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ASSOCIATION COVID-19 AND LIVER INJURY : A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Most COVID-19 patients present with typical respiratory symptoms (i.e., cough, dyspnea) and fever. However, abnormal liver function is often developed in patients with COVID-19, and liver injury has been related with severe disease. Liver damage ranges from mild asymptomatic elevation of liver enzymes to severe liver injury, while a few cases of acute liver failure have also been reported.*

The aim: *This study aims to show association COVID-19 and liver injury.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 44 articles, whereas the results of our search on SagePub brought up 334 articles. The results of the search conducted for the last year of 2013 yielded a total 7 articles for PubMed and 111 articles for SagePub. The result from title screening, a total 4 articles for PubMed and 46 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.*

Conclusion: *COVID-19-associated liver injury is caused by the cumulative effects of multiple factors, including hepatotropic SARS-CoV-2, drug-induced liver injury, hypoxic reperfusion, immune stress and inflammatory factor storms.*

Keyword: *COVID-19, Liver injury, SARS-CoV-2, Liver enzyms.*

INTRODUCTION

The eruption of coronavirus disease-19 (COVID-19) is of great concern globally and has become a substantial challenge for physicians and public health authorities alike. It has affected more than 100 million people worldwide and has been the cause of death of more than two million infected individuals. In Pakistan alone, the number of confirmed cases has surpassed 700,000, crossing a death toll of over 11,000. Although when compared to other countries around the world the number of death is not as high, likely due to the immediate precautions taken by the country's government from an early stage and the possibility of a large number of infected individuals being asymptomatic, the number is still significant enough to be seen as a dangerous amount. The virus's rapid spread across the globe has largely been due to its alarming rate of infection, primarily through respiratory droplets and secondarily through physical contact. Its usual clinical manifestations in the general population are a dry cough, fever, and flu-like symptoms, which can develop into acute respiratory distress syndrome and multiple system organ failures.[1,2]

Complications of death from COVID-19 may include respiratory failure, acute respiratory distress syndrome, sepsis and septic shock, thromboembolism, and/or multiple organ failure, including heart, liver, or kidney damage. In particular, people aged 60 and older, as well as those with underlying medical conditions such as high blood pressure, cardiorespiratory problems, diabetes, obesity, or cancer, are at higher risk of developing severe COVID-19.[3]

Liver injury is presented as elevated liver enzymes without specific symptoms and signs. The elevation of AST, ALT and/or TBIL is a very common manifestation in COVID-19 patients, while increased GGT and/or ALP is a less usual feature, observed in later stages of the disease. The elevation of the aminotransferases is usually mild; their level is mostly < 5 times ULN. Furthermore, liver injury in COVID-19 has been noted to be transient, while hepatic biochemical tests return to normal within 2-3 week. Severe liver injury, with aminotransferases > 20 times ULN, has been observed in 0.1% of COVID-19 patients on admission and in 2% during hospitalization, while acute liver failure, induced by COVID-19, has been reported in extremely rare cases. Febrile hepatitis, acute cholecystitis and hepatic artery thrombosis are, also, rare clinical presentations of COVID-19. Moreover, in some cases reports, it is suggested that SARS-CoV-2 triggered a *de novo* development of immune-mediated liver disease, such as autoimmune hepatitis and primary bile cholangitis. Interestingly, cholangiopathy, characterized by cholestasis and structural abnormalities of bile duct, has been reported in post-COVID-19 patients, who recovered from severe and critical disease.[4,5]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of association COVID-19 and liver injury. It is possible to accomplish this by researching or investigating association COVID-19 and liver injury. As the primary purpose of this piece of writing, demonstrating the relevance of the difficulties that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine about association COVID-19 and liver injury. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used " association COVID-19 and liver injury." as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((*"COVID-19*"[MeSH Subheading] OR "* Liver injury *"[All Fields] OR "*Effects of COVID-19 for liver' *[All Fields]) AND (*"Effects of COVID-19*"[All Fields] OR "* Mechanism of liver injury *"[All Fields]) AND (*"Liver injury due to COVID-19*"[All Fields]) OR (*"Liver injury because COVID-19" *[All Fields]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

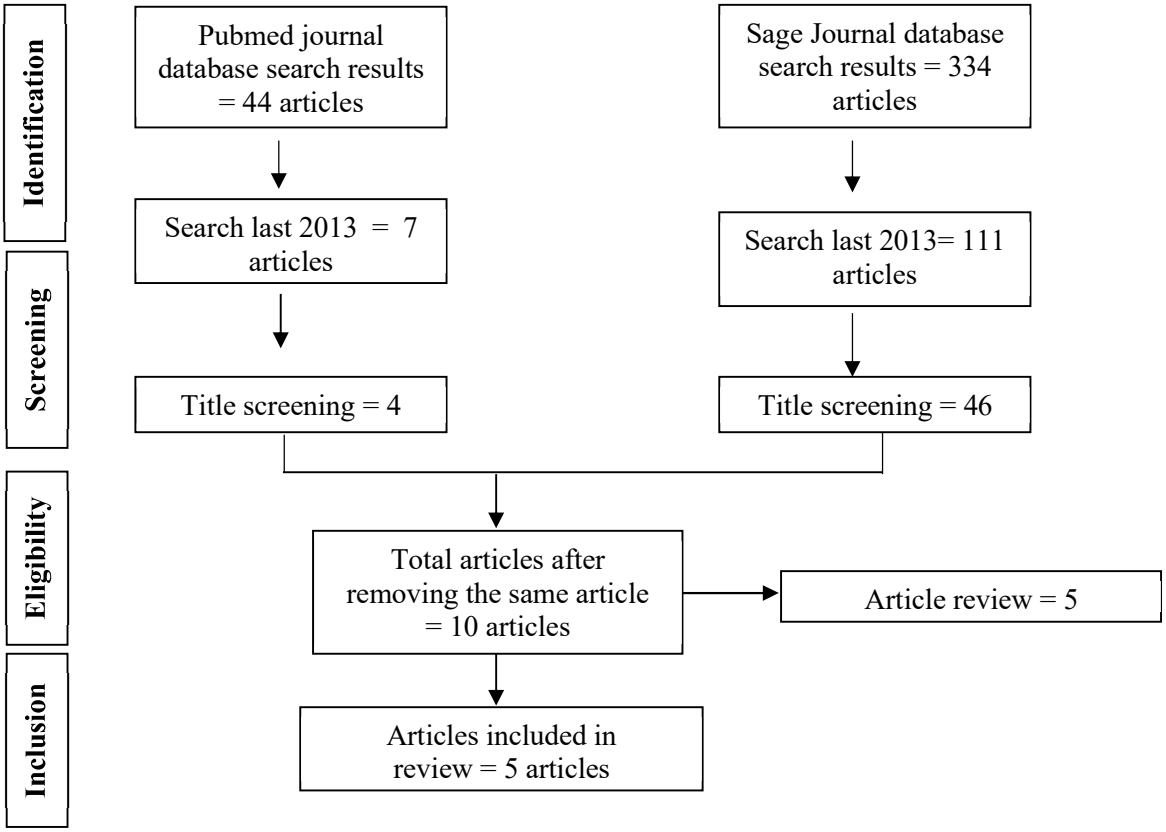

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 44 articles, whereas the results of our search on SagePub brought up 334 articles. The results of the search conducted for the last year of 2013 yielded a total 7 articles for PubMed and 111 articles for SagePub. The result from title screening, a total 4 articles for PubMed and 46 articles for SagePub. In the end, we compiled a total of 10 papers. We included five research that met the criteria.

Rajbhandari, B *et al* (2023)[6] showed increased liver enzymes were mild in the COVID-19 infection. When evaluating patients clinically, it is important to differentiate between the development of irregular liver function upon initial diagnosis and the appearance of abnormal liver function subsequent to treatment. The study findings also suggest that clinicians should consider monitoring liver function in patients with COVID-19, especially in males, and those with elevated CRP levels. Further research is needed to explore the underlying mechanisms of liver injury in COVID-19 patients and to develop effective interventions to prevent or mitigate liver injury in this patient population. Overall, this study provides important insights into the prevalence and risk factors associated with liver injury in COVID-19 patients, which has important clinical implications for the management of this disease.

Phipps, MM *et al* (2020)[7] showed in this cohort of 3,381 patients, ALI was more common among the 2,273 patients with confirmed SARS-CoV-2 than among those with a similar presentation who tested negative. However, SLI with ALT peak >5 times the ULN occurred in only 6.4% of patients. These liver enzyme elevations were rarely associated with cholestasis, but did correlate with other markers of end-organ injury as well as cytokines and markers of inflammation. Finally, SLI was associated with the most severe clinical outcomes, including death, and may be a useful prognostic marker for hospitalized patients.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Rajbhandari, B *et al*., 2023[6]	Nepal	A retrospective cross-sectional study	549 patients	Of the total, 549 (54.5%) patients had an acute liver injury. Among 549 patients, 68.1% were mild, 27.9% were moderate, and 5.0% were severe. Out of 1007 patients, 1.4% had cholestatic liver injury. Most patients with mild, moderate, and severe liver injury had greater than or equal to 10 C-reactive proteins (CRP). In multivariate logistic regression, sex, and CRP were significantly associated with the presence of liver injury. Males had 1.78 times higher odds of having a liver injury compared to females (aOR:1.78; 95% CI: 1.37–2.30, *P*-value:<0.001). Similarly, patients who had CRP greater than 10 had higher odds of having liver injury compared to those who had CRP less than 10 (aOR: 1.84; 95% CI: 1.41–2.39; *P*-value: <0.001).
Phipps, MM *et al*., 2020[7]	New York	Retrospective cohort study	3381 patients	All patients who underwent SARS-CoV-2 testing at three hospitals in the NewYork-Presbyterian network were assessed. Of 3,381 patients, 2,273 tested positive and had higher initial and peak alanine aminotransferase (ALT) than those who tested negative. ALI was categorized as mild if ALT was greater than the upper limit of normal (ULN) but <2 times ULN, moderate if ALT was between 2 and 5 times the ULN, and severe if ALT was >5 times the ULN. Among patients who tested positive, 45% had mild, 21% moderate, and 6.4% severe liver injury (SLI). In multivariable analysis, severe ALI was significantly associated with elevated inflammatory markers, including ferritin (odds ratio [OR], 2.40; $P < 0.001$) and interleukin-6 (OR, 1.45; $P = 0.009$). Patients with

				SLI had a more severe clinical course, including higher rates of intensive care unit admission (69%), intubation (65%), renal replacement therapy (RRT; 33%), and mortality (42%). In multivariable analysis, peak ALT was significantly associated with death or discharge to hospice (OR, 1.14; $P = 0.044$), controlling for age, body mass index, diabetes, hypertension, intubation, and RRT.
Chen, F *et al*., 2020[8]	China	A retrospective study	227 patients	A total of 227 (27.3%) patients exhibited LBA and 32 (3.9%) patients were categorized as having LI based on the diagnostic criteria. 32.6% (74/227) of the LBA patients had RUCAM score>3, where as the non-LBA patients had as light lower at rate of 24.2% (146/603) (P=0.047). Multivariable regression showed that a higher incidence of LBA was associated with hepatic hypoattenuation on computed tomography (CT) (oddsratio: 2.243,95% confidence interval: 1.410–3.592, p=0.001), lymphocyte proportion <20% (2.088,1.476–2.954, p<0.001), C-reactive protein (CRP) > 1mg/dL (2.650,1.845–3.806, p<0.001) and as part at etransaminase to alanine transaminase (AST/ALT) ratio > 1 (2.558,1.820−3.596, p<0.001)
Salik, F *et al*., 2021[9]	Turkey	A retrospective study	353 patients	353 (66.2%) of all patients died. Neutrophil, aPTT, CRP, LDH, CK, ALT, AST, bilirubin, procalcitonin and ferritin values in Group 2 and Group 3 were found to be statistically significantly higher than Group 1. It was detected that the days of stay in ICU of the patients in Group 1 was statistically significantly longer than others group. It was found that the patients in Groups 2 and 3 had higher total, 7-day, and 28-day mortality rates than expected.
Chela, HK *et al*., 2023[10]	USA	Retrospective cohort study	14138 patients	Propensity score matching demonstrated that abnormalities in liver chemistries at admission are significantly associated with increased risk for mortality

				(RR 1.70) and intubation (RR 1.44) in patients with COVID-19. Elevated AST is the liver chemistry abnormality associated with the highest risk for mortality (RR 2.27), intubation (RR 2.12), and prolonged hospitalization (RR 1.19). Male gender, pre-existing liver disease, and decreased serum albumin are also significantly associated with severe outcomes and death in COVID-19.

Chen, F *et al* (2020)[8] showed that patients with COVID-19 frequently exhibit liver abnormalities butonly 3.9% develop LI. For hospitalized COVID-19 patients, hep-atic steatosisis a risk factor for LBA, though LBA may not develop into LI. All test results should be taken into account, including the CRP levels, lymphocyte proportion, AST/ALT ratio, and triglyceride levels. Close clinical surveillance of hepatic function is essential for the early assessment of LI in COVID-19 patients, and RUCAM might be recommended for evaluation the probability of drug or herb induced liver injury.

Salik, F *et al* (2021)[9] showed liver dysfunction evaluated by biochemical blood analysis (AST, ALT, and total bilirubin levels) is common in critical COVID19 patients followed in the ICU. Abnormal liver biochemical parameters are closely related to an increased risk of mortality in critically ill COVID-19 patients. Therefore, these indicators should be closely monitored during the stay in the ICU and special attention should be paid to liver damage.

Chela, HK *et al* (2023)[10] showed liver chemistry abnormalities at the time of admission impact risk for mortality, intubation, and prolonged hospital LOS. The greatest risk for all three adverse outcomes is associated with elevated AST. A liver chemistry panel should be obtained with routine laboratory tests when patients test positive for COVID-19 infection. These results should be used for risk stratification. Clinicians should be cautious when derangements in liver chemistries are noted on presentation as they could be harbingers of eventual decompensation. Further studies are needed to develop more precise prediction models and scoring systems.

DISCUSSION

The COVID-19 pandemic poses a great challenge to the international healthcare system. Older adults and those at any age with hypertension, coronary heart disease and diabetes are at higher risk of SARS-CoV-2 infection and severe disease course (1, 2). Although the lung is the main target organ of SARS-CoV-2 infection; damage can occur in multiple organs. The liver is the vital organ in the human body and its exposure to the viral particles might be an additional concern for CVID-19 patients. Up to now, there is no strong evidence that the liver cells are exposed to SARS-CoV-2 in severe cases. Moreover, it remains unclear yet to what extent liver diseases are considerable risk factors of COVID-19 severity and mortality.[11,12]

While respiratory and systemic symptoms such as fever, fatigue, and myalgia have been reported to be the main manifestations of symptomatic COVID-19, the literature has also reported liver injury. The prevalence of elevated serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and gamma-glutamyl transpeptidase (GGT) have been observed. The liver is the body's largest independent organ and serves four main functions: metabolism and synthesis; storage; excretion; and detoxification of potential poisons. Tests for indicators of hepatocellular injury (ALT, AST, GGT, and ALP), liver metabolic function [total bilirubin (TBIL)], and liver synthetic function [serum albumin (ALB) and prothrombin time (PT)] should be performed to fully assess liver injury. [13]

It is currently uncertain whether and how liver injury affects the severity and mortality of COVID-19. Recent studies suggest a significant prevalence of abnormal aminotransferase levels in patients with COVID-19, including elevated AST, ALT, and total bilirubin (TBIL) levels and decreased albumin (ALB) levels. Previous studies have also suggested that the most severely affected patients present with coagulopathy, such as a prolonged PT, an increased international normalized ratio (INR), and disseminated intravascular coagulation (DIC). However, a meta-analysis related to coagulopathy, mortality and COVID-19 and a comprehensive description of the four major functions of liver injury are rare.[13]

According to the published data from global burden of diseases, over 2 million people globally pass away from liver disease each year, with 1 million of those fatalities coming from cirrhosis complications, 1 million from viral hepatitis, and 1 million from hepatocellular carcinoma. Together, liver cancer and cirrhosis account for 3.5% of all fatalities worldwide and are the 11th and 16th most common causes of death worldwide, respectively. Cirrhosis is one of the top 20 causes of disability-adjusted life years (DALY) and years of life lost. Over 2 billion people use alcohol globally, and more than 75 million have been diagnosed with alcohol use disorders or are at risk of developing such health problems.

Over a span of 30 years, cirrhosis and other chronic liver diseases witnessed a rise from 1.34% to 1.82% of total DALY, in 1990 and 2019, respectively.[14,15]

The global burden of hepatocellular carcinoma (HCC) and cirrhosis grew rapidly during the last decades. Almost 2 billion adults are obese or overweight, and more than 400 million have diabetes, both of which are risk factors for hepatocellular carcinoma and non-alcoholic fatty liver disease. The incidence of viral hepatitis is still widespread over the world, and drug-induced liver damage is becoming a more significant cause of acute hepatitis.[14]

The prevalence of non-alcoholic fatty liver disease (NAFLD) was found to be growing, causing liver mortality and morbidity. In 2017, there was an estimated 1.5 billion cases of chronic liver disease worldwide, with liver cirrhosis accounting for an estimated 1.32 million deaths. Liver cirrhosis could be caused by chronic infection with hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol-related liver disease, and non-alcoholic steatohepatitis (NASH), that are independent risk factors for HCC and cholangiocarcinoma. The global HCV prevalence was estimated at 2.5%, ranging from 2.9% in Africa and 1.3% in America.[14,16]

CONCLUSION

COVID-19-associated liver injury is caused by the cumulative effects of multiple factors, including hepatotropic SARS-CoV-2, drug-induced liver injury, hypoxic reperfusion, immune stress and inflammatory factor storms. Although liver damage is relatively common in patients with COVID-19, most patients predominantly have transient and mild liver enzyme (AST, ALT) elevations, and rarely, there are cases of COVID-19-associated ACLF. When COVID-19 patients also have ALD, NAFLD, cirrhosis or HCC, they are at a higher risk of severe disease and death.

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