Viral Hepatitis and COVID-19: A Systematic Review of the Current Evidence

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ABSTRACT

Background:
Corona Virus Disease 2019 (COVID-19) is a newly recognized illness that is spreading rapidly around the world and causes many disabilities and deaths. Some diseases, for instance, viral hepatitis, are continuously suggested as a risk factor that contributes to the severity and mortality of COVID-19. However, to date, there is no comprehensive study aiming to explain the exact relationship between viral hepatitis and COVID-19. Thus, in this study, we aimed to summarize the evidence about viral hepatitis and COVID-19 outbreak through a systematic review approach.

Materials and Methods:
A literature review was implemented in databases of Scopus, PubMed, Elsevier, Science Direct, Cochrane Library, Google Scholar, and Web of Science. Observational reviews, case-report, and case-series studies that assessed hepatitis in COVID-19 patients were included. Assessment, study selection, and data extraction was made following PRISMA checklist and, the extracted information was reported by Garrard's table.

Results:
Some studies showed that there were liver symptoms such as increasing in liver enzymes and functions. The prevalence of hepatitis B was between 0.7% to 6.4%, and the prevalence of hepatitis C was 1.9%. These patients have prolonged hospitalization, poor prognosis, severe symptoms, in addition to the mortality rate among patients with hepatitis and COVID-19 at the same time is higher than others. In addition, it is suggested that patients with hepatitis will be treated with antivirals, especially lopinavir/ritonavir that was useful for the treatment of patients with (severe acute respiratory syndrome coronavirus 1) SARS-CoV1.

Conclusion:
The results showed that hepatitis should be considered as a risk factor for the severity of symptoms of COVID-19. And the adverse effect of COVID-19 in patients with hepatitis is more than others. So, the use of antiviral drugs in patients with hepatitis and COVID-19 can prevent the reactivation of hepatitis and reduce the severity of COVID-19.

Keywords: Viral hepatitis, COVID-19, SARS-CoV-2, Complication, Treatment, Prevalence

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INTRODUCTION

Hepatitis is one of the most important chronic diseases worldwide. There are more than 350 million patients in the world, leading to more than 500,000 deaths annually, especially in developing countries(1). Chronic hepatitis is a complex liver disorder with different causes and severity that causes the inflammatory and necrosis process in the

liver tissue, which lasts for at least 6 months(2). During 2015–2018, the prevalence of hepatitis B virus (HBV) infection was 4.3% in the US(3), which was higher among men (5.3%) than women (3.4%). Also, the prevalence of hepatitis in European Union countries, reported between 0.0-7.5% and 0.0-27.6% for HBV and hepatitis C virus (HCV), respectively(4, 5). In addition, the prevalence of HCV is 0.80% in Indonesia to 5% in Georgia(6). The prevalence of HCV in middle eastern countries was estimated 0.5%-14.7% (7), similarly, the prevalence of HBV was estimated 2.8%-18.5%(8). So, an estimated 185 million people are infected with the HCV virus around the world, and 3-4 million new infections are diagnosed annually(9). This rate in patients with hepatitis B was estimated as almost 400 million people(10).

Since 31st December 2019, the first cases of acute respiratory diseases have been identified. The pathogen was identified as a novel enveloped RNA beta-coronavirus, called SARS-CoV-2(11). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia quickly became a newly recognized disease that was spreading throughout Hubei province and to other provinces in China rapidly, and continued to spread around the world(12). The World Health Organization (WHO) pronounced the official name of SARS-CoV-2-induced disease as the coronavirus disease 2019 (COVID-19). COVID-19 is an infectious acute respiratory disease caused by a novel coronavirus(13). Symptoms of COVID-19 are complex but common symptoms of patients with COVID-19 included fever, cough, dyspnea, fatigue, and lymphopenia(14). In addition, gastrointestinal symptoms were reported in many of these patients(15). Clinical symptoms are very similar to those of severe acute respiratory syndrome type 1 (SARS-CoV1) and the Middle East respiratory syndrome (MERS) (12, 16, 17). It is mainly transmitted by droplets or direct contact, feces, and infected through the respiratory tracts(18,19). Due to the novelty of the disease, the factors affecting its severity and death have remained unknown. Patients with underlying health conditions such as hepatitis are considered the high-risk group for catching the novel corona virus. Furthermore, it is considered that such patients are likely to suffer more complications, and the risk of death from COVID-19 is higher in this group(20). 2-11% of patients with COVID-19 had liver comorbidities(12). Studies have shown that patients with severe COVID-19

have abnormal liver enzymes levels(21). Among cases of COVID-19, patients with any comorbidity yielded poorer clinical outcomes than those without(22).

The increased rate of those suffering from hepatitis combined with the prevalence of COVID-19 suggests that the care for patients with hepatitis must be increased in order to reduce any further complications and the risk of death. Due to a lack of studies on the relationship between COVID-19 and hepatitis, it is difficult to suggest how exactly such increased care should look like. Thus, in this paper, we aimed to fill the lacunae in the existing literature and conduct a study to review the current evidence and provide guidelines for the prevention and treatment of people affected by both COVID-19 and hepatitis.

MATERIALS AND METHODS

Protocol and registration
The protocol for this review was registered in Kermanshah University of Medical Sciences. The aim of this review was focused on the patients with hepatitis during COVID-19 pandemic and the related common evidence about that.

Eligibility criteria
Inclusion of publications that were observational studies, such as retrospective/prospective cohorts, case reports, and case series. The editorials or review studies that just summarize other studies were excluded. Studies were considered if they focused on both viral hepatitis and COVID-19 patients.

Search strategy
An unlimited search to 20 January 2021 in Scopus, PubMed, Elsevier, Science Direct, Cochrane Library, Google Scholar, and Web of Science was conducted. We developed search strategies using keywords and MeSH terms, including hepatitis, corona, COVID, COVID-19, and SARS-CoV2. Reference lists of eligible articles were also screened for relevant studies and scanned for appropriate references.

Search validation and Data selection
All pertinent articles were discovered by using the search terms, and those that were available on the indicated databases during of this review

were included. All articles not meeting the inclusion criteria as stated above were discarded. Citations were downloaded into Endnote X8. Potentially eligible articles were exported. At this stage, the selected papers were screened again to identify articles relevant to hepatitis and COVID-19, and duplicated ones were eliminated. We obtained the full text of the remaining articles and screened them. The results were compared, and any controversies surrounding any particular included or excluded paper were resolved. Data extraction was performed using a standard extraction form. The studies were subsequently screened for reporting hepatitis and COVID-19 evidence.

Data extraction and report
Data extraction was performed in a Garrard table(19). The studies were subsequently screened for reporting the factors that could influence hepatitis and COVID-19. The characteristics of each study and the method are described and presented in the table, in which patients, the prevalence of hepatitis in COVID-19 patients, and also related factors are extracted. In addition, mortality rates and suggestions for patients or treatment are raised by the Garrard table. For studies that reported more than one data, we included all of them. The descriptions of the extracted data are guided by following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (23).

Quality assessment
The qualities of the included studies were evaluated using a checklist of items from the Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) guideline(24). The quality of studies was assessed based on the 22 items that were related to these studies. The minimum and maximum score of STROBE was 0-44. And studies were categorized into three groups based on their scores, including poor (<16) (25,26), good (30-44), median (16-29.,5), and good (30-44)poor (<16) (25, 26).

RESULTS

Study selection
We find 131 studies in the initial search. Initial and second evaluations were done based on the eligibility criteria. After removing duplicates, 104 references remained. By initial evaluation of the title and abstract, 55 citations were selected for full-text review. Of these, 22 were considered eligible for a final appraisal. Nine studies were excluded due to the lack of data on hepatitis involvement among the COVID-19 patients. Eventually, we included 13 manuscripts in this review. We adhered to reporting and guidance based on the PRISMA statement (figure.1).

Characteristics of studies
These 13 studies were published between February 2020 and July 2020. Seven studies were retrospective (12, 18, 21, 22, 27-29). Two studies were case reports (11, 30) and two other studies were case series (14, 31). In addition, two of them were cohort studies (20, 32). Most of the studies were conducted in China (11, 12, 14, 18, 20-22, 27-29, 31). One study was conducted in the United States, and one study was conducted in the United Arab Emirates (30, 32). These studies conducted in type B and C of hepatitis. In 10 studies, patients with type B hepatitis were considered (12, 14, 20-22, 27-31). In one study, patients with type C hepatitis were considered (11), and in another study, both hepatitis B and C were considered (32). In all studies, 6,539 patients were described, with sample sizes varying between 3 (14) and 2273 (32) patients. The quality of studies was evaluated by STROBE checklist, and eight studies had good qualities (11, 12, 18, 20, 21, 27, 29, 32), and five studies had medium qualities(14, 22, 28, 30, 31). (for further details see: Table 1)

Purpose of the studies
The main purpose of the studies was not a comprehensive study of people who suffered from hepatitis and were infected with COVID-19 (Table 1). There were three separate studies about liver function and treatment in patients with hepatitis infected with COVID-19. There have been, to date, two studies examining two patients with hepatitis who also suffered from COVID-19 in a case-study method (Table 1).

Prevalence of hepatitis in patients with COVID-19
Seven studies reported the prevalence of hepatitis in patients with COVID-19. In all studies, the prevalence of hepatitis was≤10% - 125 patients with hepatitis in

Table 1: Characteristics of included Studies (n = 13)

Author, Title, Journal	Year-Country	Purpose	Study design	Quality
Zou et al. Characteristics of liver function in patients with SARS-CoV-2 and chronic HBV co-infection *Clinical Gastroenterology and Hepatology*	China 2020	Describe the characteristics of liver function in patients with SARS-CoV-2 and chronic hepatitis B virus (HBV) co-infection.	Cohort	Good
Li et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan *Journal of Allergy and Clinical Immunology*	China 2020	Evaluate the severity on admission, complications, treatment, and outcomes of patients with COVID-19.	Retro	Good
Qi et al. The clinical course of COVID-19 in patients with pre-existing decompensated cirrhosis: initial report from China *Hepatology International*	China 2020	Report three patients with confirmed COVID-19 and pre-existing decompensated cirrhosis	case series	Median
Guan et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis *European Respiratory Journal*	China 2020	Evaluate the risk of serious adverse outcomes in patients with COVID-19 by stratifying the comorbidity status.	Retrospective case study	Median
Li et al. COVID-19 infection may cause ketosis and ketoacidosis *Diabetes, Obesity and Metabolism*	China 2020	Metabolic diseases caused by COVID-19, especially in patients with diabetes mellitus.	Retro	Good
Aldhaleei et al. COVID-19 Induced Hepatitis B Virus Reactivation: A Novel Case From the United Arab Emirates *Cureus*	China 2020	Report the first case of hepatitis B virus (HBV) reactivation caused by COVID-19	Case report	Median
Phipps et al. Acute Liver Injury in COVID-19: Prevalence and Association with Clinical Outcomes in a Large US Cohort *Hepatology*	China 2020	Identify the prevalence of and risk factors for the development of COVID-19 associated acute liver injury in a large cohort in the United States.	Cohort	Good
Li et al. A case series of COVID-19 patients with chronic hepatitis B virus infection *Journal of Medical Virology*	China 2020	Describe a case series of COVID-19 patients with chronic hepatitis B virus	Case series	Median
Zha et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19) *The Medical journal of Australia*	China 2020	Assess the efficacy of corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19).	Retro	Median
Ji et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study *Journal of Hepatology*	China 2020	Examine the liver injury patterns and implication of non-alcoholic fatty liver diseases (NAFLD) on clinical outcomes in Chinese patients with COVID-19	Retro	Good

Author, Title, Journal	Year Country	Purpose	Study designa	Quality
Zhang et al. Clinical features and outcomes of coronavirus disease 2019 (COVID-19) patients with chronic Hepatitis B virus infection *Clinical Gastroenterology and Hepatology*	China 2020	Report the clinical course of COVID-19 patients with chronic Hepatitis B virus (HBV) infection and provide a reference for clinical treatment of patients	Retro	Good
Zhao et al. Early Virus Clearance and Delayed Antibody Response in a Case of Coronavirus Disease 2019 (COVID-19) With a History of Coinfection With Human Immunodeficiency Virus Type 1 and Hepatitis C Virus *Clinical Infectious Diseases*	China 2020	Report the first case of coronavirus disease 2019 (COVID-19) with human immunodeficiency virus type 1 (HIV-1)/ hepatitis C virus co-infection	Case report	Good
Guan et al. Clinical Characteristics of Coronavirus Disease 2019 in China *The New England Journal of Medicine*		Clinical characteristics of Covid-19 in a selected cohort of patients throughout China	Retro	Good

Table 2: **Care and treatment of patients (n=7)**

Study	Treatment
Zou et al.	Arbidol, lopinavir/ ritonavir, interferon, and ribavirin Methylprednisolone
Aldhaleei et al.	Day 1= lactulose via a nasogastric tube Day 2= entecavir + vitamin K + thiamin
Li et al.	Lopinavir Ritonavir Interferon α-2b Arbidol Oseltamivir Antibiotic Corticosteroids Gamma globulin
Zha et al.	Non-corticosteroid
Zhang et al.	Interferon arbidol Peramivir Lopinavir/ritonavir Chloroquine Ribavirin Oseltamivir Diammonium glycyrrhizinate Reduced glutathione Compound glycyrrhizin Magnesium isoglycyrrhizinate Glucurolactone Antibiotics Herbal medicine Glucocorticoid
Zhao et al.	Oseltamivir IFN-α

6401 patients with COVID-19 included in studies by Guan (23/1099)(21), Ji (7/202)(27), Zha (2/31)(28), Phipps (59/2273)(32), Li (1/658)(18), Guan (28/1590) (22), and Li (5/548)(12). Six of these studies reported the prevalence of hepatitis B (0.7%-6.4 %)(28, 32), and one study reported the prevalence of hepatitis C (1.9%) (32).

Symptoms of patients with both hepatitis and COVID-19

In four studies, symptoms of patients with both hepatitis and COVID-19 were reported (11, 20, 30, 31). Most symptoms in patients with both hepatitis and COVID-19 were elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)(20, 30, 31). In addition, high total bilirubin (183.9 mmol/L), and elevated gamma-glutamyl transferase, and alkaline phosphatase were reported in studies (20, 30, 31). The data about a patient with hepatitis B and patients with hepatitis C in one case report showed that the clearance of COVID-19 was delayed, and the patient had a fever (38.3°C) (11).

Care and treatment of patients with both hepatitis and COVID-19

Because of the emerging nature of COVID-19, there is no data to provide insights into the possible special treatments that could be useful for patients with hepatitis
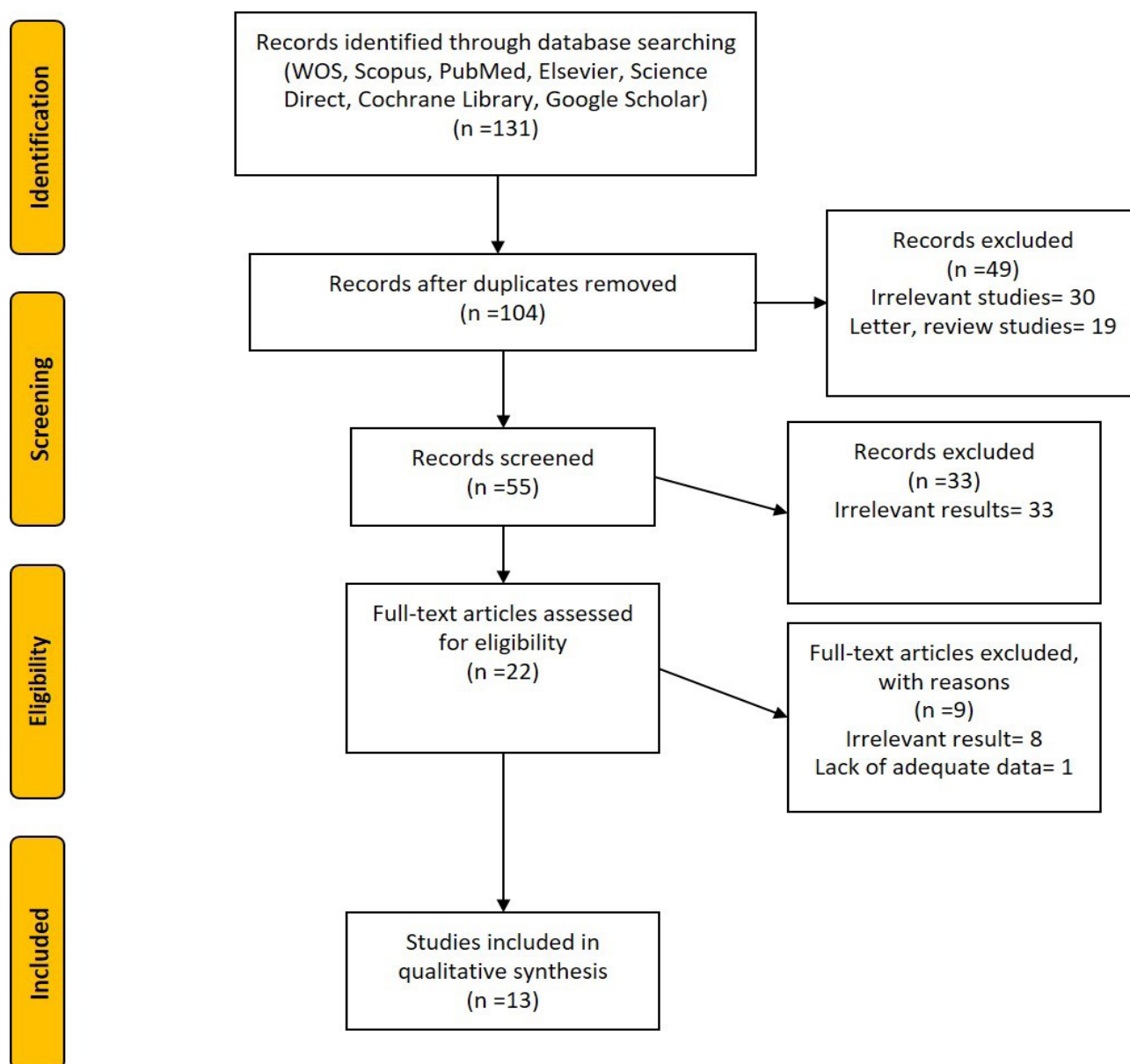
Fig. 1: PRISMA flow diagram for the literature search and study selection

and COVID-19. Only in six studies, treatment of patients with both hepatitis and COVID-19 were reported. In the study by Zou, the treatment with 1- arbidol, lopinavir/ ritonavir, interferon, ribavirin, and methylprednisolone was reported. Zou showed that chronic hepatitis co-infection was associated with severity and poor prognosis of the disease(20). In a case report in the UAE, the use of entecavir+vitamin K+thiamin was reported (30). In another case report, the patient was treated with oseltamivir and interferon α (IFN-α) (11). In a case series, lopinavir,

ritonavir, interferon α-2b, arbidol, oseltamivir, prophylactic antibiotic, and corticosteroids were used for seven patients with both hepatitis and COVID-19 (31). Also, in the study by Zhang, the researchers advised using interferon, arbidol, peramivir, lopinavir/ritonavir, chloroquine, ribavirin, oseltamivir, diammonium glycyrrhizinate, magnesium isoglycyrrhizinate, glucurolactone, glucocorticoid, and to reduce glutathione (29). The patients in Zha study were treated without corticosteroids (28). (Table 2)

Complications of hepatitis in patients with COVID-19

Li reports that hepatitis is a predicting factor for ketosis in patients with COVID-19 [18]. In Aldhaleei study, one patient who was referred with COVID-19 was a 36-year-old man who had hepatitis type B, and his hepatitis was reactivated [30]. In addition, Zhao described a man with COVID-19 and with a history of co-infection with human immunodeficiency virus type 1 and hepatitis C virus, who had a delay in antibody response [11]. Similarly, in Zha study, the clearance of coronaviruses was slower in patients with hepatitis B [28].

Qi, reported that comorbidity with hepatitis was an important factor for mortality, portal hypertension, ascites, jaundice, and coagulation among patients with COVID-19, and the patient died 48 days after the onset of the illness [14]. In Zhang's study, 23 patients with both hepatitis B and CVOID-19 infection were assessed; among them, admission to intensive care unit (ICU) was reported in 5 (21.7%), ARDS in 2 (8.7%), and deep venous thrombosis in 1 (4.3%) patients[29]. In another study on the characteristics of liver function in patients with SARS-CoV-2 and chronic hepatitis B virus (HBV) co-infection, 105 patients were assessed, and it was reported that hospitalization increased, and the proportion of severe COVID-19 was higher in patients with liver injury. Also, it was reported that acute cardiac injury and shock happened more frequently in patients with liver injury, and mortality was also higher in such individuals (28.57% vs 3.30) [20].

DISCUSSION

Hepatitis is a global health threat worldwide, which causes many complications and deaths in patients. It is the leading cause of multiple expensive complications. If it occurs in young patients, it can exclude them from the workforce. Additionally, COVID-19 is a novel respiratory illness that spreads across the world, and to date, it has infected more than 16 million people and resulted in about 650,000 deaths. We identified 13 studies about hepatitis and COVID-19 in a systematic search. Because of the heterogeneity between patients and study designs and also the lack of data from several

countries, further studies must be conducted for complete information on hepatitis in patients with COVID-19. Most of the studies were conducted in China. Due to the differences between hepatitis in different populations (33-35), it is important to conduct more studies on other populations. The prevalence of hepatitis in patients with COVID-19 was between 0.7% to 6.4%. As for diseases similar to COVID-19, the overall prevalence of hepatitis B was 81.57 per 100,000 in SARS-CoV1, and for hepatitis C this rate was lower but had faster growth. In other words, it had less prevalence at first but increased rapidly[36]. Similarly, in recent studies about hepatitis and COVID-19, the prevalence of hepatitis C was low or not reported, so it is necessary to plan for an increase in the prevalence of hepatitis C, like the results of a similar disease (SARS-CoV1). Overall the symptoms of COVID-19 in all patients are elevated AST, ALT, total bilirubin (TBIL), and fever[11, 20, 30]. In the study by Fan and colleagues, the patients with abnormal liver test results were more likely to have a moderate to a high degree of fever[37]. It seems that in patients with hepatitis, there are certain different symptoms, but this needs further studies. However, there is an agreement that symptoms are more severe among patients with hepatitis[12, 14, 20].

Li reports ketosis incidents in patients with COVID-19 and hepatitis co-infection. Also, the prevalence of admission to ICU was higher in patients with hepatitis[18, 20, 29]. Patients with both viral hepatitis and COVID-19 infection are at risk for portal hypertension, ascites, jaundice, coagulation, and prolonged hospitalization[14, 20].In other studies, comorbidity with hepatitis was a risk factor for prolonged hospitalization and readmission, especially after operative treatments [38-40]. Another study showed that liver cirrhosis was independently associated with mortality in patients with ARDS[41]. Another important issue, which was reported, was the reactivation of hepatitis in patients with COVID-19.[30]. Reactivation of hepatitis was more shown in autoimmune diseases such as psoriasis and rheumatoid conditions?? [42, 43]. The reactivation of hepatitis can be prevented by antiviral prophylaxis[44]. This can be important that antiviral therapy may have an effect on the prevalence of hepatitis, which needs further studies on antiviral drugs. In addition, in some studies, the clearance of

coronaviruses from patients' bodies was slower other patients without hepatitis. which can be due to the delay in antibody responses(11, 28).

It is well documented that hepatitis increases the severity of the COVID-19. However, the pathology is not clear. Understanding the interaction between hepatitis and COVID-19 could open a window for therapeutic measures, but there is a paucity of data on this issue. Xu reported that this could be due to the direct effect of COVID-19 on the liver because liver biopsy of patients showed moderate microvascular steatosis and mild lobular and portal activity(45). The other possible reason is binding to angiotensin-converting enzyme 2 (ACE2) receptor that was shown in SARS-CoV1 and COVID-19(46). Also, Zhao reported that the barrier and bile acid transporting functions of cholangiocytes were impaired after COVID-19 infection(47). Another reason for severe hepatitis in COVID-19 may be the use of corticosteroids in the treatment of inflammation that can increase the risk of reactivation of hepatitis(20). So, we recommend further studies and the use of corticosteroids in patients with low risk.

For the treatment of patients with both hepatitis and COVID-19, antiviral therapy is used because the nature of both is viral, and the therapy is useful for patients with COVID-19(20,, 30, 31). It can be administered with zinc supplements to enhance the clinical efficacy(48). Data about drugs is limited, but the use of antiviral therapies in hepatitis is common. In most studies for the treatment of patients with both hepatitis and COVID-19 lopinavir/ritonavir was used(20, 29, 31). Lopinavir and ritonavir are suggested in other studies for the treatment of hepatitis(49, 50). Chu reported that lopinavir/ritonavir used in SARS-CoV1 had an effect on the cure of patients compared with the use of ribavirin only, and also the adverse effect was lower in the treatment with lopinavir/ ritonavir(51). The use of corticosteroids in the treatment of COVID-19 patients co-infected with hepatitis due to their possible effect on reactivation of hepatitis(20) must be monitored. Chu also reported that the use of lopinavir/ritonavir in SARS-COV1 patients reduced the use of steroids and reduced the nosocomial infections, but there was a rise in peripheral lymphocyte count(51).

Based on the findings, hepatitis should be considered as a risk factor for the severity of symptoms of COVID-19, and the best function is reducing the exposure to corona sources. Health systems must create programs aiming to reduce exposure and the risk of disease in patients with hepatitis. Further studies must be conducted for more information.

Limitations

In this study, we maintained a comprehensive search strategy by key review tasks that included all the studies that assessed both hepatitis and COVID-19. However, even though we had no publication bias, it is possible that we missed unpublished data because we did not search the grey literature.

Implications and recommendations

This study has implications for clinical practice and further studies.

More complete reports about patients with both hepatitis and COVID-19 are needed. For further studies, other populations except China should be considered to get a conclusive estimate of the condition of patients around the world. Also, needs for further studies about medical therapy are necessary.

CONCLUSION

Hepatitis and COVID-19 are health threats, which can be spread worldwide. Hepatitis is seen as a risk factor in the severity of COVID-19, and the complications of COVID-19 in patients with hepatitis are more than others. It seems that the use of antiviral drugs can prevent the recurrence of hepatitis in patients with COVID-19 and reduce its severity.

We recommend performing further studies about viral hepatitis, especially HBV, in patients with COVID-19 who need hospitalization and /or immunosuppressive therapy.

Declarations

Consent to publish
Not applicable

Availability of data and materials
Data are in references studies.

Authors' Contributions
MJ contributed in designing the study. MJ

contribute to initial search and data extraction. the final report and manuscript were written by MJ.

All authors contributed to drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The author declares no conflict of interests related to this work.

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