Dear editor:

I would like to thank you and the reviewers for the positive and constructive comments and suggestions. We have substantially revised our manuscript according to those comments and suggestions.

In the process of modification, we found that the relationship between rs1059519 polymorphism and plasma content of MIC-1 was statistically significant when combined CHC group and control group. Therefore, some results and conclusions were modified. I promise the data were true and effective.

Thank you very much!

Best regards,

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Enclosure:

The following are the answers to academic editor and reviewer(s).

Reviewer #1 (Comments for the Author)

Thank you for your comments and suggestions. We have learned much from them.

1-The title: it is not allowed to use abbreviation in the title {macrophage inhibitory factor-1 (MIC-1)} also the term correlation is not accurate better used Associations or variations.

Answer:

We have changed the title “Correlation between MIC-1 Gene Polymorphism and Chronic Hepatitis C Virus Infection” to “The associations of content and gene polymorphism of macrophage inhibitory factor-1 (MIC-1) and Chronic Hepatitis C Virus Infection”.

2- Methods: The major defect in this study was the design of the groups; In the design of the study as regard patients with HCV the use of normal uninfected control is not recommended The problem of using healthy control subject is that about 80% of these subjects when exposed for the first time to HCV will develop chronicity while the rest showed spontaneous viral clearance (SVC). To overcome this inconstancy, subjects with Spontaneous viral clearance (SVC) should be compared to subjects with persistence of infection. so the study must include the following 3 groups: 1-chronic HCV patients:(cases with positive polymerase chain reaction [PCR] HCV >6 months), 2-controlgroup cases (cases with negative PCR HCV), 3-spontaneous virus clearance: group cases, who demonstrated HCV antibody positive but HCV-RNA negative in two successive samples at least 6 months apart. You can refer to this publication for better guidance for design of the study (The association of single nucleotide polymorphisms of Toll-like receptor 3, Toll-like receptor 7 and Toll-like receptor 8 genes with the susceptibility to HCV infection', British journal of biomedical science, 75: 175-81.

Answer:

At the beginning of the experimental design, we also considered to include the SVC group, but in the process of sample collection, we found that the number of this group was far less than that of the other two groups. In China, the natural clearance rate of HCV was less than 20%, and the number of natural scavengers collected in this study was too small to meet the

statistical requirements, so we had to exclude this group in this study. To be sure, the absence of natural population clearance as a control makes the study's conclusions somewhat controversial, we will quote the literature of "The Association of single nucleotide polymorphisms of Toll-like receptor 3, Toll-like receptor 7 and Toll-like receptor 8 genes with The susceptibility to HCV Infection" and discussed this weakness in the discussion.

3-Hetrozygosity and polymorphic information content (PIC)were not calculated in all studied groups to determine whether the single nucleotide polymorphism was polymorphic enough for statistical analysis in the Chinese population.

Answer：

After analysis by the website of CHWE (https://www.genecalculators.net/pq-chwe-polypicker.html), Heterozygosity and PIC was 0.4574 and 0.3528 in controls; 0.4916 and 0.3707 in CHC of rs1059369. While 0.4784 and 0.364 in controls; 0.396 and 0.3176 in CHC of rs1059519. These results showed both SNPs were polymorphic enough for statistical analysis in the Chinese population.

5- The Bonferroni-corrected P value (Pc) is an adjustment made to P values when several dependent or independent statistical tests must be performed simultaneously on a single dataset.

Answer：

We added results of Bonferroni-corrected P values of comparison of gene frequencies. P value (Pc) <0.05 was statistically significant. After corrected, the genotype difference was not

statistically significant. However, the allele frequency distribution at rs1059519 locus differed between the two group still have significant difference after Bonferroni-corrected (P = 0.004*2 = 0.008 < 0.05). Bonferroni Correction was also used in multiple comparisons of genotypes and expression of MIC-1 in Plasm, and the results still make sense.

Reviewer #2 (Comments for the Author)

Thank you for your comments and suggestions. We have learned much from them.

1- As a remark, attention should be paid to the title of the study. The most significant results were obtained for the correlation of MIC-1 content with a number of parameters characterizing the activity of inflammation, the severity of fibrosis, and the amount of HCV RNA. In the abstract, in the foreground in the research results, the authors placed precisely the correlations of the MIC-1 content. Information on the relationship of the MIC-1 gene polymorphism with other factors is placed in the background by the authors. In this regard, it is not clear why the title of the article deals only with the MIC-1 gene polymorphism. The reviewer believes that it is advisable to bring the title of the article and its main results into conformity.

Answer:

We have changed the title "Correlation between MIC-1 Gene Polymorphism and Chronic Hepatitis C Virus Infection" to "The associations of content and gene polymorphism of macrophage inhibitory factor-1 (MIC-1) with Chronic Hepatitis C Virus Infection".

2-The section "Research Results" contains many numbers and is difficult to understand. It makes sense for the authors to reformat the text of the research results to facilitate understanding of the data obtained.

Answer:

We have reformatted the text of the research results, Verbose content has been removed to make the result more logical and understandable. What's more, we rewrote the relationship between genotype and plasma content of MIC-1. The details have been modified in the manuscripts.

3-In the discussion, it makes sense to pay attention to why, in the future, it is necessary to study the polymorphism of the MIC-1 gene, and not be limited to determining its content.

Answer:

We have added the discussion about the sense of study the polymorphism of the MIC-gene. We have added a discussion on the significance of studying MIC-gene polymorphisms in the future. As follows:

MIC-1 as a protein that is induced to be expressed under various stresses, MIC-1 differs significantly between different individuals and at different stages of disease progression, requiring multiple measurements and dynamic observation to be of certain clinical value. Moreover, the specific mechanism of MIC-1 in HCV infection and the factors determining MIC level are still unclear. These problems

may be explained at the molecular level through the study of MIC-1 polymorphism. Besides, research for genetic susceptibility contributes to screen vulnerable populations and improve prevention measures.

All changes in the revised manuscript are red-colored text.

Also, we added new authors according to her contributions to the guidance and revision of the article. The authors declare that there are no financial or other relationships that might lead to a conflict of interest of the present article. All authors have reviewed the final version of the manuscript and approved it for publication.

Thank you very much for your guidance and support! We look forward to your decision.

Sincerely yours.

Xunjun Yang, PhD.