Response to reviewer comments

Under the current severe form of liver cancer, there are a lot of research on Hepatocellular Carcinoma (HCC), but for Non-Cirrhotic-HCC (NCHCC) research is relatively small, the author selected topic is novel, and the thinking of writing clear.From the Non-Cirrhotic Hepatocellular Carcinom epidemiological statistical methods, a variety of pathogenic factors, to the symptoms of the disease, the current diagnostic methods, as well as the key treatment measures, etc., this review all the details.And the most common chronic virulent hepatitis HBV and HCV as the representative of the current research in this field to make a specific explanation. Reading the whole article, it is not difficult to find that the author has a strong ability to search for the latest research progress in this field, especially the current clinical treatment of HBV and HCV, Locoregional therapies and Systemic treatment. In addition, while describing cutting-edge technologies and research, the author list detailed evidences in combination with his own thoughts to help readers to read.It is also commendable that, for various existing diagnostic methods, the author summarizes their advantages and disadvantages and compares them, which is more intuitive and clear. However, the article focuses on HBV and HCV, which makes the title's emphasis on Chronic Viral Hepatitis (including HDV, etc.) seem a bit broad. Furthermore, the article should use some diagrams to make the tedious text concise, and make some suggestions for possible future research directions in this area.

Response: We thank the reviewer for the comments on the manuscript. As reviewer suggested, we revised the title. We have provided figures (to elucidate mechanisms of hepatitis B and hepatitis C in the pathogenesis of NCHCC) and additional tables (to compare imaging characteristics, treatment of cirrhotic and NCHCC). This has abbreviated the article. Furthermore, as the reviewer suggested, a section on the future research directions have been provided.

Future Research Direction

Improved cross-sectional imaging characteristics are expected to identify NCHCC at an earlier stage and provide increasing treatment options in the future. Survival and recurrence rates in NCHCC have been improving and expected to reach HCC patients with efficacy of antiviral treatment options, living donor liver transplantation, parenchymal sparing liver resection and two stage liver resections. Use of artificial intelligence, deep learning models (convolutional neural network) are being utilized for identification of NCHCC. Messenger RNA (mRNA) is a family of RNA molecules which are involved in coding proteins and convey genetic information. On the contrary, microRNAs (miRNAs) are non-coding molecules (22 nucleotide length) that regulate gene expression especially in post-transcriptional state. Dysregulated miRNA can lead to DNA damage with alter gene expression playing a role in NCHCC tumor pathogenesis. Use of micro RNA and messenger RNA (miRNA-mRNA) networks with bioinformatic analysis and experimental validation are being development for therapeutics for NHCCC. Use of miRNA as a potential serum biomarker for diagnosis, prognostication, survival after liver resection and systemic therapy have been studied. Despite these advances, further research on molecular

mechanism of mRNA and miRNA regulation in NCHCC, and validation of genes involved in NCHCC are urgently needed.

Authors summarized the current literature on epidemiology, risk factors, pathogenesis, screening and treatment of HCC in patients with non-cirrhotic viral hepatitis B and C. My comments are as follow: *The parts related to primary liver cancers other than HCC should be omitted. *Overall, the manuscript should be revised to emphasize the differences between epidemiology, risk factors, pathogenesis and screening of HCC developing in cirrhotic vs. non-cirrhotic liver. * Treatment section can be omitted or extensively reducted, because basic approach is same in all patients with (non)cirrhotic HCC, except the liver reserve is better in non-cirrhotic patients.

Response: We thank the reviewer for their highly valuable comments. As reviewer suggested, we reduced few sentences on the primary liver cancer. The manuscript has been revised to emphasize on differences between HCC and NCHCC. Furthermore, we included a table comparing key characteristics of NCHCC and HCC. Finally the treatment sections have been abbreviated as well.

Table 2: Key differences between NCHCC and HCC

	HCC	NCHCC
Epidemiology	Eighty percent of HCC develops with a cirrhotic background. A unimodal age distribution (peak in 7th decade) noted. Male: female ratio-3:2	Twenty percent of tumors develop in non-cirrhotic liver. A bimodal age distribution (peak in 2nd and 7th decade) noted. Male: female ratio-2:1
Risk factors	Development of cirrhosis from any etiology can progress to HCC. Hepatotropic viruses, environmental and life style factors (alcohol, tobacco), metabolic conditions (nonalcoholic fatty liver disease, diabetes mellitus, obesity) play a predominant role	NCHCC develops without a background of underlying cirrhosis. Viral (HBV, HCV infection) and non-viral risk factors (obesity, diabetes mellitus, toxin exposure, germline mutations and genetic disorders) noted
Clinical features	Symptoms could be related to underlying cirrhosis (from portal hypertension) or HCC (early satiety, upper abdominal pain) itself. Paraneoplastic signs such as hypercalcemia, hypoglycemia have been reported	Generalized fatigue, abdominal pain and weight loss are common symptoms. Can present at late stage with large tumor burden, extrahepatic metastasis
Diagnosis	High quality cross-sectional	Although CT and MRI are increasingly

	imaging (CT/MRI) are used with typical arterial phase hyper-enhancement and portal venous washout. LI-RADS classification is used in classification of radiological findings in HCC	utilized for diagnosis, liver biopsy are utilized in patients when cross-sectional imaging is equivocal. LI-RADS classification cannot be utilized for NCHCC and instead tumor characteristics (size, imaging features) are utilized for staging
Treatment	Given the underlying cirrhosis, liver transplant candidacy need to be evaluated for HCC patients. Resectability of the lesion, amount of liver reserve, vascular invasion, performance status determines the treatment outcomes	Antiviral treatment recommended when etiology of NCHCC is HBV/HCV. Surgery remains the main treatment modality. Systemic and local therapy options are increasingly being utilized for NCHCC

Note: Key differences in epidemiology, risk factors, clinical presentations, diagnosis and treatment for NCHCC and HCC. A multidisciplinary team evaluation is frequently utilized for diagnosis and treatment. HCC- hepatocellular carcinoma, NCHCC- non cirrhotic hepatocellular carcinoma, LI-RADS- Liver Reporting and Data System, HBV- hepatitis B, HCV- hepatitis C. Please refer to text for references.

Table 3: Treatment options for NCHCC

Treatment	Comments
Antiviral therapy	If HBV or HCV are identified as potential causes of NCHCC, aggressive treatment should be pursued. Entecavir, tenofovir have been used for HBV and direct acting antiviral (DAA) agents are used for HCV infection
Surgery	Mainstay for the treatment of NCHCC. BCLC staging cannot be used for NCHCC patients. Tumor size, elevated bilirubin level, low platelet count, vascular invasion can predict prognosis in NCHCC individuals
Locoregional therapy	Limited data available in NCHCC patients. Isolated cases and case series showed improved prognosis with these treatment options
Systemic therapy	Multikinase inhibitors (sorafenib, regorafenib), immunotherapy (nivolumab), chemotherapeutic agents (epirubicin, cisplatin, 5-fluororuacil, capecitabine, docetaxel, GEMOX) have been used in NCHCC with various success

Note: Potential treatment options for NCHCC. Antiviral therapy is indicated if HBV or HCV is identified as a potential cause. While surgery remains the mainstay of the treatment, locoregional and systemic therapy options have been tried. HCC- hepatocellular carcinoma, NCHCC- non cirrhotic hepatocellular carcinoma, BCLC- Barcelona-Clinic Liver Cancer, HBV- hepatitis B, HCV- hepatitis C, GEMOX- gemcitabine and oxaliplatin regimen. Please refer to text for references.

figure1 and table1 is absent in the main manuscript.

Dear editor I have attached a document with tables and figures. Thank you