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Post-COVID-19 cholangiopathy: A systematic review

Zippi M *et al*. Post-COVID-19 cholangiopathy

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Abstract

BACKGROUND

The recent and still ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entailed various long-term complications, including post-infectious cholangiopathy.

AIM

To identify the available literature studies concerning post-coronavirus disease 2019 (COVID-19) cholangiopathy.

METHODS

An extensive bibliographical search has been carried out in PubMed and in Cochrane Library to identify the articles (retrospective and prospective studies, cohort studies, case series and case reports) published between January 1, 2020 and August 22, 2022, using both MeSH terms and free-language keywords: cholangiopathy; COVID-19; post-COVID-19 cholangiopathy; SARS-CoV-2.

RESULTS

It has been found that thirteen studies fulfilled the inclusion criteria for 64 patients suffering from this condition, mainly male in 82.8% of cases. Liver transplant has been executed in six patients and scheduled in other seven, while two subjects refused the surgical approach. Therefore, in 23.4% of the cases examined performing this procedure has appeared to be necessary.

CONCLUSION

This review has revealed that generally the involvement of the liver in the course of SARS-CoV-2 infection is mild and transient, inducing cholestasis of cholangiocytes, but can also turn out to a severe level, enough to cause organ failure in some cases.

Key Words: Cholangiopathy; COVID-19; Post-COVID-19 cholangiopathy; SARS-CoV-2; Transplantation

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Core Tip: As severe acute respiratory syndrome coronavirus 2 infection keeps spreading, its long-term complications, like cholangiopathy post-coronavirus disease 2019 (COVID-19), become manifest. This pathology begins to be most commonly identified in patients hospitalized in the intensive care unit and shows histological characteristics reminiscent of the ones of secondary sclerosing cholangitis. Post-COVID cholangiopathy represents a serious complication that may evolve into liver failure, even requiring its transplant.

INTRODUCTION

It is well known that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the disease named coronavirus disease 2019 (COVID-19), can induce liver damage in addition to the prevailing respiratory diseases[1]. This pathogen determines gastrointestinal symptoms, especially hepatic, with a multi factorial modality: direct damage, intestinal translocation, drug hepatotoxicity and immune-mediated inflammation secondary to "cytokine storm"[2-4]. The first mechanism described is due to the presence of angiotensin converting enzyme-2 (ACE-2) receptors expressed on the liver cells, in particular on the epithelial cells of cholangiocytes[5,6]. To the best of our knowledge, the first pathological description of the liver has been reported in 2020 by Xu *et al*[7], who have described a mild lobular and portal inflammation, thus exhibiting direct liver damage sustained by this virus. The reported incidence of liver injury ranges have stood between 14.8% and 53% of infected patients, of which 2%-11% suffering from known hepatic pathologies (nonalcoholic fatty liver disease, chronic viral hepatitis, immune-mediated liver disease and alcoholic hepatitis)[7,8]. The hepatic symptoms characterized by an increase of the transaminases and/or of the cholestasis indices are widely described in literature and tend to appear during the course of the infection and regressing at its end[9]. In particular, an increase in serum of gamma-glutamyl transferase (GGT) levels has been present in 27.9% of severe forms of COVID-19 disease, suggesting an ongoing damage to the cholangiocytes[7,10]. Cholestasis is induced by high simultaneous values of GGT and alkaline phosphatase (ALP)[9]. In 2021, Roth *et al*[11] have described a new hepatic manifestation characterized by severe cholestasis developed during the recovery phase in patients with the critical form of COVID-19, named "post-COVID-19 cholangiopathy"[12]. Several mechanisms inducing the cholangiocyte damage have been proposed by researchers and will be briefly described below.

Mechanisms of cholangiocytic damage

SARS-CoV-2 may infect the intestine, the liver, the kidneys and the brain cells and this variety of clinical manifestations is detectable not only during the acute phase of the disease, but also in the recovery process[13]. The entry of the virus into the cell is preceded by the interaction of the pathogen with the ACE-2 receptors. The interaction is widely distributed in all the human tissues and well observable in the liver and in the biliary tract[14,15]. In particular, increased mitotic activity of swollen hepatocytes, an enhanced rate of apoptosis visible in cells obtained from liver biopsies of COVID-19 patients, as well as the abundance of the ACE-2 receptors in the different types of liver cells, provide evidences that SARS-CoV-2 exhibits a substantial affinity for these hepatic cells[16]. Therefore, cholangiocytes, hepatocytes and bile duct cells represent an ideal reservoir for SARS-CoV-2[17]. A high expression of ACE-2 receptors and transmembrane serine protease 2 (TMPRSS2) has been reported in enteric neurons and in glial cells of the small and large intestines [18]. A recent study has shown that this enteric nervous system allows SARS-CoV-2 to reach the biliary tract of the liver by exploiting the well-known gut-liver axis[17]. ACE-2 receptors in cholangiocytes support a retrograde mode of liver damage after the virus has entered the biliary tree cells[19,20]. Liver biopsies confirm the presence of viral RNA in the liver tissues. Atypical signs of hepatocyte damage have been observed too, such as cellular apoptosis along with swelling, acidophilic bodies and lobular inflammation, characterized by the mechanism of direct viral damage[21]. Some pathogenetic mechanisms have been correlated with tissue damage in these individuals, including ACE-2 mediated direct viral infection of hepatocytes. The virus could even infect cholangiocytes and dysregulate the functions of both the biliary tract cells and the entire hepatic gland, causing a direct liver injury[22-24] owing to the generation of organelles damage[10,22]. Acute and persistent lobular inflammatory damage may occur in the liver of patients with COVID-19. This process is characterized by: (1) elevated levels of circulating pro-inflammatory cytokines/chemokines and other mediators, eventually triggering a cytokine storm and inducing liver dysfunction, as observed in a series of viral infections[22,25-27]; (2) a close association between liver injury and inflammatory responses whilst in SARS-CoV-2

infection[27], as patients with COVID-19 may incur hepatocellular damage, ranging from mild injuries to liver failure; and (3) hepatotoxicity of drugs[22]. SARS-CoV-2 virions have been isolated in the bronchoalveolar fluid, in the sputum and in the blood samples of patients with COVID-19. However, recent evidence suggests the gastrointestinal tract represents a potential route of infection and transmission of this pathogen. Viable viral particles and RNA of SARS-CoV-2 have also been found in the feces of people suffering from COVID-19[28], meaning they may also represent a potential route of transmission. In synthesis, available studies show that: (1) it's possible a fecal-oral route of SARS-CoV-2 transmission in the gastrointestinal system and the virus replicates in the mucosa of the intestinal epithelial cells[29]; (2) a high expression of receptors and candidate co-receptors/auxiliary proteins can be identified in the gastrointestinal tract with an affinity for SARS-CoV-2; (3) an elevated expression of TMPRSS2 of the host is detectable in the cells of the gastrointestinal tract; (4) following COVID-19 infection, the stool test for viral SARS-CoV-2 RNA gives a positive result for a considerable time in approximately 64% of patients with negative nasopharyngeal swab[30,31]; and (5) SARS-CoV-2 mRNA and its intracellular nucleocapsid protein can be observed in gastric, duodenal and rectal epithelia[32].

In order to pursue the objective of this research, we have performed an extensive bibliographic search of the published works available in the literature concerning post-COVID-19 cholangiopathy. Then we have conducted a systematic review of this topic.

MATERIALS AND METHODS

A systematic computer-based search of articles available in literature has been led through two electronic databases (MEDLINE/PubMed and Cochrane Library) with the aim of identifying relevant papers about post-COVID-19 cholangiopathy published between January 1, 2020 and August 22, 2022. All the articles edited in all the languages, besides the English one, have been taken into account. The MeSH terms and the keywords used have been: "cholangiopathy", "COVID-19", "post-COVID-19 cholangiopathy" and "SARS-CoV-2". The authors have used the PRISMA 2009

Checklist and the manuscript has been prepared and revised according to it[33]. Two of the authors (de Biase D and Gallo CG) independently and in parallel have carried out the literature search and identified the relevant articles based on the title and/or the abstract. The inclusion criteria considered in our analysis have been: retrospective and prospective studies, cohort studies, case series and case reports. Other two authors (Hong W and Grottesi A), have independently extracted and tabulated all the relevant data from the selected studies. Fiorino S has controlled the accuracy of them. When an inconsistency of the results have emerged between the selected papers, a consensus among all the Authors has been required. To avoid possible duplicates, we have looked for the first Author's name of the research, the place and the period of the enrollment of the subjects. The identified studies are depicted in Figure 1.

Statistical analysis

The heterogeneity of data, as well as their small size, has limited the chance to perform a comparative statistical analysis or a meta-analysis. Only a descriptive analysis with percentages has been carried out, not using any specific software.

RESULTS

Available studies

A total of 16 articles have been identified describing patients with post-COVID-19 cholangiopathy. Three of them have been excluded for the following reasons: two papers have described the cholestasis caused by intravenous ketamine used for the sedation of patients with acute respiratory distress syndrome (ARDS)[34,35]; the third one has concerned a retrospective research about 72 cholestatic patients observed as early as 28 d after the admission[36]. The collected studies are shown in Table 1.

Taking into account the descriptive analysis of these 13 studies[11,37-48], the following data have been obtained: (1) 64 patients have been examined, with a prevalence of males (53 males *vs* 11 females, that is 82.8% of the group); (2) the average peak of ALP values has been 75.5 d; (3) a liver biopsy has been performed in 24 of the 64 patients

(37.5%); (4) a total of 17 endoscopic retrograde cholangiopancreatography (ERCPs) have been carried out, mainly to extract sludge and stones. During an examination, cholangioscopy has been used to directly view the stenosed intrahepatic segment[43]; and (5) six patients have received a liver transplant (LT), while seven have been scheduled for surgery and two have refused it, for a total of 15 patients (23.4%).

DISCUSSION

Secondary sclerosing cholangitis in critically ill patients (SC-CIP) is a rare cholestatic condition encountered in patients developing sepsis or ARDS during a prolonged stay in the intensive care units. This pathology rapidly induces cirrhosis, leading to liver failure. Its prognosis is poor and the only option consists of a LT. Some risk factors for post-COVID-19 cholangiopathy have been identified: mechanical ventilation, prone position and excess intraperitoneal fat[49]. Its pathogenesis is complex and is suggestive of a damage of ischemic origin that may involve the biliary tract until its stenosis and at the end a subsequent over infection caused by multidrug-resistant bacteria[49]. Roth *et al*[11] first have noticed that the histological characteristics have been similar to the ones of SSC-CIP occurring in their patients, with severe damage to cholangiocytes. The injury of the cells has been characterized by a marked cytoplasmic vacuolization and by intrahepatic microangiopathy. This recognized pattern has highly suggested a direct liver damage induced by SARS-CoV-2[11]. These findings have been the very first observations of secondary sclerosing cholangitis post-COVID-19. Hence, the authors have suggested a post-infectious cholestasis could be due to an overlap of SSC-CIP. This assumption is supported by a higher elevation of serum alkaline phosphatase levels registered in correlation with a direct hepatic damage[11]. In a recent prospective cohort study, 461 patients with COVID-19 have undergone liver function tests both during hospitalization and at 1, 3, 6 and 12 mo after their discharge[50]. The results have showed that they markedly improved over time, with only 13.2% of tests altered at 12 mo compared to 25.1% in the first month[50]. Unfortunately, this study has considered only GGT levels as a cholestasis index, with corresponding median values of 27 U/L (range:

18-40) in the first month of follow-up and 20 U/L (range: 13-29) after one year, without having tested ALP and serum bilirubin levels[50].

Even the fact remains that cholangiopathy experienced in patients affected by the virus is also associated with the histological characteristics of sclerosing cholangitis, except the well-known direct damage caused by the virus other factors should be taken into account.

In these subjects, the presence of a persistent cholestatic condition combined with jaundice requires diagnostic radiological integration. An intravenous contrast computed tomography scan of the abdomen may show both dilation of the intrahepatic bile ducts and of the common bile duct with hyperpotentiation of their walls[51]. A magnetic resonance cholangiopancreatography can provide other additional details, including the presence of diffuse periductal edema[52]. Finally, an invasive and therapeutic examination (ERCP), as we have observed in the works listed in Table 1, can show tortuosity of intrahepatic bile ducts[53].

The drugs used for the treatment of this infection include antivirals, antibiotics, antipyretics and immune-modulators that often provoke transient hepatotoxicity[54,55]. With specific regard to its medical therapy, in most examined works it is reported that drugs such as ursodeoxycholic acid and obeticholic acid have been used, with the aim of not resolving the disease, but only of slowing down the liver damage produced by the accumulation of the not excreted bile acids[56].

We are of the opinion that post-COVID-19 cholangiopathy represents a topic of interest that could entail future developments. Unfortunately, the low number of actually available studies and the small cases of enrolled patients constitute a current limit to our evaluation. We hope that in the near future the scientific world carries out investigations focused on this new emerging pathology based on a greater sample of subjects, in order to be able to better identify the best treatment to offer.

CONCLUSION

Liver involvement during SARS-CoV-2 infection is mild and transient, as reported in the literature, but unfortunately some cases of severe liver damage can occur, leading to the failure of the organ. According to the data emerged by reviewing the previous works, it can be asserted that post-COVID cholangiopathy may represent a clinico-pathological condition needing a strict control owing to the high risk of developing a progressive liver damage that might need a transplant. This research is quite innovative and shows interesting results, but because of its recent discoveries it meets some limitations, such as the still poor published studies and the low number of patients enrolled. Further investigations including a larger amount of them could help in a better comprehension of the pathogenesis and of the development of this disease, in this way preventing or at least mitigating its clinical course improving its treatment.

ARTICLE HIGHLIGHTS

Research background

Post-coronavirus disease 2019 (COVID-19) cholangiopathy is a recently identified clinical entity that develops during the recovery phase from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Research motivation

Early recognition of this complication is critical to ensure prompt and adequate management, which could affect the prognosis of these patients.

Research objectives

The main objectives of this review have been to identify the available data contained in the studies accessible from the literature concerning post-COVID-19 cholangiopathy.

Research methods

We have searched within two electronic databases (PubMed and the Cochrane Library) works on this topic, performed from January 1, 2020 to August 22, 2022, using MeSH

terms and free-language keywords: cholangiopathy; COVID-19; post-COVID-19 cholangiopathy; SARS-CoV-2.

Research results

Thirteen studies have been included in this descriptive revision about 64 patients suffering from this condition.

Research conclusions

This review analyzes the possible causes and the clinical course of post-COVID-19 cholangiopathy, aiming to understand both its possible causes and its consequent clinical evolution.

Research perspectives

Cholangiopathy is a medium-to-long-term complication of this virosis, in which biliary damage is generally progressive up to liver failure. Researchers should focus on both early recognition and timely treatment of this complication.

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