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ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Dr. Tsolakis is an interventional endoscopist (Senior Consultant) and group leader for endoscopic ultrasound and duodenal polyps at Karolinska University Hospital, Stockholm, Sweden. Dr. Tsolakis became a Specialist in Internal Medicine (2010) and Gastroenterology (2011) at the Uppsala University Hospital, Sweden, where he was subsequently appointed as Consultant Gastroenterologist focusing on endoscopy and neuroendocrine tumors in the Departments of Gastroenterology and Endocrine Oncology. He completed training in advanced therapeutic endoscopy in Canada, initially at the University of Calgary (2014) and later at St. Michael's Hospital in Toronto (2015). His ongoing career research interests include advanced endoscopy and neuroendocrine tumors, yielding several peer-reviewed publications in the field of endoscopy and neuroendocrine tumor disease. (L-Editor: Filipodia)

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High prevalence of hepatic steatosis and vascular thrombosis in COVID-19: A systematic review and meta-analysis of autopsy data

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) disease can frequently affect the liver. Data on hepatic histopathological findings in COVID-19 is scarce.

AIM

To characterize hepatic pathological findings in patients with COVID-19.

METHODS

We conducted a systematic review with meta-analysis registered on PROSPERO (CRD42020192813), following PRISMA guidelines. Eligible trials were those including patients of any age and COVID-19 diagnosis based on a molecular test. Histopathological reports from deceased COVID-19 patients undergoing autopsy

Riquelme A, Arrese M, Leise MD and Arab JP contributed critical revision of the manuscript for relevant intellectual content; Díaz LA and Candia R contributed statistical analysis.

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or liver biopsy were reviewed. Articles including less than ten patients were excluded. Proportions were pooled using random-effects models. *Q* statistic and *I*² were used to assess heterogeneity and levels of evidence, respectively.

RESULTS

We identified 18 studies from 7 countries; all were case reports and case series from autopsies. All the patients were over 15 years old, and 67.2% were male. We performed a meta-analysis of 5 studies, including 116 patients. Pooled prevalence estimates of liver histopathological findings were hepatic steatosis 55.1% [95% confidence interval (CI): 46.2-63.8], congestion of hepatic sinuses 34.7% (95% CI: 7.9-68.4), vascular thrombosis 29.4% (95% CI: 0.4-87.2), fibrosis 20.5% (95% CI: 0.6-57.9), Kupffer cell hyperplasia 13.5% (95% CI: 0.6-54.3), portal inflammation 13.2% (95% CI: 0.1-48.8), and lobular inflammation 11.6% (95% CI: 0.3-35.7). We also identified the presence of venous outflow obstruction, phleboscrosis of the portal vein, herniated portal vein, periportal abnormal vessels, hemophagocytosis, and necrosis.

CONCLUSION

We found a high prevalence of hepatic steatosis and vascular thrombosis as major histological liver features. Other frequent findings included portal and lobular inflammation and Kupffer cell hyperplasia or proliferation. Further studies are needed to establish the mechanisms and implications of these findings.

Key Words: Pathology; SARS-CoV-2; COVID-19; Autopsies; Liver; Liver biopsies

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Core Tip: In this systematic review of 18 studies, we identified that hepatic steatosis, congestion of hepatic sinuses, and vascular thrombosis are the main histological findings in deceased coronavirus disease 2019 (COVID-19) patients. Fibrosis is a common histological finding in deceased COVID-19 patients. Kupffer cell hyperplasia, portal inflammation, and lobular inflammation are related to the severe acute respiratory syndrome coronavirus 2 inflammatory process and are frequent histological findings. Other vascular abnormalities (such as venous outflow obstruction, phleboscrosis of the portal vein, herniated portal vein, periportal abnormal vessels) are frequent histological finding in deceased COVID-19 patients.

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INTRODUCTION

The pandemic of the novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (also known as coronavirus disease 2019, COVID-19) has infected more than 59 million individuals worldwide and caused more than 1.4 million deaths. Although the main manifestations of COVID-19 are related to respiratory symptoms, the compromise of multiple organs has been described in the literature, including the digestive system^[1]. There are several gastrointestinal manifestations, including anorexia, diarrhea, nausea/vomiting, and abdominal pain. Those symptoms have a pooled prevalence of 17.6% and are frequently observed in hospitalized patients^[1,2].

The liver is also one of the most common organs affected in COVID-19. In fact, between 2%-11% of affected patients have liver comorbidities and 16%-53% of cases reported abnormal liver tests^[3,4]. The most frequent abnormalities are mildly elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and are more

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common in hospitalized patients^[4,5]. Elevation of alkaline phosphatase and gamma-glutamyl transferase (GGT) has also been reported^[6]. Those alterations have been related to expression of angiotensin-converting enzyme 2 (ACE-2), the putative receptor of SARS-CoV-2, in endothelial cells of the liver and the biliary epithelium^[7]. In addition, since the frequency of liver dysfunction increases as COVID-19 is more severe, liver damage might be directly caused by the infection of liver. Abnormal liver tests can also be partially explained by drug-induced liver injury (DILI), cytokine storm, and/or pneumonia-associated hypoxia^[4].

Pathological studies in patients with SARS-CoV-2 infection have confirmed the presence of the virus in liver tissue^[8]. This finding was also described in SARS and MERS infection^[9]. Although histopathological information is scarce, previous reports from SARS and MERS showed steatosis, mild portal tract and lobular lymphocytic inflammation, as well as mild cellular hydropic degeneration in hepatic parenchyma^[7,9-11]. Regarding SARS-CoV-2 infection, initial reports of autopsies performed in COVID-19 patients have described steatosis, mild lobular and portal activity, lymphocytic endotheliitis, and necrosis^[12-14]. However, data about the main histopathological findings in COVID-19 is still scarce. Thus, aiming to provide a comprehensive synthesis of the pathological findings in liver injury due to SARS-CoV-2 reported so far, we performed a systematic review and meta-analysis of each histopathological finding in liver samples from autopsies and biopsies of COVID-19 patients.

MATERIALS AND METHODS

Overview

This systematic review with meta-analysis was registered on PROSPERO (ID: CRD42020192813) and followed a prespecified analysis plan. This study is reported in accordance with the Preferred Reporting Items for a Review and Meta-analysis (PRISMA) guidelines^[15].

Eligibility criteria

Eligible trials had to include patients diagnosed with COVID-19, regardless of age and gender. The diagnosis of COVID-19 had to be based on a compatible clinical history and molecular evidence with a quantitative real-time polymerase chain reaction (qRT-PCR) for SARS-CoV-2. We included liver histopathological reports from deceased COVID-19 patients who subsequently were studied with autopsy or liver biopsies performed in alive COVID-19 patients.

We planned to include all the studies that report liver histopathological data, regardless of the design (case-reports, case-series, descriptive cases, cross-sectional studies, cohort studies, and randomized controlled trials). We excluded studies performed *in vitro*, animal models, or lacking evidence of SARS-CoV-2 infection from this systematic review. We did not include manuscripts performed before December 1, 2019.

Search strategy and selection process

We performed an electronic search from December 1, 2019, to June 3, 2020, in MEDLINE (*via* PubMed) and Embase databases. We used keywords and free-text words related to SARS-CoV-2 infection, autopsies, and liver biopsies. We reported the search strategy used in PubMed and Embase databases in the appendix. We hand searched (up to June 3, 2020) preprint servers (bioRxiv, medRxiv, and SSRN) and coronavirus resource centers of The Lancet, JAMA, and New England Journal of Medicine. We did not limit our search by language. Two investigators (Díaz LA and Idalsoaga F) independently screened the titles and abstracts to ascertain whether each study met the eligibility criteria. The full texts of the identified eligible articles were then evaluated to determine whether they should be included in the analysis. Disagreements between the two reviewers were resolved by consensus. In case of persistent disagreement, arbitration by a third reviewer (Arab JP) settled the discrepancy.

Data collection and risk of bias assessment

Two authors (Díaz LA and Cannistra M) independently extracted data from included studies using forms specially designed for this purpose. The following data were extracted describing the study, participants, source of sample (liver biopsy or

autopsy), and the main liver histopathological findings. Discrepancies were resolved by a third reviewer (Arab JP). Two investigators (Díaz LA and Idalsoaga F) independently assessed the risk of bias of each included trial with the Appraisal tool for Cross-Sectional Studies (AXIS) checklist for cross-sectional studies, the Institute of Health Economics (IHE) checklist tool for Case Series, the Newcastle-Ottawa Scale (NOS) for case-control studies and cohort studies, and the Cochrane Risk of Bias Tool for randomized trials and quasi-experimental studies.

Outcomes

The outcomes were defined by consensus with an expert pathologist (Graham R). The main outcomes were the frequency of vascular thrombosis (presence or absence), venous outflow obstruction (presence or absence), frequency of portal and lobular Inflammation and severity (mild, moderate, or severe), Kupffer cell hyperplasia (presence or absence), steatosis (presence and fat percentage), fibrosis (based on METAVIR score, scores range from F0 to F4, with higher numbers reflecting greater fibrosis), and ductopenia (presence or absence). Secondary outcomes were the frequency phlebosclerosis of the portal vein, herniated portal vein, congestion of hepatic sinuses, and necrosis.

Data analysis

Data were synthesized per each histopathological finding of SARS-CoV-2 infection. We estimated the prevalence of event rates in the form of a proportion (with a confidence interval of 95%). Proportions were pooled using random-effects models. Only those studies with a sample size of at least ten patients were included in the meta-analysis. We used Q statistic and I^2 to quantify heterogeneity. We planned a subgroup analysis according to the liver sample source (biopsy in alive patients or autopsy), ethnicity, and gender. We planned sensitivity analysis excluding the high risk of bias studies. A small study effect was evaluated with a funnel plot. As such, subgroup and sensitivity analyses should be considered exploratory. All statistical analyses were performed using MedCalc Statistical Software version 19.3.1 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020).

Grading of evidence

The quality of evidence for the outcomes was graded with the GRADE framework.

Role of the funding source

The funding source only provided support for the financing of paid manuscripts during the review process. The researchers did not receive payment or other incentives.

RESULTS

We identified 3060 records and 905 were duplicates. After a screening process against title and abstract, we obtained 58 full-text articles that were assessed for eligibility. We finally selected 18 studies for our systematic review from 7 countries (Austria, Belgium, China, Germany, Italy, Switzerland, and the United States). The selection process is described in [Figure 1](#). All studies were observational in design; no randomized trials were identified. Among the 18 studies, 4 were case reports and 14 case series. The study with the largest sample size included a total of 48 cases^[16]. Fifteen studies reported the proportion of each finding and the other three studies presented the pooled data without the prevalence of each finding. All the studies included autopsy data (*i.e.*, no liver biopsies from living patients were identified). The risk of bias assessment was considered high.

The pooled studies included a total of 167 patients. All the patients were over 15 years old and 67.2% were male. The grade of evidence was considered very low since all the information emerged from case reports and case series. For the meta-analysis of each finding, we included only five studies with at least ten patients. There was a maximum of 116 cases included in each meta-analysis. We did not perform subgroup analyses due to the low number of studies included. [Table 1](#)^[17-30] summarizes the main baseline characteristics of each study. The main findings described in the selected studies were hepatic steatosis, congestion of hepatic sinuses, vascular thrombosis, fibrosis, Kupffer cell proliferation or hyperplasia, portal inflammation, lobular inflammation, venous outflow obstruction, phlebosclerosis of the portal vein, herniated portal vein, periportal abnormal vessels, hemophagocytosis, and necrosis.

Table 1 Main characteristics of studies included in the analysis

Ref.	Date	Country	Sources of samples	N° of pts	Age (yr)	Gender	Ethnicity	Comorbidities
Barton <i>et al</i> ^[17]	April 2020	United States	Autopsy	2	77 and 42	2 Males	Not reported	Obesity (2/2), hypertension (1/2), splenectomy (1/2), myotonic dystrophy (1/2)
Bradley <i>et al</i> ^[18]	April 2020	United States	Autopsy	12	70.4 (42-84)	5 Males and 7 females	Not reported	Not reported
Bryce <i>et al</i> ^[29]	May 2020	United States	Autopsy	22	Not reported	Not reported	Not reported	Not reported
Buja <i>et al</i> ^[19]	May 2020	United States	Autopsy	3	62, 34 and 48	2 Males and 1 female	2 Hispanic and 1 afro-american	Obesity (3/3), hypertension (1/3), heart failure (1/3), diabetes (1/3) and microcytic anemia (1/3)
Craver <i>et al</i> ^[20]	April 2020	United States	Autopsy	1	17	Male	Afro-american	None
Lacy <i>et al</i> ^[21]	April 2020	United States	Autopsy	1	58	Female	Not reported	Diabetes, obesity, hyperlipidemia, Asthma, and chronic lower extremity swelling with ulceration
Lax <i>et al</i> ^[27]	May 2020	Austria	Autopsy	11	80.5 (66-91)	8 Males and 3 females	Not reported	Hypertension (9/11), diabetes mellitus (5/11), coronary artery disease (2/11), previous malignant disease (2/11), COPD (2/11), cerebrovascular disease (4/11), and dementia (4/11)
Martines <i>et al</i> ^[22]	May 2020	United States	Autopsy	8	73.5	4 Males and 4 females	7 Caucasian and 1 hispanic	Arterial hypertension (6/8), chronic kidney disease and (6/8) cardiovascular disease (6/8), obesity (5/8), diabetes (4/8), chronic lung disease (2/8), immunocompromised condition (3/8), among others
Menter <i>et al</i> ^[23]	May 2020	Switzerland	Autopsy	17	Adult patients	Not specified	Not specified	Not specified
Prilutskiy <i>et al</i> ^[28]	March 2020	United States	Autopsy	4	64-91	3 Males and 1 female	3 Afro-american and 1 caucasian	Not reported
Rommelink <i>et al</i> ^[24]	May 2020	Belgium	Autopsy	17	72 [62-77]	12 Males and 5 females	Not reported	Cirrhosis (2/17), liver transplantation (1/17), hypertension (10/17), diabetes (9/17), cerebrovascular disease (4/17), coronary artery disease (4/17), and solid cancer (4/17)
Schaller <i>et al</i> ^[25]	May 2020	Germany	Autopsy	10	79 (64-90)	7 Males and 3 females	Not reported	Fatty liver disease (1/10), hypertension (7/10), atrial fibrillation (4/10), chronic kidney failure (3/10), COPD (2/10), heart failure (2/10), obesity (2/10), diabetes (1/10), among others
Sonzogni <i>et al</i> ^[16]	May 2020	Italy	Autopsy	48	71.2 (32-87)	35 Males and 13 females	Not reported	Not specified
Tian <i>et al</i> ^[14]	April 2020	China	Autopsy	4	78, 74, 81, 59	3 Males and 1 female	Asian	Chronic lymphocytic leukemia; Cirrhosis, DM2, HTA
Varga <i>et al</i> ^[13]	April 2020	Switzerland	Autopsy	1	58	Female	Not reported	Diabetes, hypertension, and obesity
Wang <i>et al</i> ^[26]	May 2020	China	Autopsy	2	50 and 79	1 Male and 1 female	2 Asian	Not reported
Xu <i>et al</i> ^[12]	February 2020	China	Autopsy	1	50	Male	Asian	Not reported
Yao <i>et al</i> ^[30]	May 2020	China	Autopsy	3	63, 69, and 79	2 Males and 1 female	3 Asian	Diabetes (1/3), hyperglycemia (1/3) bronchiectasis (1/3), solid cancer (1/3)

We did not find ductopenia in the selected studies. Figure 2 summarizes the major liver histological features. A detailed assessment of each feature is provided below. Funnel plot of the studies included in each meta-analysis are provided in Supplementary Figure 1 (Supplementary material).

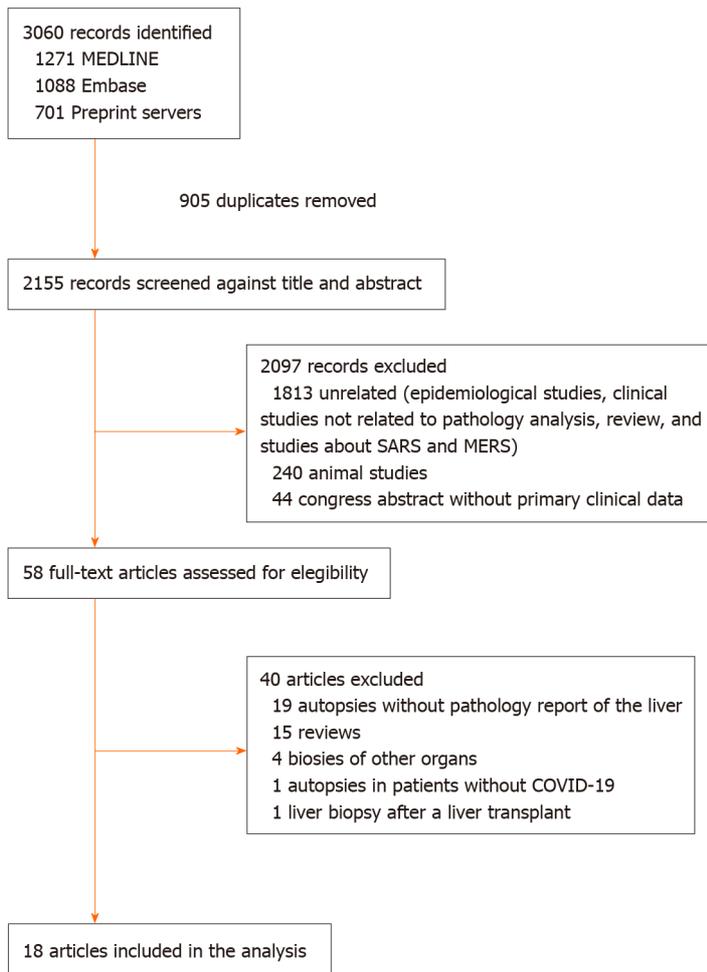


Figure 1 Study selection for the systematic review.

Hepatic steatosis

A total of 78 from 139 (65.1%) patients demonstrated hepatic steatosis. Lipid droplet size was described in only 7 cases (9%): 4 macrovesicular, 1 microvesicular, and 2 mixed (macrovesicular and microvesicular). The studies of Lax *et al*^[27] and Prilutskiy *et al*^[28] also described the presence of hepatic steatosis without the proportion of this finding. When meta-analyzed, data showed a pooled prevalence of hepatic steatosis of 55.1% [5 studies, 116 patients; 95% confidence interval (CI): 46.2-63.8], without significant heterogeneity among the studies ($P = 0.411$; $I^2 = 0\%$) (Figure 3A).

Congestion of hepatic sinuses and necrosis

A total of 28 from 163 cases (17.2%) reported congestion of hepatic sinuses. Additionally, the study of Prilutskiy *et al*^[28] described the presence of mild centrilobular congestion without the frequency of this finding. In the meta-analysis, the pooled prevalence of congestion of hepatic sinuses was 34.7% (5 studies, 79 patients; 95%CI: 7.9-68.4) (Figure 3B). The heterogeneity was significant among studies ($P < 0.001$; $I^2 = 90.2\%$). Regarding necrosis, 14 of 91 patients (15.4%) presented this finding. Necrosis was also described without a proportion in the study of Yao *et al*^[30]. We could not perform a meta-analysis of this finding due to the low number of patients and studies that adequately described the presence or absence of necrosis.

Vascular thrombosis and other vascular alterations

A total of 63 from 139 (45.3%) cases presented vascular thrombosis. The type of vessel thrombosed was not specified in the studies. When meta-analyzed, data showed a pooled prevalence of vascular thrombosis of 29.4% (5 studies, 116 patients; 95%CI: 0.4-87.2). The heterogeneity was significant among studies ($P < 0.001$; $I^2 = 97.7\%$) (Figure 3C).

Other vascular alterations were identified in the studies. The presence of venous

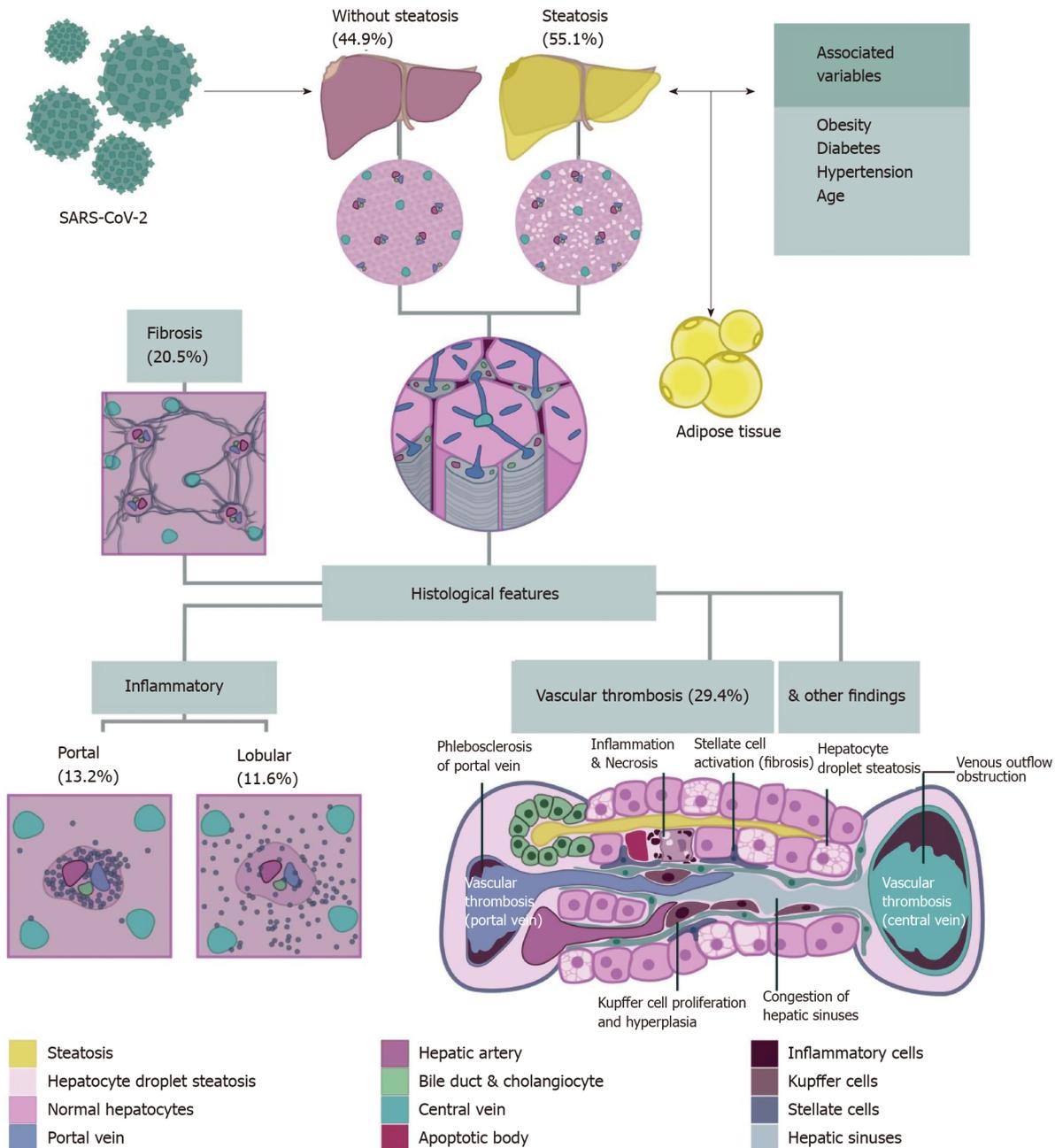


Figure 2 Major liver histological features observed in 6 studies (n = 116 autopsies from deceased coronavirus disease 2019 patients). Steatosis was the most frequent finding (55.1%). Studies also reported congestion of hepatic sinuses (34.6%), vascular thrombosis (29.4%), fibrosis (20.5%), Kupffer cell hyperplasia (13.5%), portal inflammation (13.2%), and lobular inflammation (11.6%), Other findings observed were venous outflow obstruction, phlebosclerosis of the portal vein, herniated portal vein, periportal abnormal vessels, hemophagocytosis, and necrosis.

outflow obstruction was described exclusively by Bryce *et al*^[29], with a prevalence of 36.4% (8 of 22 cases), and 5 of these cases (62.5%) were acute. The study by Sonzogni *et al*^[16] reported additional vascular alterations in a serial of 48 cases: 29 patients demonstrated phlebosclerosis of the portal vein (60.4%), 36 had a herniated portal vein (75%), and 48 (100%) had abnormal periportal vessels (27 focal, 18 multifocal, and 3 diffuse).

Hepatic fibrosis

A total of 51 from 139 (36.7%) patients had fibrosis. The grade of fibrosis was only described in 7 cases: 1 case was graded as F3 (METAVIR scale) and 6 cases were graded as F4. The study by Lax *et al*^[27] and Prilutskiy *et al*^[28] also described the presence of fibrosis without the proportion of this finding. In the meta-analysis, the pooled prevalence of fibrosis was 20.5% (5 studies, 116 patients; 95%CI: 0.6-57.9), with

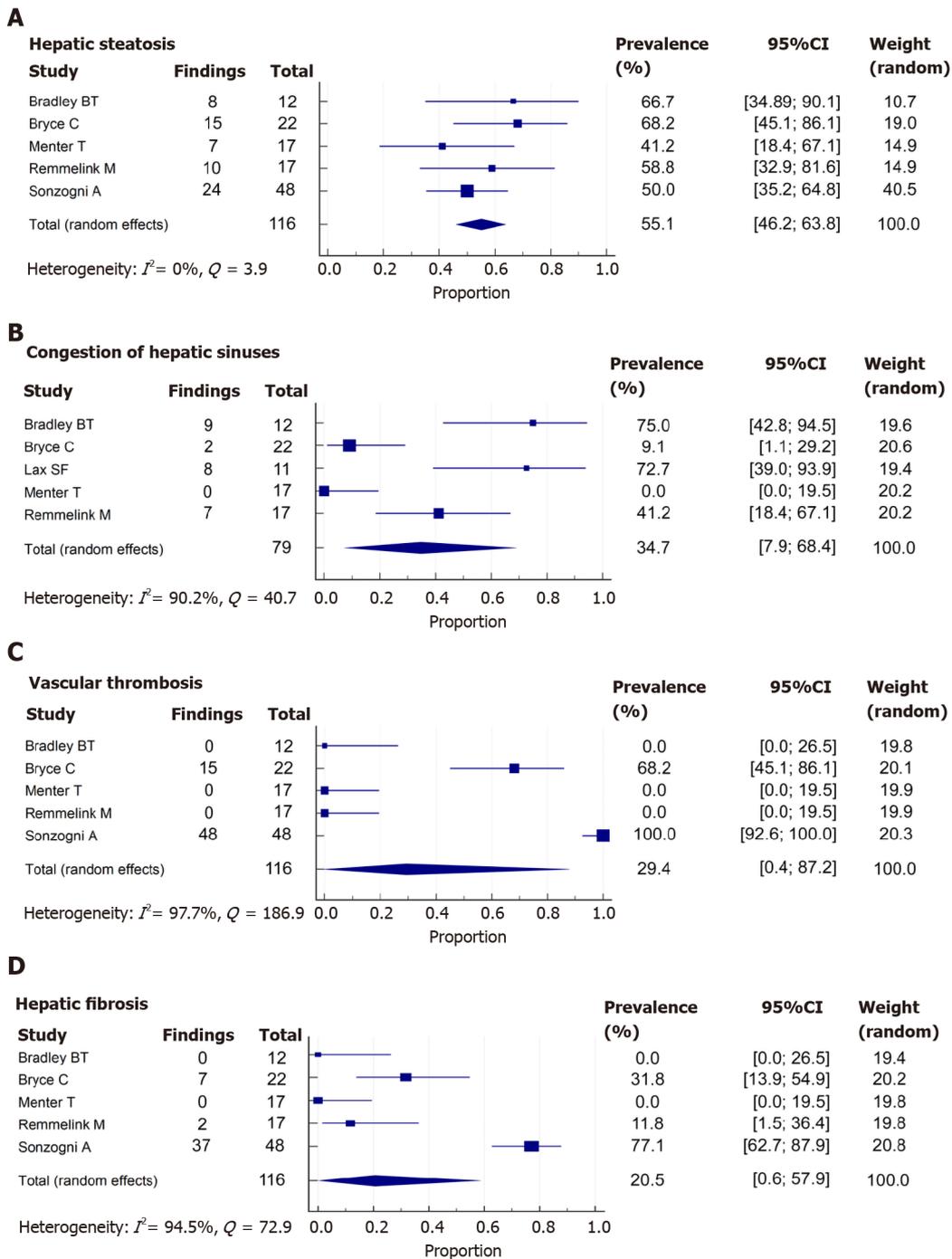


Figure 3 Forest plots of major liver histological features from deceased coronavirus disease 2019 patients. A-D: The figure includes forest plots of hepatic steatosis (A), congestion of hepatic sinuses (B), vascular thrombosis (C), and fibrosis (D). Heterogeneity was assessed using I^2 and Q statistics. CI: Confidence interval.

significant heterogeneity among the studies ($P < 0.001$; $I^2 = 94.5\%$) (Figure 3D).

Kupffer cell proliferation or hyperplasia

Only 12 of 115 cases (10.4%) reported Kupffer cell proliferation or hyperplasia. The studies by Sonzogni *et al*^[16] and Prilutskiy *et al*^[28] also described the presence of this phenomenon, but without a prevalence. Additionally, the study of Bryce *et al*^[30] described the presence of hemophagocytosis. In the meta-analysis, the pooled prevalence of Kupffer cell hyperplasia was 13.5% (5 studies, 79 patients; 95%CI: 0.6-54.3%). The heterogeneity was significant among studies ($P < 0.001$; $I^2 = 94.3\%$) (Figure 4A).

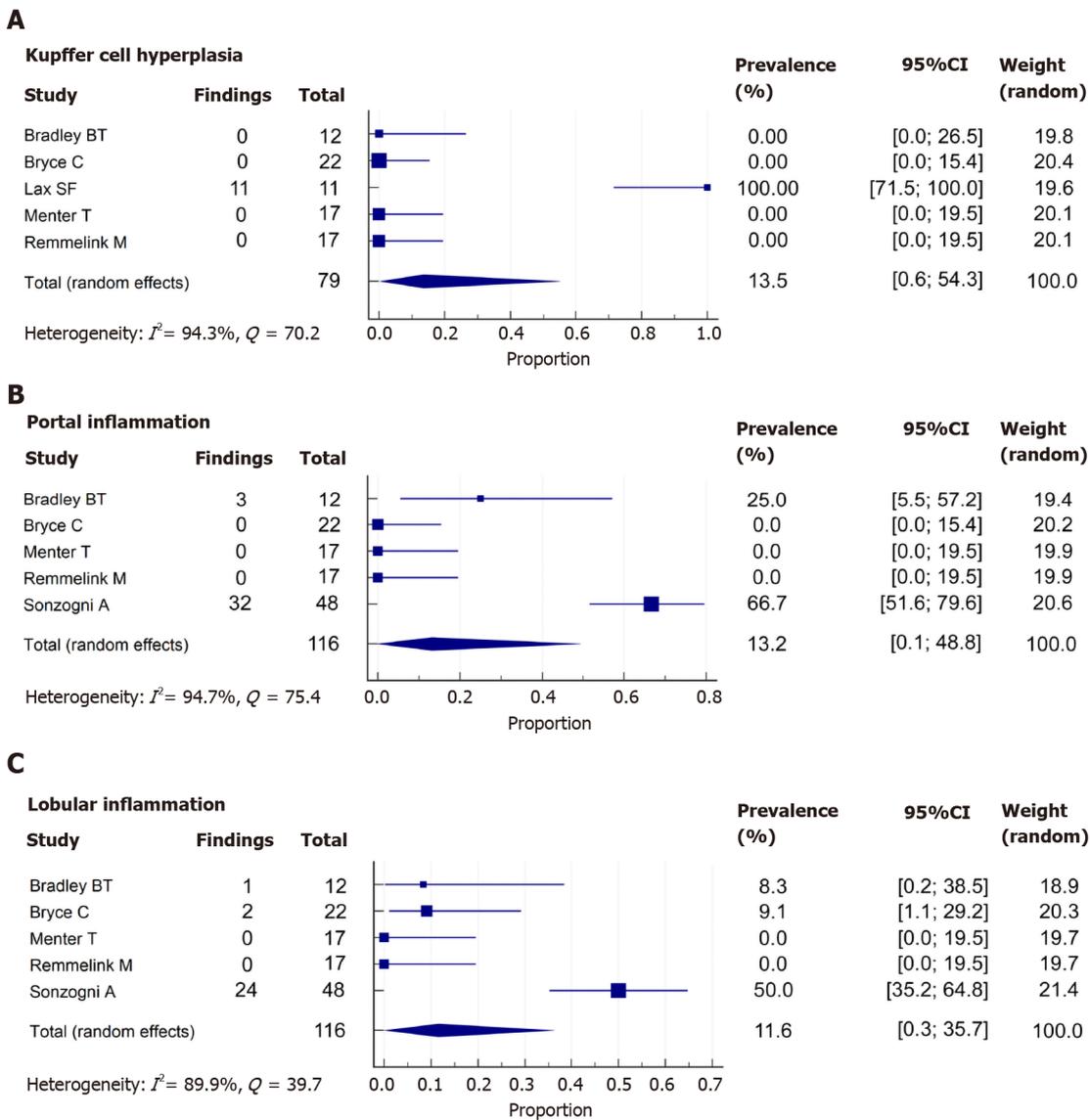


Figure 4 Forest plots of inflammatory liver histological features from deceased coronavirus disease 2019 patients. A-C: The figure includes forest plots of Kupffer cell hyperplasia (A), portal inflammation (B), and lobular inflammation (C). Heterogeneity was assessed using I^2 and Q statistics. CI: Confidence interval.

Portal and lobular inflammation

Histologic evaluation in a total of 41 out of 139 (29.5%) patients showed portal inflammation. The grade of inflammation was reported in 37 of 41 cases (90.2%); all were graded as mild, and the cells were lymphocytes and plasma cells. When meta-analyzed, data showed a pooled prevalence of portal inflammation of 13.2% (5 studies, 116 patients; 95%CI: 0.1-48.8), with significant heterogeneity noted among studies ($P < 0.001$; $I^2 = 94.7\%$) (Figure 4B).

In the case of lobular inflammation, a total of 31 from 139 (22.3%) showed this finding. The grade of inflammation was reported in 28 of 31 cases (90.3%): 26 cases were mild (92.9%) and 2 were moderate (7.1%). The predominant cells were neutrophils and lymphocytes. In a meta-analysis, the pooled prevalence of lobular inflammation was 11.6% (5 studies, 116 patients; 95%CI: 0.3-35.7), with significant heterogeneity noted among studies ($P < 0.001$; $I^2 = 89.9\%$) (Figure 4C).

DISCUSSION

As previously reported for patients with SARS and MERS, the liver is frequently affected during a SARS-Cov-2-related disease (COVID-19)^[3,5]. In this systematic review, we identified 18 studies from 7 countries (case reports and case series) that

include data from autopsies of deceased patients with COVID-19. We identified multiple histopathological findings, including hepatic steatosis (55.1%), venous outflow obstruction (36.4%), congestion of hepatic sinuses (34.7%), vascular thrombosis (29.4%), fibrosis (20.5%), necrosis (15.4%), Kupffer cell hyperplasia (13.5%), portal inflammation (13.2%), and lobular inflammation (11.6%).

Several of the hepatic histopathological findings observed in this study have also been described in SARS and MERS patients. It may be related to the ongoing systemic inflammatory process and sepsis, affecting the liver rather than a direct manifestation of SARS-CoV-2^[7,9-11]. There is still debate about whether SARS-CoV-2 directly causes liver injury or if the observed abnormalities in liver chemistries seen in COVID-19 are an indirect consequence of the disease reflecting severity, inflammation, and potentially confounding muscle injury that occurs in 19% of patients^[31]. A recent study by Bloom *et al*^[32] showed that AST-dominant aminotransferase elevation is common in COVID-19, is not associated with muscle damage markers and correlates with disease severity, probably reflecting true hepatic injury. In a series including 148 patients from a single-center in China, 55 (37.2%) had abnormal liver chemistries on admission. Patients with elevated admission liver chemistries were also more likely to have a high-grade fever and higher C-reactive protein^[33]. In two large Chinese cohorts, 6.2% and 11.6% of patients with COVID-19 developed liver chemistries over 3 times the upper limit of normal, suggesting that a minority of patients experience significant biochemistry elevations^[34,35].

The most frequent histopathological finding was steatosis. This prevalence is higher than the general population^[36]. This can be partially explained by the baseline characteristics of the population. Admitted COVID-19 patients suffer from more severe disease and more frequently exhibit chronic diseases (*i.e.*, diabetes mellitus, age, hypertension, obesity, and cardiovascular disease), which are also associated with hepatic steatosis^[37]. However, existing data suggest that SARS-COV-2 may affect lipid metabolism^[38]. In general, all viruses alter lipid synthesis and signaling in host cells as they hijack and utilize the cellular machinery to produce lipids for their envelope. Also, it has been shown that COVID-19 patients have elevated serum levels of fatty acids and infection with other SARS viruses determine long-lasting alterations in lipid metabolism^[39]. It has been shown that metabolic-dysfunction associated fatty liver (MAFLD)^[40] condition is independently associated with a higher risk of severe COVID-19 (odds ratio 2.67)^[41]. Also, advanced MAFLD (*i.e.*, fibrotic disease) is associated with a more severe disease irrespective of metabolic comorbidities. Since the liver hosts a significant mass of innate immune cells, hepatic release of proinflammatory cytokines may contribute to COVID-19 severity^[42]. Also, some authors suggest NAFLD progression could be accelerated or exacerbated by COVID-19^[42].

We observed an increased frequency of hepatic vascular alterations in patients with COVID-19. This may be due to endothelial dysfunction (endotheliitis), a pro-coagulant state, and direct vascular injury of the disease^[13,43,44]. Congestion and necrosis are features of venous outflow obstruction and may also be explained by circulatory dysfunction, heart failure, and ischemia, which may complicate multiorgan failure.

Liver fibrosis was also frequently found in the published series of COVID-19 patients. Whether this is related to sustained liver injury or by prior history of chronic liver disease is unclear, though the latter is favored given the acute nature of COVID-19 disease. Of note, patients with cirrhosis have been shown to have a higher risk of mortality due to COVID-19 (relative risk of 4.6)^[45].

It is important to notice that no specific histologic indicator of direct infection (*i.e.*, viral cytopathic effect) in the liver tissue. Notably, there was a report from a pediatric living donor liver allograft recipient who, on a post-operative day 4, developed respiratory distress, fever, and an approximately 5-fold elevation of liver enzymes. The patient and donor were positive for SARS-CoV-2. Liver biopsy showed moderate acute hepatitis with prominent clusters of apoptotic hepatocytes, associated cellular debris, and lobular lymphohistiocytic inflammation. Typical portal features of mild to moderate acute cellular rejection were also noted^[46]. This case report raises consideration for possible direct liver injury.

The possible mechanisms by which SARS-CoV-2 exerts its pathogenetic role in the liver have been speculated in the literature. There is a known tropism of SARS-CoV-2 for ACE-2 receptors, and they are abundantly expressed in cholangiocytes. Nevertheless, a cholestatic pattern of liver injury is not the most common finding on presentation, as one might expect^[47]. A second proposed mechanism is the cytokine storm, which leads to a surge in inflammatory cytokines affecting the liver^[48]. SARS-CoV-2 induced acute respiratory distress syndrome and systemic inflammatory response syndrome lead to hypoxemia and shock, which can cause ischemia-reperfusion injury^[49]. It has been reported that SARS-CoV-2 can infect the endothelial

cells directly and result in widespread endotheliitis^[13]. Furthermore, administration of multiple drugs attempting to treat the disease have the potential to produce DILI, exacerbating the liver involvement of the disease^[50].

The main limitation of our study is the inclusion of autopsies only, resulting in bias towards the most severe disease, with great influence by pre-existing co-morbid conditions. In our literature search, there were no reported liver biopsies from non-severe COVID-19 patients. A correlation between clinical condition, biochemistry, liver imaging, and autopsies would be desirable to explore. Another limitation of this systematic review is the high heterogeneity in the published articles. Finally, since this is a systematic review from autopsy data, relevant clinical information to interpret the causes of steatosis (such as alcohol consumption or body mass index) was not available.

CONCLUSION

In summary, in this systematic review and meta-analysis of autopsies from patients with COVID-19, we found a high prevalence of hepatic steatosis and the presence of vascular thrombosis as major histological liver features. Further studies are needed to establish the mechanism and implications of these findings.

ARTICLE HIGHLIGHTS

Research background

The liver is frequently involved during severe acute respiratory syndrome coronavirus 2 infection and coronavirus disease 2019 (COVID-19). However, there is no consensus about the main histopathological findings in COVID-19.

Research motivation

Identifying the main histopathological findings could help understand the mechanism of liver injury frequently observed in COVID-19 patients.

Research objectives

The characterization of the liver histopathological findings will impact the interpretation of liver chemistries and liver biopsies in COVID-19 patients.

Research methods

We conducted a systematic review and meta-analysis, including liver biopsies and autopsies of COVID-19 patients. Proportions were estimated using random-effects models.

Research results

We included 18 studies. The major histological findings are hepatic steatosis (55.1%), congestion of hepatic sinuses (34.7%), vascular thrombosis (29.4%), fibrosis (20.5%), Kupffer cell hyperplasia (13.5%), portal inflammation (13.2%), and lobular inflammation (11.6%). Other abnormalities can be identified, such as venous outflow obstruction, phlebosclerosis of the portal vein, herniated portal vein, periportal abnormal vessels, hemophagocytosis, and necrosis.

Research conclusions

Steatosis, vascular thrombosis, fibrosis, and inflammatory abnormalities are the most frequent liver histopathological findings in COVID-19 patients.

Research perspectives

The multiple liver histopathological findings observed in COVID-19 demonstrate the susceptibility to liver injury in risk populations, the inflammatory response, and thrombosis associated with this infection.

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