Dear Editors and Reviewers,

Thank you very much for giving us an opportunity to revise our manuscript. We are very grateful for the editors' and reviewers' positive and constructive comments and suggestions. All amendments are highlighted in red in the revised manuscript. We want to re-submit it for consideration and hope that the modification is acceptable. I look forward to hearing from you soon.

Once again, we would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Best Wishes

Ruobing Qi and Zhenghao Wu

A list of responses and changes to the editor and reviewers are as follows：

1. Replies to Reviewer 1

Comment 1:

The MS need the suitable table or figure or any conclusive summary that convey the impact of MS.

Response：

Thanks for your rigorous consideration. In order to make the mini review clearer, we have made a corresponding overview summary of the content of each paragraph, and the arguments of each paragraph have been charted as follows(**table 1)**:

	Conclusion of each part
Mechanism	SARS-CoV-2 can bind to the host angiotensin-converting enzyme 2 (ACE2) receptor, allowing the virus to enter cells and actively replicate in the liver. And severe disease outcomes depend on the high affinity of the virus to ACE2. Besides, SARS-CoV-2 infection can lead to severe host hyper immunity in the lungs, triggering a life-threatening cytokine storm[21,22], a systemic inflammatory response syndrome driven by viral infection. This leads to tissue damage and multiple organ damage or failure. In addition, symptoms due to COVID-19 complications are also underlying

	pathological mechanisms of extensive liver injury.
Diagnosis	Liver biochemical abnormalities are common in COVID-19-related CLD patients. The main manifestations of patients with COVID-19-related CLDs are moderately elevated serum transaminase activity and elevated LDH levels. And the severity of CLD during the COVID-19 course can be effectively judged by detecting serum transaminase, LDH, bilirubin levels, and albumin concentrations.
Damage	Invasion of SARS-CoV-2 may lead to significant systemic disease, some can even develop severe lung disease, leading to respiratory compromise, which in turn may progress to multiple organ failure, coagulopathy, and death. Typically, COVID-19 patients are more vulnerable and susceptible to underlying metabolic diseases. Besides, SARS-CoV-2 can cause CLD in four aspects, including direct cytopathies, immune-mediated, hypoxia/ischemia and microvascular thrombosis.
Treatment	Immunosuppression therapy is meaningful for both COVID-19 and

	CLD. Therefore, immunosuppressive drugs should be evaluated during the co-occurrence of both disorders. Common immunosuppressive drugs include calcineurin inhibitors (CNIs) and mTOR inhibitors. Medication side effects need to be considered during treatment, including increasing susceptibility to SARS-CoV-2 infection and secondary bacterial or fungal infection and prolonged viral clearance. In addition, currently prescribed drugs for COVID-19 are all metabolized in the liver, and these antiviral drugs may lead to abnormal liver function. Therefore, it is necessary to balance the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19, and minimize the use and dosage of immunosuppressants to reduce the impact of liver damag.

2. Replies to Reviewer 2

Comment 1:

Data from the following studies would adequately serve such purpose: PMID: 34202689, PMID: 17151316, http://dx.doi.org/10.4236/jdm.2011.13006, PMID:

17151319, PMID: 15362483, https://doi.org/10.4236/ajps.2018.96091, https://thescipub.com/abstract/ajptsp.2006.21.25, PMID: 32460808.

Response:

We gratefully appreciate your valuable suggestion. To make the article more convincing, we have added these citations to the article with more details in reference part([2,6,11,12,13,16,17,18]).

Comment 2:

One major concern that should be addressed: What time range of publication did this review article cover, what keywords did the search for literature include, what were the inclusion criteria, how many studies did the search find and how many were primary research vs review articles, of those, how many were selected for evaluation in this study, and finally what criteria were used for selecting the articles that were reviewed (was it the subject of the study, its novelty or both).

Response:

Thanks for your valuable comment. We searched for studies reporting COVID-19 outcomes among CLD patients in databases including Medline and EMBASE from inception of the pandemic until August 2022. We mainly conduct studies researching from the following two aspects:

Eligibility criteria

We included studies with any of the following study designs: prospective or retrospective cohort, case control, and cross-sectional. Only published full-text studies were included; conference abstracts, unpublished data, and gray literature were excluded. Studies conducted among COVID-19 patients were included; studies among COVID-19 patients with comorbidities other than CLD were excluded.

Studies reporting the mechanism of COVID-19, diagnostic indicators in patients with COVID-19 and chronic liver disease, possible diseases in

patients with COVID-19, and treatments for patients with chronic liver disease and COVID-19 were included. The CLD conditions most commonly found in COVID-19 patients included in our review were cirrhosis, viral hepatitis, NAFLD, and MAFLD.

Search strategy

We conducted a comprehensive, systematic, and extensive search in the electronic databases Medline and EMBASE. We selected the terms required for the search during the protocol stage. We used both the Title/Abstract and medical subject headings (MeSH) while searching these databases. The keywords and their synonyms were searched using appropriate truncations, wildcards, and proximity searching. The terms used to search were "liver disease"/exp OR "hepatic disease":ti,ab OR "hepatic disorder":ti,ab OR "hepatopathy":ti,ab OR "liver cell disease":ti,ab OR "liver disease":ti,ab OR "liver diseases":ti,ab OR "liver disorder":ti,ab OR "liver illness":ti,ab) AND "coronavirus disease 2019"/exp OR "SARS-CoV-2". We also searched for crucial concepts using corresponding subject headings in each database. The last search was carried out by combining the individual search results using appropriate Boolean operators ("OR" and "AND"). The search was narrowed down using the available filters on the type of studies. We restricted the search from the inception of the pandemic to August 2022 and published in English only. Bibliographies of the retrieved articles were also hand-searched to identify any themes missed during the database search.

Comment 3:

Proofreading is needed. • The list of references needs to be diversified and more inclusive. IF considered, the following studies would help addressing that concern and provide more insights into molecular bases of anti-inflammatory mechanisms of different biomolecules: PMID: 34662244, PMID: 35211395, PMID: 35517830, PMID: 35740022, PMID: 35177980, PMID: 33255507, https://doi.org/10.1039/D0NA00958J,

10.1097/HM9.0000000000000008,
https://doi.org/10.1186/s41936-020-00177-9,
https://doi.org/10.1186/s41936-021-00251-w.

Response:

Thanks for your valuable suggestion. We have checked the grammar and sentence formation throughout the article with professional English editors' assistance. The article has been proofreaded. Besides, to make the list of references be diversified and more inclusive, we have removed some of the citations and added new ones, see the citation list for more details([19,20,25,27,32,36,37,39,40,46]).

3. Replies to Reviewer 3

Comment 1:

What are the relationship between the immunosuppressants drugs and antiviral process? Can you explain more bout that in relation to viral infection?

Response:

We gratefully appreciate your valuable suggestion. Therefore, we revised the manuscript and explained the process of viral infection and the relationship between the immunosuppressants drugs and antiviral process as follows (Page 3-4):

Viral infection

Successful coronavirus infection requires direct interaction between the coronavirus spike protein and the host cell surface recepto. In addition to their protein receptors, coronavirus spikes recognize a broad array of cell surface molecules, which serve to facilitate virus attachment or entry. Similar to SARS-CoV and human coronavirus NL63 (HCoV-NL63), the SARS-CoV-2 spike protein recognizes angiotensin-converting enzyme 2(ACE2) as the cell receptor for entry.

SARS-CoV-2 can bind to the host angiotensin-converting enzyme 2 (ACE2) receptor, allowing the virus to enter cells and actively replicate in the liver. And ACE2 expresses in multiple organs, such as the lung, gastrointestinal tract, and liver. In addition to recognition of cell surface molecules by the spike protein for attachment and entry, proteolytic activation of the coronavirus spike protein at the S1/S2 and S2′ sites is essential for membrane fusion and infection of host cells. Cleavage of spike begins during virus egress along the secretory pathways by pro-protein convertases such as furin. Additional spike cleavage occurs during virus entry and is mediated by host proteases including transmembrane protease serine 2 (TMPRSS2) and cathepsin L, which are the representative protease for the plasma membrane entry and endosomal entry pathway, respectively.

The relationship between the immunosuppressants drugs and antiviral process:

Immunosuppressants have antiviral activity against coronaviruses. The antiviral effects of different types of immunosuppressants are as follows:

(1) Glucocorticoid

Glucocorticoids (GCs) inhibit different aspects of inflammation by stimulating or inhibiting the expressi12on of gene transcription, mediators, receptors, adherent molecules, and cytokines. While GCs can promote viral replication, they are effective anti-inflammatory drugs that can help fight the cytokine storm of disease.

(2) Calcineurin inhibitor

Cyclosporine or tacrolimus is a potent inhibitor of lymphocyte calcineurin activity. They are usually used in combination with MMF or everolimus to lower plasma levels and avoid adverse effects. Cyclosporine A binds to the intracellular receptor cyclosporine to form

an active complex that inhibits the phosphatase activity of calcineurin phosphatase. Calcineurin dephosphorylation can activate the cytoplasmic component of T cell nuclear factors so it can enter the nucleus and activate genes involved in IL-2 synthesis. Therefore, cyclosporine A inhibits T cell proliferation by inhibiting calcineurin and by preventing cloning expansion of helper T cells and cytotoxic T cells.

(3) Micofenolato mofetilo

MMF is a prodrug that is converted into mycophenolic acid (MPA) in the body. The metabolism of MPA is mainly involved in the glucuronylation of urisidase 5'-diphosphate glucuronyltransferase. MPA is a reversible, non-competitive inhibitor of inosinate-5'-monophosphate dehydrogenase (IMPDH). It inhibits the proliferation of T and B lymphocytes and the production of immunoglobulins by depleting the guanosine and deoxyguanosine libraries in lymphocytes. MP A is also able to inhibit in vitro and in vivo hcv replication by increasing interferon gene expression and guanosine consumption.

(4) mTOR inhibitors

mTOR inhibitors need to function by forming a complex with immune cells. They bind to FKBP-12 and block the signaling of IL-2 receptors by inhibiting the proliferation of T cells and B37 cells.

Comment 2:

Do you think that the issue with metabolism of drugs is in liver? Can we replace them with drugs have different metabolism ways?

Response:

We gratefully appreciate your rigorous consideration and revise the manuscript as follows (page 3-4). Current prescription drugs to treat COVID-19(e.g., oseltamivir, lopinavir/ritonavir, and chloroquine) are

all metabolized in the liver. We have not yet found drugs have different metabolism ways to replace the classical therapeutic drugs. Although there is currently no recognized effective antiviral drug for COVID-19, nearly half of the critically ill patients were prescribed antiviral drugs such as oseltamivir, abidol, lopinavir, and ritonavir. These antiviral drugs may cause abnormal liver function. In particular, patients with CLD, such as hepatitis B or C, may have elevated aminotransferase levels before treatment, which may increase the risk of drug-induced liver injury (DILI). Therefore, attention should be paid to abnormal liver test indicators during the treatment process and the management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19 must be balanced to reduce DILI.

Comment 3:

What about the dosages of these drugs? can we manage the dosages according to chronic diseases and hepatic diseases?

Response:

Thanks for your valuable suggestion. After searching for some relevant studies, we found some descriptions and revised the manuscript as follows (page 3-4). Usually we regulate the dosages of immunosuppressants according to their biochemical indicators (serum aminotransferase, lactate dehydrogenase, bilirubin level and albumin concentration) and blood routine (leukocytes, platelets, red blood cells).

GC

GC dosage is usually kept low and high doses of GC cannot be applied to the treatment of covid-19. In most cases, GC dosage is 20 to 60 mg per day depending on the patient's various indicators.

Calcineurin inhibitor

For patients with mild covid-19, it is generally recommended not to

modify anticalcineurin drugs unless a highly disturbing antiviral drug such as tacrolimus is used. In this case, the dose of tacrolimus can be 0.5 mg every 3-5 days. Anticalcineurin levels need to be monitored to regulate dosage of calcineurin inhibitor and avoid adverse effects of their interaction with other drugs.

Micofenolato mofetilo

Studies have shown that MMF should be removed if a patient with chronic liver disease develops severe SARS-CoV-2 infection at any stage of the disease. Regardless of its immunosuppressive effects, it can lead to leukopenia, lymphopenia, thrombocytopenia, and bone marrow hypoplasia. And these complications may affect the immune system.

mTOR

In the absence of specific indications of medication, the dosage needs to be regulated by assessing the pharmacological interaction of mTOR with other agents and associated leukocytosis and lymphopenia.

Comment 4:

Do you have any special recommendation with your conclusions?

Response：

We gratefully appreciate your valuable suggestion. The special recommendation with our conclusions are as follows: The management of immunosuppressive therapy and drug interactions in patients with CLD infected with COVID-19 must be balanced. In the treatment of new crown pneumonia, the effects of drugs on liver toxicity, steatosis, necrotic inflammation, fibrosis and biometabolism should be comprehensively considered, and abnormalities in liver detection indicators (biochemical indicators and blood count) should be noted. This helps to avoid severe DILI, while exerting an adequate immune response and antiviral effects, and enabling the rational application of immunosuppressants.

4. Replies to Re-reviewer

Comment: none

Response：

Thanks for your comments.