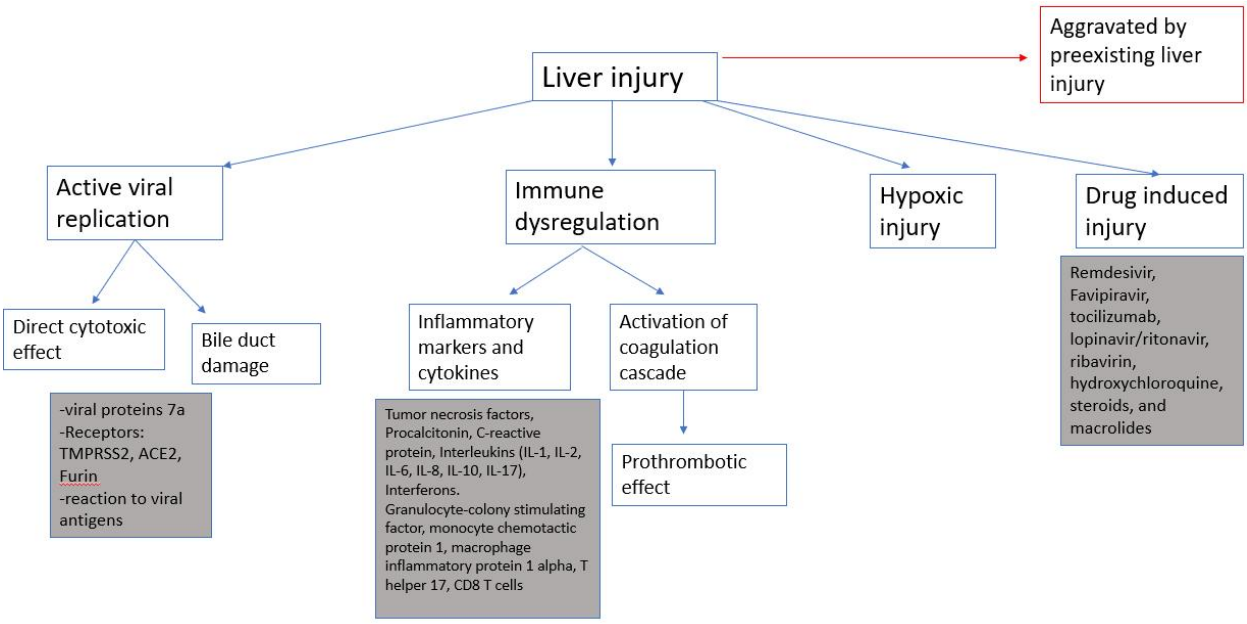
We would like to thank the Editor and the Reviewers for their valuable comments that made the manuscript a better version.

Reviewer #1:
The study design is not clear, whether it's a systematic review ± meta-analysis or a narrative review. Therefore, the study cannot be accepted in its current form.

Thank you. The study is a narrative review. This is added in the Methods section "This narrative review was conducted".

Many changes were done in all the sections of the manuscript to make it better for your kind review.

Reviewer #2:
1. Diagram on Pathogenesis must be included in manuscript
Thank you. Figure 2 will be replaced to show a diagram as requested.



2. Does liver injury due to covid -19 was secondry to Respiartory distress or it can primarily be involved also?
As added in pathophysiology section, there are many factors that can contribute to liver injury in Covid-19 patients.

Also a paragraph will be added in section: Liver injury due to Covid-19
“The incidence rate of liver injuries in patients with Covid-19 widely varies. Abnormal liver function was defined as an elevation of any parameter (ALT, AST, Alkaline phosphatase ALP, Gamma-glutamyl transferase GGT, and total bilirubin). Liver injury is defined as mild (<2 times upper level of normal), moderate (2-5 times upper level of normal), and severe (>5 times upper level of normal) [16,17]. Studies found that liver injury in patients with SARS-Cov-2 infection is between 14%-53% [16,17]. However, even asymptomatic infected patients with Covid-19 have the same viral load, and consequently, liver damage can happen with elevation of liver enzymes, but to a lesser extend than the severe symptomatic patients [59]. In a retrospective cohort study conducted by Phipps et al. on 2273 Covid-19 patients in the USA, 45% had mild, 21% had moderate, and 6.4% had a severe liver injury [18].”

3. conclusion may be rewritten with suggestion of what are possibilty and tools for further research
The conclusion will be changed to:
“Despite the lack of evidence to elucidate the mechanisms of liver injury induced by Covid-19 infection, this review provides a comprehensive approach to several theories investigated. Further research is needed to clarify the factors in cause and determine factors that might exacerbate liver injury in Covid-19 infected patients. Meticulous attention should be focused on the liver function of patients infected with Covid-19, especially during hospitalization. It is not clear yet on how to treat liver damage in patients with Covid-19 infection. There are no clear guidelines for proper treatment of liver injury in Covid-19 patients. Comparative studies might be needed for better evidence..”

4. Liver injury assocaition with Antivirals used during covid (do they have a role)?
Thank you. Antiviral drugs have a major role. The section about drugs was moved to the pathophysiology, and a paragraph about this was added.

“Antiviral treatments for Covid-19 are prescribed to approximately 50% of critical patients, and these drugs cause hepatotoxicity. Evidence suggests that the use of lopinavir or ritonavir can contribute to liver injury in patients with Covid-19, as those with liver injury were found to have higher usage rates of these medications compared with those with normal livers [33]. Patients treated with lopinavir/ritonavir show commonly liver damage, and liver injury in this group may be up to 3.58 times greater than patients who did not receive treatment [50]. Liver damage is increased by 12.1% after drug treatment [50]. Ribavirin-induced hemolysis could exacerbate tissue hypoxia and further liver ischemia and injury. The National Health Commission of the People’s Republic of China had to stipulate that long-term treatment with these drugs, especially in high doses, can lead to hepatotoxicity [26]. Remdesivir was approved in May 2020 for the treatment of COVID-19. Remdesivir is metabolized by Cytochromes P450. The use of remdesivir reduces the time to recovery of hospitalized COVID-19 patients [44]. In COVID-19 patients treated with remdesivir, reversible elevations of ALT and AST were found with 6% of patients having a marked increase in AST and ALT while only 2% having a life-threatening situation [44]. “

Reviewer #3:

1. Many causal relationships are poor in many places in this article. For example, the second paragraph of the Pathophysiology section, "COVID-19 might contribute to liver damage through active viral replication in liver cells and through the angiotensin-converting enzyme 2 (ACE 2) receptor", does not seem to draw a conclusion that: " These conflicting observations lead us to find other contributing factors to liver injury, such as the presence of co-receptors or increased ACE-2 presentation on liver cell surfaces."

Thank you, the whole paragraph "Pathophysiology" will be corrected to make it more clear, more information is added and the above sentence is rephrased.

"A possible reason for this is that other contributing factors are in cause and can raise the serum aminotransferase levels in liver injury. As example, a study discusses the possibility of the presence of co-receptors on the liver or an increase of the ACE-2 receptors on liver cell surfaces"

2. The drawing is rough, the arrow position is wrong in Figure 1, there is no arrow pointing to the liver in the vessels thrombosis in Figure 2, and the meaning of expression is unclear.

Figures were adjusted and uploaded in a powerpoint document.

Figure 2 was changed to a diagram as suggested by Reviewer 2.

3. The epidemiological data of liver damage in patients with COVID-19 should be analyzed in more detail. For example, among patients with COVID-19, which groups of people in different ages are more likely to have liver damage? Are there any differences in the incidence rate of liver damage among COVID-19 subtypes?

Thank you. A paragraph about the incidence of liver injury in symptomatic and asymptomatic Covid-19 patients was added. Also, we discussed the incidence of liver damage in patients with Delta variant compared to Omicron variant.

"The incidence rate of liver injuries in patients with Covid-19 widely varies. Abnormal liver function was defined as an elevation of any parameter (ALT, AST, Alkaline phosphatase ALP, Gamma-glutamyl transferase GGT, and total bilirubin). Liver injury is defined as mild (<2 times upper level of normal), moderate (2-5 times upper level of normal), and severe (>5 times upper level of normal) [16,17]. Studies found that liver injury in patients with SARS-Cov-2 infection is between 14%-53% [16,17]. However, even asymptomatic infected patients with Covid-19 have the same viral load, and consequently, liver damage can happen with elevation of liver enzymes, but to a lesser extend than the severe symptomatic patients [59]. In a retrospective cohort study conducted by Phipps et al. on 2273 Covid-19 patients in the USA, 45% had mild, 21% had moderate, and 6.4% had a severe liver injury [18]. The severity of liver injury was significantly associated with the severity of the Covid-19 disease [19]. Moderate and severe liver injury was found to be more common in patients who required admission to the Intensive Care Unit [18]. Liver injury is more common in patients with high viral load. Thus, patients infected with Delta

mutations and relatively large viral loads, the risk of initial liver injury may be increased [19]. A study by Deng et al. compared liver injury in patients with Delta and Omicron variant-infected patients. The extend of inflammation and liver injury was similar among the two groups. However, male gender and high peak viral load were independent factors associated with liver injury [20]. A study conducted in young children with COVID-19 and liver injury showed that these patients have a milder course with fewer radiological and laboratory changes compared to adults [21]."

4. In this paper, the mechanism of COVID-19 causing liver injury is described extensively but not in depth (such as the direct injury of liver cells by viruses, and the immune mechanism also plays an important role in liver injury, which can be described in depth).

Thank you. The pathophysiology paragraph was edited. Each mechanism was described in depth. The below information was added:

"Three receptors are the most commonly involved in this: Transmembrane serine protease 2 TMPRSS2, Furin, and Angiotensin converting enzyme 2 ACE2 proteins. ACE2 receptors are present abundantly in the liver and the gastrointestinal mucosa. The virus binds to ACE2 receptors, abundantly present in the liver cells and GI mucosa [26]. The Covid-19 was detected inside the cytoplasm of the hepatocytes, leading to dilatation of the endoplasmic reticulum system, mitochondrial swelling, and cell membrane impairment."

"Immune dysregulation caused by Covid-19 plays a role in liver damage. Covid-19 leads to an inflammation in the lungs with elevation in serum inflammatory markers and production of pro-inflammatory cytokines, such as tumor necrosis factors, procalcitonin, C-reactive protein (CRP) and interleukins (IL-1, IL-2, IL-6, IL-8, IL-10, IL-17). Interferons are released, initiating a cascade that induces the expression of genes responsible for antiviral activity and viral replication disruption [41]. However, the consequence of rapid viral proliferation is a generalized inflammatory reaction with elevated inflammatory markers [26,42,43]. This can indirectly contribute to liver damage [26,42,43]. Research conducted on severe cases of COVID-19 have demonstrated the involvement of tumor necrosis factor-α, granulocyte-colony stimulating factor, interferon-inducible protein-10, monocyte chemotactic protein 1, and macrophage inflammatory protein 1 alpha, T helper 17, CD8 T cells, and IL-2, IL-6, IL-7, IL-10 in the immune response [44]."

"Hypoxemia can also be a cause of liver injury. Cases of severe COVID-19 generally ends in sepsis state particularly when patients have gut microbiota imbalance and pre-existing liver disease [44]. Hepatic damage post sepsis is usually associated with shock, cholestasis, drug toxicity, and inflammation [44].
Hypoxemia is one cause of liver injury with bad prognosis [44]. Recent data shows that hypoxic liver injury in Covid-19 patients is related to metabolic acidosis, calcium overloading and abnormality in the mitochondrial permeability transition pore protein [44]."

“Antiviral treatments for Covid-19 are prescribed to approximately 50% of critical patients, and these drugs cause hepatotoxicity. Evidence suggests that the use of lopinavir or ritonavir can contribute to liver injury in patients with Covid-19, as those with liver injury were found to have higher usage rates of these medications compared with those with normal livers [33]. Patients treated with lopinavir/ritonavir show commonly liver damage, and liver injury in this group may be up to 3.58 times greater than patients who did not receive treatment [50]. Liver damage is increased by 12.1% after drug treatment [50].

Remdesivir was approved in May 2020 for the treatment of COVID-19. Remdesivir is metabolized by Cytochromes P450. The use of remdesivir reduces the time to recovery of hospitalized COVID-19 patients [44]. In COVID-19 patients treated with remdesivir, reversible elevations of ALT and AST were found with 6% of patients having a marked increase in AST and ALT while only 2% having a life-threatening situation [44].”

Secondly, between COVID-19 and various liver diseases, the author mainly describes the clinical symptoms (such as elevated transaminase, elevated bilirubin), but the corresponding mechanism is reviewed less.
More information was added in the section: “Covid-19 in patients with chronic liver disease”.

“Patients with NAFLD had a higher probability of disease progression and higher risk of elevating liver tests upon admission to discharge [47] “
“Mushtak et al studied 589 symptomatic Covid-19 patients with who were hospitalized in the state of Qatar. They found that NAFLD is an independent predictor of mild to moderate liver injury while it was not a predictor of mortality, disease severity or disease progression [57].”

“Cirrhosis have been associated with inflammation and dysregulation of the immune system. This dysregulation may explain the increased severity and mortality due to Covid-19.”
“ In patients with ALD, the superimposed cytokine storm caused by Covid-19 could aggravate the increased inflammatory process, resulting in worse outcomes [39].”

5. The review is rich in content, but not deep enough, the focus is not prominent enough, and the key scientific issues are not well refined.
Thank you. Many changes were done through the manuscript, in track changes. The pathophysiology section was more elaborated, information about liver injury were added. The conclusion was changed. New references were added.

6. The full name of English abbreviations should be written when they first appear, for example, AASLD and HCC are not indicated. The upper and lower case of words are inconsistentt, such as COVID and Covid.
Thank you. This was corrected in the text.