Response to reviewer

- **Incompleteness in two of the references. The journal names, issues, and page numbers of references 9 and 12 are missing, please complete them.**

Thank you very much for your comment. We would like to inform you that we have updated the references as advised.

- **English revision is needed.**

Thank you very much for your suggestion. The article has been revised for language editing by the senior author who is a native speaker (British citizen) with 15 years of clinical and academic practice in London, UK.

- **The quality of the article would increase if additions could be made regarding patients with chronic hepatitis B or hepatitis C, concurrent with MAFLD.**

Thank you very much for your insightful comment. On this topic we have added a new section in order to increase the quality of the article. Specifically, as highlighted in the manuscript, we added the following section.

"TRIPLE NEXUS: CHRONIC HEPATITIS B AND C, MAFLD AND COVID-19

The triple association of chronic viral hepatitis B (CHB) and chronic viral hepatitis C (CHC), MAFLD, and COVID-19 introduces a complex interplay. Notably, there is a significant gap in the existing literature specifically addressing this triple association. The influence of pre-existing liver conditions on COVID-19-associated liver injury remains a topic of debate. Despite studies revealing the severity of COVID-19 in patients with chronic liver diseases (CLD), with MAFLD and alcoholic liver disease identified as independent risk factors for severe COVID-19, the relationship between COVID-19 and CLD caused by HCV and HBV has received less attention[5,18,39]. According to Elemam et al., there are conflicting results regarding the impact of viral hepatitis on COVID-19 outcomes[12]. Some studies suggest that individuals with viral hepatitis experienced more severe liver dysfunction due to pre-existing immune dysregulation, while other studies indicated that individuals with pre-existing liver disease or hepatitis B infection did not show more severe symptoms of COVID-19[12,18,39]. Postulated reasons for these discrepancies in literature, have been suggested by Lin et al. and include small sample size of patients with co-infection of HBV and COVID, heterogeneity of included patients and lack of thorough understanding of the complexity of enhanced liver injury caused by inflammatory response[40]. This conflicting evidence underscores the need for further research to elucidate the specific relationship between viral hepatitis and COVID-19-related liver injury. However, liver cirrhosis stands out as a critical factor contributing to severe outcomes in COVID-19, with CHB and CHC playing major roles in its development[5,12,38]. The World Gastroenterology Organisation underscores the need for

more data to assess the risk of adverse outcomes in individuals with CHB or CHC without cirrhosis exposed to COVID-19[38]. While uncertainties persist about the susceptibility of patients with CHB or CHC to SARS-CoV-2-induced liver damage, those with advanced fibrosis or cirrhosis face a higher risk of severe outcomes, necessitating vigilant monitoring and tailored interventions[38].

The potential mechanisms underlying the association between viral hepatitis B and C with COVID-19 require thorough investigation and seem to be similar with those observed in the interplay between MAFLD and COVID-19. The enhanced liver injury induced by SARS-CoV-2 and HBV co-infection has been characterized as the hepatocyte type rather than the cholangiocyte type, emphasizing the primary involvement of hepatocytes in the pathogenesis[40]. One key aspect of this interaction is the inflammatory response and cytokine 'storm'. Inflammatory factors, including abnormal lactate dehydrogenase, D-dimer, and IL-6 production, may contribute significantly to liver injury following SARS-CoV-2 coinfection[40]. Thrombocytopenia, more pronounced in COVID-19 cases with HBV co-infection, indicates a potential role of inflammatory factors in liver injury[40,41]. Furthermore, DILI poses a significant concern[42]. Corticosteroids, commonly administered in severe COVID-19 cases, introduce a dual risk by not only suppressing the immune response but also activating HBV replication[42]. This activation occurs through the suppression of cytotoxic T cell function and direct stimulation of HBV genomic sequences[42]. Similarly, tocilizumab raises concerns as it can cause liver injury and induce reactivation of hepatotropic viruses[42].

Notably, while some studies indicate that related inflammatory factors contribute to abnormal liver function, the exact mechanisms of enhanced liver injury caused by the inflammatory response need further elucidation[40]. Some mechanistic insights revealed stable expression levels of HBV-associated markers during SARS-CoV-2 infection, suggesting that chronic HBV infection alone may not significantly increase the severity of COVID-19[43]. Nevertheless, caution is warranted, as reactivation of hepatitis B has been observed, particularly when corticosteroids are employed, emphasizing the need for continuous antiviral therapy to manage and prevent such occurrences[42]. Similarly, for individuals co-infected with HCV and SARS-CoV-2, the continuation of antiviral therapy remains crucial[42]. Both the American Association for the Study of Liver Disease and the European Association for the Study of the Liver strongly recommend ongoing antiviral therapy in individuals diagnosed with COVID-19[42]. The parallel complexity seen in the MAFLD-COVID association prompts a closer examination of each potential mechanism to unveil common threads linking the diverse conditions of CHB/CHC and MAFLD to COVID-19 progression.

It is crucial to highlight that both CHB and CHC are frequently associated with hepatic steatosis, forming a connection with obesity, dyslipidemia and insulin resistance[44]. This shared link to metabolic factors is compounded by MAFLD as a common comorbidity, further emphasizing the interconnected nature of these conditions. This interplay highlights the need for comprehensive research to elucidate the complex dynamics of the triple association between CHB and CHC, MAFLD and COVID-19. While existing studies shed light on the impact of individual components, the triple association remains a relatively unexplored area in medical literature. Future investigations should aim to unravel the mechanisms underlying the interactions between these three entities. Understanding the synergistic effects could provide valuable insights into tailored interventions and preventive strategies."