Reviewer # 1

Reviewer Comments	Authors Response
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.	1. Thank you for your feedback. 2. The reviewer, didn't request any changes in the manuscript.

Reviewer # 2

Reviewer Comments	Author Response
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).	Thank you for your feedback.
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?	1. We used the ICD-10 diagnostic code of Heredity Hemochromatosis "275.01 (ICD-9) and E83.110 (ICD-10)" 2. We removed patients from the HH cohort if they had a primary or secondary diagnostic code of cirrhosis (alcoholic, non-alcoholic, and biliary), viral hepatitis, alcoholic liver disease, and Non-Alcoholic Fatty Liver Disease (NAFLD), and Non-Alcoholic Steatohepatitis (NASH). 3. We removed these patients from the HH cohort to rule out bias or ICD-10 diagnosis errors of HH. 4. The abstract, methodology, and limitation sections are updated in the revision.
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]."	1. Thank you for the recommendation, we rearranged for better tracking of ideas. 2. References were rearranged accordingly.
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	We emphasize that HCC risks **<u>in HH</u>** without liver cirrhosis is an understudied part of hepatology/liver cancer studies. Sentences were rephrased so hopefully they look clearer now.

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.	We confirm that the pathogenesis is beyond the topic of our study. This is why proper citations/references were mentioned accordingly as these results are not our study's results. E.g.: citations 10,23, 25,26.
The tables should be formatted adequately.	All tables are formatted in the revision.
The results from the multivariate analysis are not clear.	The explanation of table 3 (multivariate analysis) is revised in the results section.
All the ratios (OR) related to HCC are associated with known liver diseases and diabetes mellitus. There is no clear explanation for these results, and it is out of the objective of the manuscript.	secondary outcomes on the HCC cohort investigated HH without cirrhosis as an independent risk factor for HCC after accounting for all known other risk factors of HCC. We included known risk factors in the prediction model to ensure the completeness of the model.

Reviewer # 3

Reviewer Comments	Author Response
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.	Thank you for taking the time and reviewing this manuscript.
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.	Thank you for the feedback. The abstract was edited so it addresses this review: In the conclusion part of the abstract, we emphasized the main endpoints from this study. (hospitalizations' trend, LOS, costs) in addition to HH being an independent risk factor for HCC without cirrhosis. -The ACG recommendation was moved to discussion with its citation to make the conclusion more compatible with our study aims We hope this makes it easier to read. -The results and conclusion were rephrased so they are easier to read and navigate through
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	1. The abstract and the methodology section are revised to explain the presence of the HH and the HHC cohort. 2. The manuscript (methods) is revised to clarify that patients were excluded from the HH cohort only. 3. We removed these patients from the HH cohort to rule out bias or ICD-10 diagnosis errors of HH.

(NASH)'. If this is true it stands against study eligibility criteria.	
Author has over interpreted the results while providing the risk of HCC in 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).	1. We performed the multivariate analysis on the HHC and non-HHC matched cohort and analyzed HH without cirrhosis (removing HH patients with a diagnosis of cirrhosis) as an independent risk factor of HCC after adjusting all known risk factors of HCC in the multivariate model. 2. For the risk of HCC in HH, we used all HCC and nob-HCC age-, sex, - and race-matched cohort. 3. Table 2 is revised. We changed the statistic from un-weighted to weighted. The number of patients with no HCC in HH without cirrhosis is 25 and with cirrhosis 55 respectively.
Moreover, using ICD-based codes has inherited risk of missing the cases.	1. This is the limitation of the study. The limitations section is revised.
How author differentiated between cirrhosis and no cirrhosis.	1. We used ICD codes for all types of cirrhosis to differentiate b/w 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?	1. From the HH cohort ((n=18,031), we excluded patients with 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).
Same goes for the 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.	1. From the NIS database, we lack some of the patients' information like iron levels and other lab values. 2. We have revised the limitations section to address this issue.
Minor The 3rd affiliation is not associated to any author.	The 3rd affiliation is added.
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.	This was taken care of as recommended
Hereditary hemochromatosis (HH) is a 'genetic disorder of iron metabolism' not 'genetic metabolic	This was taken care of as recommended

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.	This was taken care of as recommended Nonstandard abbreviations were avoided where needed.
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	The methods section is revised to explain the weighted database and the sampling mythology.
Why was age used as categorical variable?	We categorized age into "NIS-HCUP" categories for standardized demographic analysis.
Results: what was the total number of patients accounting for 18,031 hospitalizations?	1. NIS entry is equivalent to one hospitalization. If a patient is admitted more than once, one patient may contribute multiple entries. 2. The limitations section is revised.
Percentage normally given with 95% CI not SE, mean with SD or SE and median with IQR or range.	Table 1 is revised as per the reviewer recommendation.
is the 1.2% cumulative incidence or absolute risk of HCC in HH?	The incidence of liver cancer in HH patients is 1.2% (95%CI; 0.78 – 1.53), unrelated to cirrhosis, viral hepatitis, alcoholic liver disease, NAFLD, and NASH.
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 create an additional supplementary table with these informations.	1. Hospital characteristics and payer information were removed from table1 and moved to supplementary table S1. 2. Table 3 moved to supplementary table S2.
What is weighted and unweighted?	Unweighted information removed from all the tables.
What author thinks is explanation for rising number of admissions in HH?	Was explained as likely related to advances in diagnostic approaches and testing which can increase both admission rate and costs, and we think that length of stay remained the same as most managements can be done as outpatient.
Start discussion with summarizing your important findings before comparing them to published literature. The study is not unique, there are prior studies investigating the subject matter of discussion	Taken care of by adding the fist paragraph in the discussion. What makes our study unique in the large and diverse cohort number with socioeconomic trends. All strengths are mentioned in the manuscript as well. References were rearranged accordingly.

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.	This is out of scope for this project goals.
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.	We have drawn the conclusion based on the multivariate analysis results on the HCC and non-HCC matched cohort. The multivariate analysis found HH without cirrhosis (aOR, 28.8; 95% CI, 10.4 - 80.1; P < 0.0001) after adjusting other known risk factors.

Reviewer # 4

Reviewer Comments	Author Response
The manuscript showed novelty information about HCC risk in HH patients.	1. Thank you for your feedback. 2. The reviewer, didn't request any changes in the manuscript.