Dear Editor-in-Chief,

As you requested, we are resubmitting the revised version of our manuscript. We want to thank the reviewers for their fruitful criticism, which significantly improved the quality of our manuscript. We addressed all comments point-by-point as outlined below. All modification in the manuscript are easily visible (highlighted in yellow color).

Yours sincerely,

Daniel Simon

Reviewers' comments:

Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: It is an interesting article about "Association of IFNL4 rs12979860 polymorphism with hepatocellular carcinoma in patients with chronic hepatitis C infection". My concern is determined in the following points.

(1) Diagnosis of fibrosis (METAVIR F1-F3) was performed by anatomopathological examination: Does this mean that diagnosis of fibrosis in all patients was performed by finding of liver biopsy? Additional results about fibrosis in liver should be assessed with Fibroscan, Elastgraphy, Fib-4 index, APRI score, levels of serum hyalulonate, PIV-P, PIII-P and M2BPGi and platelet counts. These results should be revealed.
Answer: *Firstly, we thank the reviewer for the valuable review of our manuscript.*
Since fibrosis was assessed by liver biopsy in all patients included, non-invasive fibrosis markers were not applied.
We changed the text in the manuscript.

(2) Diagnosis of cirrhosis was performed through clinical, laboratorial and anatomopathological and/or imaging data. Diagnosis of liver cirrhosis was performed by anatomopathological examination: Does this mean that diagnosis of fiver cirrhosis in all patients was performed by finding of liver biopsy? Additional results about liver cirrhosis should be assessed with Fibroscan, Elastgraphy, Fib-4 index, APRI score, levels of serum hyalulonate, PIV-P, PIII-P and M2BPGi, albumin, prothrombin time, platelet counts, albumin, total bilirubin and imaging examinations including abdominal ultrasonography, computed tomography, and magnetic resonance imaging. These results should be revealed.
Answer: *Cirrhosis was diagnosed either by liver biopsy or clinical evidence, such as liver imaging (abdominal ultrasonography, computed tomography and magnetic resonance) abnormalities or endoscopic findings, as well as current or past clinical evidence of decompensation, including Child–Pugh B or C classification (score of >6), ascites on physical examination, hepatic encephalopathy, or variceal bleeding.*
We changed the text in the manuscript.

(3) Diagnosis of HCC was performed through dynamic imaging tests, and/or anatomopathological markers: Results about imaging examinations including abdominal ultrasonography, computed tomography, and magnetic resonance imaging and levels of serum AFP, PIVKA-II should be revealed.

Answer: *HCC was diagnosed through liver biopsy or, in cirrhotic patients, through dynamic computed tomography or magnetic resonance by the presence of a nodule of at least 1cm featuring arterial phase enhancement with decreased enhancement during the portal venous phase, as recommended by international guidelines.*
We changed the text in the manuscript.

(4) Patients with HCV/HIV (human immunodeficiency virus) and/or HCV/HBV coinfection were excluded: Additional revaluation about patients infected with HBV and Patients with NASH should be revealed. (5) In the control group, 260 HCV-negative samples were obtained from donors of the HCPA blood bank., therefore they should be focused on bare essentials to better understand: Control group should be excluded not only HCV-negative samples, but also HBV-negative, and healthy controls. *Contents of this article are difficult to understand because of insufficient evidences, therefore authors should more elucidate points as above of this article.
Answer: *Patients with HCV/HIV and/or HCV/HBV coinfection, as well as patients with other causes of liver diseases such as HBV, metabolic associated fatty liver disease, alcohol abuse (more than 20 ou 30g daily consumption of ethanol for females and males, respectively), and/or hemochromatosis were excluded. The control group comprised 260 samples obtained from the donors at the HCPA blood bank. As Brazilian laws for blood donation requires, all have been tested negative for HBV, HCV, HIV, syphilis and Chagas disease.*
We changed the text in the manuscript.

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: As we know, the IFNL4 rs12979860 polymorphism has been associated with spontaneous and treatment-induced clearance of HCV infection, and however it is unclear whether it plays a role in chronic hepatitis C patients with progressed liver diseases. Authors investigated the association of the IFNL4 rs12979860 polymorphism with fibrosis, cirrhosis, and HCC in chronic HCV-infected patients. There are some problems as below.

1. In the section of “materials and Methods”, the criteria of diagnosis of liver cirrhosis and HCC should be further clarified in addition to pathological examination.
Answer: *We thank all the comments and suggestions, which have contributed to the improvement of the manuscript. In the first paragraph of the "Material and Methods" section, we added more detailed information, to better understand the criteria of diagnosis.*

2. Why are there no data on HCV RNA, HCV genotype, number of patients with antiviral treatment, diabetes, and steatosis in the liver fibrosis group in Table 1?
Answer: *Unfortunately, these data are missing in our database. A sentence about this limitation was included in the discussion.*

3. Demographic data and clinical characteristics showed that there were differences in age, gender composition, BMI, smoking and drinking habits among the three groups. It is suggested that these variables should be adjusteded in statistical analysis to eliminate the influence of confounding factors on the conclusion.

Answer: *We analzyed logistic regression models aiming to control for potential confounding factors (variable associated with the study factor and with the outcome at p<0.20). The previously observed associations remained significant when the logistic regression models were analyzed. We included this information in the "Statistical Analysis" and in the "Results".*

4. A few relevant studies were listed in the discussion. How is the current study different from them? Where is the "innovation"?
Answer: *Our study provides additional information about the association of the genetic variants of IFNL4 rs12979860 polymorphism with disease progression and clinical features of hepatitis C in a Brazilian sample, demonstrating that this polymorphism has relevance not only in the HCV spontaneous and treatment-induced clearance of HCV infection. In addition, the present study can contribute to meta-analysis studies on the association of this polymorphism and HCC, with data of a Western population, as well as stimulating clarification of this issue by the analyzes of correlation of genetic variants with gene expression and protein interactions.*

Reviewer #3:
Scientific Quality: Grade E (Do not publish)
Language Quality: Grade B (Minor language polishing)
Conclusion: Rejection
Specific Comments to Authors: In this study, Bitencorte et al. investigated the association of the IFNL4 rs12979860 polymorphism with fibrosis, cirrhosis, and HCC in chronic HCV-infected patients, and demonstrated that T allele from IFNL4 rs12979860 polymorphism is associated with the development of cirrhosis and HCC in chronic HCV-infected patients. Although this story is interesting, there is a major flaw that need to be addressed and I cannot recommend it for publication.

Major comment; They compared the risk of cirrhosis and HCC between control (260 HCV-negative samples obtained from donors of the HCPA blood bank) group and fibrotic (F1-3)/cirrhotic (F4)/HCC group and concluded that T allele from IFNL4 rs12979860 polymorphism is associated with the development of cirrhosis and HCC. Since Hepatitis C is an infectious disease, HCV infection does not depend on genetic factors (SNPs), but the status of blood transfusion or drug use. The authors need to compare the risks between non-fibrotic (F0) group infected with HCV (or asymptomatic HCV carrier (persistent normal ALT: PNALT)) vs F1-3/F4/HCC groups. At least, it seemed like that there were no significant differences between F1-3 vs F4 or F4 vs HCC (Table 2 and 3). How about F1-3 vs HCC?
Answer: *We thank the comments and suggestions, which have contributed to the improvement of the manuscript. Similar to F1-F3 vs F4 and F4 vs HCC (data shown in Tables 2 and 3), we did no observed difference between F1-F3 vs HCC (data not shown). Regarding the non-fibrotic (F0) HCV-infected group, certainly the analysis of this group would make the study more comprehensive and we included the lack of this group as a limitation of the study in the Discussion. However, it is important to highlight that there are several case-control studies in literature that analyzed the association of gene polymorphisms with HCC and they also used healthy individuals as a control group (e.g, see Qin et al. The influence of interleukin 28B polymorphisms on the risk of hepatocellular carcinoma among patients with HBV or HCV infection: An updated meta-analysis. Medicine (Baltimore). 2019;98(38):e17275. doi: 10.1097/MD.0000000000017275).*

Minor comment; Ref. 13 is incorrect.
Answer: *The reference was corrected.*