gene causing mutation [10,23]." I might say that the high risk of HCC in patients without cirrhosis is a well-known concept, and thus, not original. The previous paragraph makes the reader believe that this is quite new, when it is an old knowledge. The authors discuss the possible pathogenesis of this relation but they have not studied the pathogenesis per se, hence it would only be a discussion of a possible hypothesis, not based on the results. Please justify this and make it clear in the

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discussion session. The tables should be formatted adequately. The results from the multivariate analysis are not clear. All the ratios (OR) related to HCC are associated with known liver diseases and diabetes mellitus. It There is no clear explanation for these results and it is out of the objective of the manuscript.

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05923441
Position: Peer Reviewer
Academic degree: MBBS, MRCP
Professional title: Academic Fellow, Academic Research, Doctor
Reviewer's Country/Territory: United Kingdom
Author's Country/Territory: United States

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Review time: 16 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [Y] 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
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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Thank you very much for providing the opportunity to review the study titled 'Heredity Hemochromatosis: Temporal trends, sociodemographic characteristics, and independent risk factor of Hepatocellular cancer – Nationwide Inpatient Analysis. The author claims to analyse data from National Inpatient Sample (NIS) Database for ICD-9 and ICD-10 primary and secondary admission diagnosis of hereditary haemochromatosis (HH) from January 2011 to December 2019 to determine the change in yearly temporal trend of hospitalization, identify associated high-risk characteristics, common symptoms, and outcomes of hospitalization. Moreover, the author investigated the increased risk of HCC in HH. This is area worth investigating with limited evidence available. However, I have the following concerns which will require further clarification. Major concerns The abstract does not present a true summary of the study. Author has not provided results as per set objectives. The result presented and conclusion given are disjointed, most of conclusion has no results given to support. It seems author presented results on two different cohorts. 1st the cohort of patients with ICD-9 or ICD-10 diagnosis of HH (n=18,031) and 2nd the cohort of patients with HCC with all cause of cirrhosis (n=110,887+ n=110,88). Author has not clarified this in title, abstract or methods in contrast the exclusion criteria read as 'Patients were excluded if they had a primary or secondary diagnostic code of cirrhosis (alcoholic, non-alcoholic, and biliary), viral hepatitis, alcoholic liver disease, Non-Alcoholic Fatty Liver Disease (NAFLD), and Non-Alcoholic Steatohepatitis (NASH)'. If this is true it stands against study eligibility criteria. Author has over interpreted the results while providing the risk of HCC in

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HH. There are few major flaws with the model such as (a) the at-risk population are patients with all cause chronic liver disease not only patients with HH, (b) small sample size for any meaningful statistics (the number of patients with no HCC in HH without cirrhosis is 5 and with cirrhosis 11). Moreover, using ICD based codes has inherited risk of missing the cases. How author differentiated between cirrhosis and no cirrhosis. I have noted in the limitation section the missing information on liver fibrosis stage. Does author have any information in primary cohort of admissions (n=18,031): how many were cirrhotic; how many were non-cirrhotic and how many had HCC? Same goes for assumption for correlation author withdrawn for iron overload and increased risk of HCC in HH. Without knowing serum ferritin level or hepatic iron (siderosis grade) this feels counter intuitive and pure assumption. Minor The 3rd affiliation is not associated to any author. Please rectify Abstract: author has provided background then objectives. Either remove background and only provide objectives or update the heading. Also, I would suggest presenting as primary and secondary aims. Introduction: Hereditary hemochromatosis (HH) is a 'genetic disorder of iron metabolism' not 'genetic metabolic disorder'. -HH has increased risk of HCC both due to genetic risk and iron overload. Please clarify -Split aims into primary and secondary not first or second part -Avoid non-standard abbreviations, it is better to spell them out. Methods: what author meant by weighted database and stratified sample of all discharges. -Year trend of what? Please specify. Same for hospital outcomes please specify -Why was age used as categorical variable? Results: what was the total number of patients accounting for 18,031 hospitalizations? -Percentage normally given with 95% CI not SE, mean with SD or SE and median with IQR or range -is the 1.2% cumulative incidence or absolute risk of HCC in HH? Move table 3 to supplementary material For table 1, I would suggest providing baseline population characteristics. Remove headings like bed size, payer status. If required, the author can

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create an additional supplementary table with these informations. What is weighted and unweighted? What author thinks is explanation for rising number of admissions in HH? Start discussion with summarising your important findings before comparing them to published literature The study is not unique, there are prior studies investigating the subject matter of discussion Overall, I suggest if author concentrates on expanding on how these patients present to hospital, what are high risk characteristics and comorbidities related to poor outcomes in hospital in these patients this can make and important contribution. I am not sure about the section on HCC in HH and conclusion drawn based on data provided in the study. Although historically there is evidence to support the claim.

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Reviewer's code: 05759338
Position: Editorial Board
Academic degree: MD
Professional title: Assistant Professor
Reviewer's Country/Territory: Thailand
Author's Country/Territory: United States

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Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The manuscript showed novelty information about HCC risk in HH patients.