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Post-COVID-19 Cholangiopathy: Systematic Review

Post-COVID-19 Cholangiopathy

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Abstract

BACKGROUND

The COVID-19 pandemic has had a profound impact on global health, primarily characterized by severe respiratory illness. However, emerging evidence suggests that COVID-19 can also lead to secondary sclerosing cholangitis, referred to as post-COVID-19 cholangiopathy.

AIM

This systematic review aims to synthesize currently reported cases to assess the current state of knowledge on post-COVID-19 cholangiopathy.

METHODS

Medical Subject Headings and Health Sciences Descriptors were used to retrieve relevant studies, which were combined using Boolean operators. Searches were conducted on electronic databases including Scopus, Web of Science, and MEDLINE (PubMed). Studies published in English, Spanish, or Portuguese were included, with no restrictions on the publication date. Additionally, the reference lists of retrieved studies were manually searched. Simple descriptive analysis was used to summarize the results.

RESULTS

The initial search yielded a total of **192 articles**. After screening**, 85 articles** were excluded due to duplication, **leaving 107 articles** for further review. Of these, **63 full-length articles** met the inclusion criteria and were included in the analysis. The majority of the patients were male (78.2%), and most exhibited elevated liver function tests (93.4%). Magnetic resonance imaging (MRI) revealed duct thickening with contrast enhancement, as well as beading of the intrahepatic ducts with peribiliary contrast enhancement on diffusion. Liver biopsy results confirmed sclerosing cholangitis in the majority of cases. Four patients underwent liver transplantation, with three experiencing successful outcomes.

CONCLUSION

Post-COVID-19 cholangiopathy is a serious condition that is expected to become increasingly concerning in the coming years, particularly in light of Long COVID syndromes. Although liver transplantation has been proposed as a potential treatment option, more research is necessary to establish its efficacy and explore other potential treatments.

Key Words: COVID-19; SARS-COV-2; Cholangiopathy; Liver Function Tests; Liver Transplantation.

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Core Tip: Post-COVID-19 cholangiopathy is a rare but serious complication that can occur after contracting COVID-19. It is characterized by inflammation and damage to the bile ducts, which can lead to jaundice, abdominal pain, and liver damage. To better understand this condition and its treatment, we conducted a systematic review of available cases of post-COVID-19 cholangiopathy. Our search retrieved a total of 132

articles. After screening, 85 articles were excluded due to duplication, leaving 47 articles for further review. Of these, 18 full-length articles met the inclusion criteria and were included in the analysis, representing a total of 46 cases. Males over 50 years old were found to be more prone to developing this condition, which is often accompanied by elevated liver function, bile duct thickening, and kidney failure after prolonged use of mechanical ventilation. While liver transplantation has been suggested as a possible treatment, further research is needed to confirm its effectiveness in treating post-COVID-19 cholangiopathy.

INTRODUCTION

On March 2020, the World Health Organization WHO declared a global health pandemic after the first case was recognized on 12.2019 in Wuhan City, China of what was called severe acute respiratory syndrome coronavirus 2 disease (SARS-CoV-2 disease)[1]. This led to catastrophic events in the world resulting in more than 6 million deaths globally, and the pandemic has led to a great financial and humanitarian loss due to prolonged lockdowns, which have had a tragic effect on the global economy[2].

Also, COVID-19 keeps enduring a second and third waves outbreaks in many countries, probably caused by mutant new variants of the virus[2]. Despite the accelerated speed of the vaccine development for prevention of COVID-19 in order to control the disease, and robust mass vaccination worldwide including booster doses, these new variants of SARS-CoV-2 threaten the progress made so far with the purpose of controlling the spreading of the disease[2, 3].

Respiratory symptoms are the most common manifestation of the disease. These can range from mild to severe and may include fever, dry cough, shortness of breath, anosmia, ageusia and fatigue[4]. It may lead to viral pneumonia with severe complications, such as acute respiratory failure; an acute respiratory distress syndrome requiring intubation, mechanical ventilation and intensive care management[5, 6].

In addition to respiratory symptoms, COVID-19 might also cause a range of extra-pulmonary manifestations, including cardiovascular, neurological, and renal

complications[7]. Gastrointestinal symptoms, including diarrhea, nausea, and vomiting, are also commonly reported[8]. Post COVID-19, derangement of liver enzymes (LFT) is a potential complication observed in admitted COVID-19 patients, with a prevalence ranging from 14% to 83%[9]. Other liver-related conditions such as autoimmune hepatitis, vascular thrombosis, and hemophagocytic lymphohistiocytosis have also been associated with the post-COVID-19 period[9] [10].

However, one emerging complication of Covid-19 is post-COVID-19 cholangiopathy (PCC), a novel clinical entity characterized by inflammation and damage to the bile ducts in individuals who have recovered from COVID-19 infection[11]. The clinical presentation of PCC can vary, but common symptoms may include abdominal pain, fever, and jaundice[12]. PCC has been observed in patients without a history of prior liver disease. This condition can manifest in various clinical settings, such as in individuals with severe COVID-19 infection requiring mechanical ventilation, as well as in those experiencing milder forms of the disease.[5, 13]. The prevalence of PCC is not yet well understood, and it is not clear if it is more common in certain patient populations. Some researchers have suggested a potential association between certain drugs, including immunomodulator agents, ketamine, and antiviral medications, and the development of PCC. However, the available evidence regarding these drugs causing cholangiopathy remains insufficient.[9] This systematic review aims to comprehensively analyze and synthesize the existing evidence pertaining to post-COVID-19 cholangiopathy. The primary objective is to explore the clinical presentation and management approaches documented in the available cases reported in the literature. By conducting this review, we aim to provide a comprehensive overview of the current understanding and knowledge gaps surrounding post-COVID-19 cholangiopathy, which can contribute to the development of effective strategies for diagnosis and treatment in clinical practice.

MATERIALS AND METHODS

Study design

This study was conducted in accordance with the guidelines for preferred reporting items for systematic reviews and meta-analyses protocols guidelines.[14]

Data sources

The studies included in this review were identified using the search strategy outlined in Appendix 1. Searches were run on the electronic databases Scopus, Web of Science and Medline (PubMed). Languages were restricted to English, Spanish and Portuguese. There was no date of publication restrictions. The reference lists of the retrieved studies were also manually searched. The databases were searched in **March of 2023.**

Inclusion and exclusion criteria

Inclusion criteria were clinical case reports or case series of post-covid cholangiopathy. Studies must include detailed information about the clinical presentation, diagnosis, management and outcomes. Articles unrelated to the topic were excluded and that do not provide sufficient detail about the cases. If there was more than one study published using the same case, the variables were complemented with both articles. Studies published only as abstracts were included, as long as the data available made data collection possible.

Study selection and data extraction

A comprehensive search of various databases was conducted using the search terms listed in the appendix. The initial screening process involved reviewing titles and abstracts to identify potentially relevant studies. These studies were then analyzed in full, and some were excluded due to a lack of clinical information. Two reviewers independently extracted data from eligible studies using a standardized form and assessed the characteristics of the subjects and outcomes measured. Any discrepancies in study selection or data extraction were resolved by a third party.

Data collection

Variables included were age, gender, clinical presentation, liver function tests, renal function test, imaging findings, histopathology, and whether or not the patient had undergone liver transplantation (OLT) and outcome.

Data processing and analysis:

Data were analyzed and summarized using descriptive techniques such as frequency, means, and median. The analysis was performed using Microsoft Excel 2010.

RESULTS

The search strategy retrieved **192 articles, 85 articles were excluded because they were duplicates, 107 articles were screened in the review, from 89 articles a 88 articles full length were included and retrieved, from 88 eligible articles a 63 articles included in the** review. A PRISMA flowchart illustrating the search strategy is shown in Figure 1. Studies reviewed were either a case report or a case series.

This systematic review included a total of **756** patients, with **36 (78.2**%) being male. The majority of the patients (65.2%) were over 50 years old. Almost all patients (93.4%) had elevated liver enzymes in the acute phase, with increase of this levels in chronic phase. Total bilirubin was elevated in 23 patients **(50%),** while only 4 (**14.8**%) had levels lower than 1.2 mg/dL. Data on bilirubin levels was not reported for 19 cases. Levels of alkaline phosphatase and gamma-glutamyl transferase were consistently elevated, often surpassing 1000 U/L.

In this study, based on imaging findings, **19 out of 22 (86**.3%) patients had biliary ductal dilatation with fibrosis on ultrasound, while 2 (9.1%) patients any alteration was found. Furthermore, according to MRI results, 22 (47.8%) patients had bile duct thickening with contrast enhancement, 18 (39.1%) had beading of the intrahepatic ducts, and **13 (28.1**%) had peribiliary enhancement on diffusion.

Moreover, 19 (41.3%) patients with post-COVID-19 cholangiopathy had respiratory failure type 2, which was characterized by acute respiratory distress syndrome (ARDS). One of these patients underwent bilateral lung transplantation, but unfortunately died.

Additionally, **30 patients (65.2%)** had acute renal injury that required either dialysis or renal transplantation after liver transplantation (OLT). Data on renal function were not reported for 16 patients.

According to liver biopsy results, **33 patients (71.7%)** had sclerosing cholangitis, while 1 patient did not show this finding.

Moreover, **4 patients (8.6%)** with post-COVID-19 cholangiopathy underwent orthotopic liver transplantation (OLT). Of these, 3 patients (75%) experienced successful outcomes, with an improvement in liver enzyme levels post-transplantation.

DISCUSSION

After the first of case of SARS-CoV-2 disease on 2019[1], a novel clinical entity has emerged. This condition has been reported in a small number of patients who have recovered from the virus and is characterized by elevated liver enzymes, biliary ductal dilatation on imaging, and histopathological findings of secondary sclerosing cholangitis[11]. This systematic review examined the clinical presentations and outcomes of 46 patients with post-COVID-19 cholangiopathy, a rare complication of COVID-19 that affects the biliary system.

It is important to consider the differential diagnosis, as other diseases may present with similar presentation[15]: Ketamine-induced cholangiopathy can lead to fusiform dilatation of the common bile ducts (CBDs), without evidence of extrinsic or intrinsic obstruction[16]. The severity depends on the duration of using ketamine, and it is reversible in abstinent patients. Another differential is ischemic cholangitis, which occurs by a deficiency of blood flow of the biliary system[17]. This can affect the bile ducts leading to segmental strictures and cholangiectasis leading to mechanical restriction of bile acid flow.

Sclerosing cholangitis (SC) is a medical condition characterized by destruction of the bile ducts due to inflammation and fibrosis and severe progressive stenosis of the bile tracts including three types; primary sclerosing cholangitis (PSC), IgG related sclerosing cholangitis, and secondary cholangitis such as bacterial cholangitis, viral cholangitis (cytomegalovirus), postoperative biliary stenosis, choledocholithiasis and usually the

patients present with similar cholestatic features such as itching, jaundice, and lab blood results reveal high cholestatic enzymes[18, 19]. Although the clinical presentation of PSC and IgG4-SC are nearly the same, but both differ in treatment response, outcomes and comorbidities, and how to differentiate it from cholangiocarcinoma[18, 19]. The difference between them is that IgG4-SC patients respond actively to prednisolone and steroid therapy, while PSC has no standard treatment approved, only ursodeoxycholic acid (UDCA) can be used in some patients, but it does not improve overall prognosis[18-21].

Distinguishing and differentiation between PSC-high IgG from IgG-SC still challenging, thus a promising study of calculation of serum IgG4:IgG1 ratios shows an excellent specificity to distinguish IgG4-SC and PSC high IgG4[18, 19]. The most used diagnostic test for PSC is cholangiography, which shows pruned tree appearance, beaded ducts, band like stricture thus ERCP or MRCP are highly recommended. PSC is also highly associated with IBD (ulcerative colitis more than Crohn's disease), thus a colonoscopy is recommended in the diagnosis and this increases risk of cholangiocarcinoma and gallbladder carcinoma[18, 19]. Therefore more studies are required in the diagnostic procedures of PSC, IgG4-SC and cholangiocarcinoma and the treatment and management[18, 19].

The present results on PCC have shown that most of the patients were males (78,2%) more than 50 years old, consistent with previous literature[9]. Every patient had elevated liver enzymes in the acute phase and their levels increased in chronic phase if left untreated.

Also, the effects showed on radiology; by the ultrasound findings; almost of the patients 19 (41.3%) presented biliary ductal dilatation. The MRI findings in this systematic review showed that only a small number of patients (28.2%) had peribiliary enhancement on diffusion, while a larger number of patients (47.8%) had bile duct thickening and enhancement, and 18 patients (39.1%) had beading of the intrahepatic ducts. In contrast, a previous retrospective study by Faruqui *et al* 2021[13], found that a higher proportion of patients (11/12, 92%) had beading of the intrahepatic ducts, 7/12

(58%) had bile duct wall thickening with enhancement, and 10/12 (83%) had peribiliary diffusion high signal[11]. Details can be found in table 1 and 2.

PCC appears to have different histologic characteristics compared to SSC-CIP caused by other factors. Biopsy samples from patients with post-COVID-19 cholangiopathy show extensive degeneration and injury of cholangiocytes, as well as unique microvascular features such as swelling of hepatic artery endothelial cells, phlebitis in the portal vein, and sinusoidal obstruction syndrome[5]. Several studies have suggested that COVID-19 cholangiopathy is a result of progressive paucity of bile ducts the exact pathophysiology to explain the histologic finding of bile duct paucity is not well known[11]. Our histopathology biopsy results showed SSC (secondary sclerosing cholangitis) in 33 patients (71.7%).

On the other hand, PCC presentation is difficult to treat, and sometimes requires orthotopic liver transplantation (OLT)[5, 6, 21]. Almost all patients presented respiratory failure type 2 as they had ARDS and one patient had bilateral lung transplant and unfortunately died. Every patient presented acute kidney injury, which required either dialysis or renal transplantation post OLT. As described in literature, PCC is often accompanied by respiratory failure and acute renal injury[23, 24, 25]. Also, some cases of biliary casts have been described, removed *via* ERCP. The diagnosis and management of post-COVID 19 cholangiopathy requires an ERCP, especially in the presence of a dilated choledocus in imaging studies[9,26].

Also, 4 patients (8.6%) underwent OLT, which can be a viable treatment option for this condition[5, 27]. One of these cases was reported by Durazo *et al* 2021[5], which was comprised of a secondary sclerosing cholangitis in a 47 years old patient who was recovering from severe acute respiratory distress syndrome caused by COVID-19 infection. He was admitted to the ICU for prolonged mechanical ventilation (29 days) and was listed for liver transplantation with a Model for end-stage hepatic disease score of 37. On day 108 from his presentation, the patient underwent successful orthotopic liver transplantation (OLT) with a whole liver allograft from a deceased donor.

CONCLUSION

In conclusion, this paper presents an extensive review of post COVID-19 cholangiopathy published in medical journals. Our analysis indicates that post COVID-19 cholangiopathy is a serious systemic illness that can affect the liver in addition to the lungs. Most cases were found among males over 50 years old, and patients with cholangiopathy exhibited elevated liver enzymes particularly alkaline phosphatase and gamma-glutamyl transpeptidase, and signs of liver dysfunction. Radiology showed bile duct thickening and enhancement, beading of the intrahepatic ducts, and peribiliary enhancement on diffusion. Additionally, every patient had severe respiratory distress syndrome and kidney failure reported as complications. Liver transplantation has been suggested as a potential management option for PCC, although its efficacy as a curative treatment requires further validation. Not all PCC patients require liver transplantation, as some may recover without undergoing this procedure. Studies have demonstrated that liver enzymes, especially alkaline phosphatase, total bilirubin and gamma-glutamyl transferase decrease after medical treatment of PCC. While liver transplantation is not suitable for all PCC patients, it remains the most effective option for select cases. Further research, clinical studies, and international collaborations are needed to gain a better understanding of this novel disease and explore potential treatment avenues.

ARTICLE HIGHLIGHTS

Research background

+ADw-html+AD4APA-p+AD4-The COVID-19 pandemic, declared by the World Health Organization in March 2020, has had devastating global impacts, resulting in millions of deaths and significant economic and humanitarian losses. Despite vaccination efforts, new variants of the virus continue to pose a threat, hindering control measures. While respiratory symptoms are common in COVID-19, extra-pulmonary manifestations and derangement of liver enzymes have been observed. One emerging complication is post-COVID-19 cholangiopathy (PCC), characterized by bile duct inflammation and damage in recovered individuals. PCC presents with symptoms such as abdominal pain, fever,

and jaundice, affecting both severe and milder cases. The prevalence and potential drug associations with PCC remain uncertain.+ADw-/p+AD4APA-/html+AD4-

Research motivation

+ADw-html+AD4APA-p+AD4-Understanding post-COVID-19 cholangiopathy is crucial due to its novelty and potential impact on recovered patients. Exploring the clinical presentation and management of PCC can provide valuable insights into its diagnosis and treatment. By addressing the knowledge gaps surrounding this condition, future research can develop effective strategies for patient care and improve outcomes in clinical practice. The significance of solving these problems lies in advancing our understanding of this novel disease and facilitating evidence-based approaches to manage post-COVID-19 cholangiopathy.+ADw-/p+AD4APA-/html+AD4-

Research objectives

+ADw-html+AD4APA-p+AD4-The primary objectives of this systematic review are to comprehensively analyze and synthesize existing evidence on post-COVID-19 cholangiopathy, focusing on the clinical presentation and management approaches documented in reported cases. By realizing these objectives, we aim to provide a comprehensive overview of the current understanding of post-COVID-19 cholangiopathy, identify knowledge gaps, and contribute to the development of effective diagnostic and therapeutic strategies for this condition. The findings from this study can guide future research endeavors, leading to improved patient care and outcomes in the field of post-COVID-19 cholangiopathy.+ADw-/p+AD4APA-/html+AD4-

Research methods

+ADw-html+AD4APA-p+AD4-The research methods employed in this study adhered to the guidelines for preferred reporting items for systematic reviews and meta-analyses protocols. A comprehensive search was conducted in electronic databases (Scopus, Web of Science, and Medline/PubMed) using specified search terms. The search was limited

to English, Spanish, and Portuguese language publications without any date restrictions. In addition to database searches, the reference lists of identified studies were manually searched. The inclusion criteria encompassed clinical case reports or case series focusing on post-COVID cholangiopathy, with detailed information on clinical presentation, diagnosis, management, and outcomes. Studies that lacked relevant clinical information or were unrelated to the topic were excluded. Two independent reviewers performed data extraction using a standardized form, and any discrepancies were resolved through discussion or consultation with a third reviewer. The extracted data included variables such as age, gender, clinical presentation, liver and renal function tests, imaging findings, histopathology, liver transplantation status, and outcomes. Data analysis involved descriptive techniques, including frequencies, means, and medians.+ADw-/p+AD4APA-/html+AD4-

Research results

This systematic review identified a total of 46 patients with post-COVID-19 cholangiopathy, predominantly male (78.2%) and over 50 years old (65.2%). Elevated liver enzymes were observed in nearly all patients during the acute phase, persisting in the chronic phase. Total bilirubin levels were elevated in 50% of cases, while alkaline phosphatase and gamma-glutamyl transferase levels consistently exceeded 1000 U/L. Imaging findings revealed biliary ductal dilatation with fibrosis on ultrasound in 86.3% of patients and bile duct thickening with contrast enhancement on MRI in 47.8% of patients. Respiratory failure type 2, associated with acute respiratory distress syndrome (ARDS), was observed in 41.3% of patients, with one patient undergoing lung transplantation. Acute renal injury requiring dialysis or renal transplantation was present in 65.2% of cases. Liver biopsy showed sclerosing cholangitis in 71.7% of patients. Four patients (8.6%) underwent orthotopic liver transplantation, with successful outcomes observed in 75% of these cases. These findings provide important insights into the clinical characteristics and complications of post-COVID-19 cholangiopathy, highlighting the

need for further research to elucidate its pathogenesis and optimal management strategies.

Research conclusions

+ADw-html+AD4APA-p+AD4-This study proposes several new theories and methods in the field of post COVID-19 cholangiopathy (PCC). Firstly, the study suggests that PCC is a serious systemic illness that affects not only the lungs but also the liver. It provides evidence that PCC is characterized by elevated liver enzymes, biliary ductal dilatation, and histopathological findings of secondary sclerosing cholangitis. The study highlights the importance of considering the differential diagnosis, as other diseases may present with similar symptoms, such as ketamine-induced cholangiopathy and ischemic cholangitis. The study emphasizes the diagnostic procedures for PCC. It recommends the use of cholangiography, ERCP, or MRCP to visualize the biliary system and identify characteristic features of PCC, such as pruned tree appearance, beaded ducts, and band-like strictures. +ADw-/p+AD4APA-/html+AD4-

Research perspectives

The direction of future research in the field of PCC should focus on several key aspects. Firstly, further studies are needed to better understand the pathophysiology of PCC and the exact mechanisms underlying bile duct paucity. Investigating the unique microvascular features observed in PCC, such as swelling of hepatic artery endothelial cells and phlebitis in the portal vein, could provide valuable insights into the disease process.

Additionally, more research is required to improve the diagnostic procedures for PCC. Exploring novel imaging techniques or biomarkers that can aid in the early and accurate detection of PCC would be beneficial. Further studies comparing PCC with other cholangiopathies, such as primary sclerosing cholangitis and IgG4-related sclerosing cholangitis, could help in differentiating these conditions and improving treatment approaches.

Moreover, the management and treatment of PCC require further investigation. Evaluating the efficacy and outcomes of liver transplantation as a potential treatment option for PCC is essential. Identifying factors that can predict the need for liver transplantation and determining the long-term prognosis of PCC patients would be valuable areas of research.

Overall, future studies should aim to deepen our understanding of PCC, develop improved diagnostic methods, and explore effective treatment strategies to enhance patient outcomes. Collaboration among researchers and international efforts would be crucial in advancing the knowledge and management of this novel disease.

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