World Journal of Gastroenterology

Submit a Manuscript: https://www.f6publishing.com

World J Gastroenterol 2023 January 7; 29(1): 200-220

DOI: 10.3748/wjg.v29.i1.200

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

SYSTEMATIC REVIEWS

Liver pathology in COVID-19 related death and leading role of autopsy in the pandemic

Martina Zanon, Margherita Neri, Stefano Pizzolitto, Davide Radaelli, Monica Concato, Michela Peruch, Stefano D'Errico

Specialty type: Pathology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Bataga SM, Romania; He F, China

Received: September 13, 2022
Peer-review started: September 13, 2022
First decision: October 30, 2022
Revised: November 14, 2022
Accepted: December 21, 2022
Article in press: December 21, 2022
Published online: January 7, 2023

Martina Zanon, Davide Radaelli, Monica Concato, Michela Peruch, Stefano D'Errico, Department of Medical Surgical and Health Sciences, University of Trieste, Trieste 34149, Italy

Margherita Neri, Department of Medical Sciences, University of Ferrara, Ferrara 44121, Italy

Stefano Pizzolitto, Department of Pathology, Santa Maria della Misericordia University Hospital, Udine 33100, Italy

Corresponding author: Stefano D'Errico, PhD, Assistant Professor, Department of Medical Surgical and Health Sciences, University of Trieste, Strada di Fiume, Trieste 34149, Italy. sderrico@units.it

Abstract

BACKGROUND

Information on liver involvement in patients with coronavirus disease 2019 is currently fragmented.

AIM

To highlight the pathological changes found during the autopsy of severe acute respiratory syndrome coronavirus 2 positive patients.

METHODS

A systematic literature search on PubMed was carried out until June 21, 2022.

RESULTS

A literature review reveals that pre-existing liver disease and elevation of liver enzyme in these patients are not common; liver enzyme elevations tend to be seen in those in critical conditions. Despite the poor expression of viral receptors in the liver, it seems that the virus is able to infect this organ and therefore cause liver damage. Unfortunately, to date, the search for the virus inside the liver is not frequent (16% of the cases) and only a small number show the presence of the virus. In most of the autopsy cases, macroscopic assessment is lacking, while microscopic evaluation of livers has revealed the frequent presence of congestion (42.7%) and steatosis (41.6%). Less frequent is the finding of hepatic inflammation or necrosis (19%) and portal inflammation (18%). The presence of microthrombi, frequently found in the lungs, is infrequent in the liver, with only 12% of cases presenting thrombotic formations within the vascular tree.

CONCLUSION
To date, the greatest problem in interpreting these modifications remains the association of the damage with the direct action of the virus, rather than with the inflammation or alterations induced by hypoxia and hypovolemia in patients undergoing oxygen therapy and decompensated patients.

Key Words: Liver; COVID-19; Autopsy; Immunohistochemistry; *In situ* hybridization; Immunofluorescence

Core Tip: A literature review, about liver pathology in coronavirus disease 2019 (COVID-19) patients, demonstrates the presence of liver damage, which is represented mainly by congestion, steatosis, hepatic inflammation and necrosis, and portal inflammation. The problem to date is whether the damage is COVID-19 related (meaning from direct virus damage/inflammatory related/systemic pathology related) or drug induced. However, this demonstration involves the need to be careful during drug treatment in patients with altered liver enzyme values to prevent further clinical worsening.

Citation: Zanon M, Neri M, Pizzolitto S, Radaelli D, Concato M, Peruch M, D'Errico S. Liver pathology in COVID-19 related death and leading role of autopsy in the pandemic. *World J Gastroenterol* 2023; 29(1): 200-220
URL: https://www.wjgnet.com/1007-9327/full/v29/i1/200.htm
DOI: https://dx.doi.org/10.3748/wjg.v29.i1.200

INTRODUCTION

The new coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been well studied in relation to pulmonary and cardiac histologic manifestations, but little is yet known regarding hepatic manifestations. COVID-19 has, in fact, to be considered a systemic infectious and inflammatory disease with histological changes also in other organs apart from its main target represented by the lungs. Liver involvement to date is recognized and defined as any liver damage occurring during the course of the disease or its treatment[1], meaning that liver damage can be caused by direct cytotoxicity or inflammatory response and hypoxic/cardio-vascular changes, or it may be drug-induced[2-4]. SARS-CoV-2 liver tropism is also well studied, with many authors demonstrating the presence of angiotensin converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2 in the liver, mainly expressed on cholangiocytes, where the levels of expression are similar to those on alveolar cells, though they are only minimally expressed on hepatocytes. No ACE2 expression was demonstrated on sinusoidal endothelial cells or Kupffer cells, apart from Wanner *et al*[5] who demonstrated minimal expression of ACE2 on Kupffer cells through immunofluorescence and Pirisi *et al*[6] who demonstrated the presence of virus-like particles in endothelial cells of hepatic sinusoids. Curiously, in patients with liver fibrosis/cirrhosis and in cases of hypoxia, the expression of ACE2 is increased, therefore pre-existing liver injury or hypoxic conditions, common in patients with COVID-19, could favor SARS-CoV-2 liver tropism[4,7-9]. Liver infection could also be explained by its immunological role and the proximity to the digestive organs, which exhibit a strong SARS-CoV-2-tropism, that could favor the entry of the virus through the portal system. Hepatic macrophages (mainly Kupffer cells) and sinusoidal endothelial cells have a key role in the activation of the immune response through pathogen recognition receptors, thus favoring virus entry[10].

The incidence of liver injury in COVID-19 patients is seen in 14%-53% cases[9,11,12] mainly demonstrated through abnormal liver function enzymes. In the literature, only a small number of studies focus on liver damage and even fewer on histological changes in patients who died with or from COVID-19. The purpose of this review is to summarize the results of studies in the literature and evaluate the biochemical and histological changes in the liver, demonstrating that the execution of autopsies is not obsolete, but represents a fundamental tool to create a bridge between clinical manifest-ations and cytological damage.

MATERIALS AND METHODS

A systematic literature search on PubMed was carried out until June 21, 2022. No time restrictions were applied. The review was conducted using MeSH terms, Boolean operators, and free-text terms to broaden the research. Studies focusing on autopsies of COVID-19 deaths and in particular on liver

pathology were initially searched using the terms "((COVID-19) AND (autopsy) AND ((death) OR (liver))" in title, abstract, and keywords. Study design included case reports, case series, and retrospective and prospective studies. Reviews were excluded in order not to create duplication of data, but were analyzed to search for any studies not resulting from the search in the database. No unpublished or gray literature was searched. A total of 526 articles were found in the database. The evaluation of references during full text screening allowed the inclusion of further seven studies. After evaluation of abstracts and full text, 46 articles were included because of their compliance with the inclusion criteria. We also conducted a relevant search using Reference Citation Analysis (https://www.referencecitationanalysis.com/) database to supplement and improve the highlights of the latest cutting-edge research results. Data from each included study were extracted using Microsoft Excel spreadsheets, including information on authors, publishing year, nation, sample size, gender, age, type of autopsy, laboratory results, pre-existing liver disease, macroscopic and microscopic results, additional staining, cause of death, medications, and search of the virus in the liver (Table 1).

RESULTS

Demographics

A total of 11 case reports and 35 case series were analyzed, with a total of 994 autopsy cases of COVID-19 patients. Studies were from all over the world: One from Hungary, Romania, Japan, South Africa, and United States in association with Brazil each, two from Austria, Belgium, India, Iran, and Turkey each, three from the United Kingdom, four from Italy, five from Germany, Switzerland, and China each, and nine from the United States. Gender was specified in 882 cases, of whom 54% (540) were male and 35% (342) were female. Age ranged from 18 to 102 years with a mean age of 53 years. Age distribution is summarized in Figure 1.

Liver disease

Pre-existing liver diseases were described in 61 (6%) cases, comprising 28 cases of fatty liver disease, 19 cases of chronic liver disease, 11 cases of cirrhosis, and 1 case each of hepatitis B and C. In 161 cases, body mass index (BMI) was over 30 kg/m^2.

Laboratory findings

Laboratory values of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were described in 350 cases, with only 1 case described with values within the ranges of normality. The description of the laboratory values differed somewhat between the various studies, with only 5 studies (55 cases) reporting AST and ALT values at admission and 8 (64 cases) reporting the maximum values during hospitalization. Additional 4 reports for AST (51 cases) and 5 papers for ALT (61 cases) described the laboratory values without specifying the timing of the sampling. Data is summarized in Table 2. Abnormal AST and ALT values were described in 105 and 91 additional cases, respectively.

Hospitalization and medications

For the subsequent analysis of the macroscopic and microscopic findings, it was decided to evaluate whether the patients were hospitalized and whether drug therapies capable of causing liver alterations, such as antibiotics, antivirals, and quinine, were administered. In 861 cases the place where the death took place was described. In 752 cases the patient was hospitalized and died in hospital, 76 cases died at home, 22 cases died in community settings, and 11 cases were not hospitalized and died in other circumstances such as car accidents and falls from a height. In 133 cases a hospital stay or the place of death was not described. Medication administration was described in 201 cases, of which 22 were administered with hydroxychloroquine only. In 41 cases quinine was administered together with an antibiotic or antiviral, in 17 cases antibiotics and antivirals were given, and in 56 only an antibiotic was administered. In 766 cases the administration of hepatotoxic drugs was not reported.

Type of autopsy

Autopsies were performed in all 994 cases; in 508 (51%) cases autopsies were complete, of which 2% (22) had a complete autopsy without the evaluation of the brain to avoid the risk of COVID-19 infection, in 38% (372) of the cases a core biopsy was performed, in 51 (5%) cases a partial autopsy was carried out, and in 41 cases information about the type of autopsy performed was not reported.

Macroscopic results

Macroscopic results were described in only 265 (27%) cases. The most frequent finding, in 79 cases, was the presence of congestion, followed by steatosis in 39 cases. A nutmeg or yellow aspect of the liver surface was seen in 16 cases, a fibrosis-indurated consistency in 6 cases, and only 1 case showed the macroscopic presence of cancer. Lastly, 11 livers were described of increased size (hepatomegaly) and 10 livers as normal. For 144 patients weight was reported; mean weight was 1805 g with a range from 520

Table 1 Literature review results

Ref.	Country	Cases (*n*)	Age (mean, range)	Sex	Type of autopsy	Pre-existing liver disease or other diseases	Laboratory findings	Macroscopi-c results	Microscopi-c results	Additional stainings	Cause of death	Medications	Hospitalizat-ion	Virus identificatio-n in liver
Aguiar *et al* [13], 2020	Switzerland	1	31	F	Complete	Obesity	NR	Nutmeg appearance	Microabs-cesses	None	Respiratory failure in COVID-19	None	Home death	No search
Arslan *et al* [14], 2021	Turkey	7	56, 43-68	M 6, F 1	Partial	3 obesity, 2 hypertension, 1 in hemodialysis	NR	NR	4 mild steatosis, 1 biliary microhamart-oma	None	Respiratory failure in COVID-19	NR	5 hospit-alized, 2 NR	No search
Barton *et al* [15], 2020	United States	2	59, 42-77	M 2	Complete	2 obesity, 1 hypertension and 1 myotonic muscular dystrophy	NR	Case 1: weight: 2232 g, steatosis. Case 2: weight: 1683 g, cirrhosis	Nr	None	1 respiratory failure in COVID-19, 1 complic-ations of hepatic cirrhosis	NR	1 hospit-alized and 1 home death	No search
Beigmo-hammadi *et al*[16], 2021	Iran	7	68, 46-84	M 5, F 2	Core-biopsy	4 hypertension, 1 immuno-compromised and 1 valvular hearth disease	NR	NR	7 congestion, 7 steatosis, 7 portal inflam-mation, 7 hepatitis, 4 ballooning degeneration of hepatocytes, 2 bile plugs, 7 focal confluent necrosis, 4 focal hepatocyte drop out	Masson's trichrome: 1 case of mild fibrosis	NR	7 were treated with hydroxychol-orquine and 6 with antivirals	All hospit-alized	No search
Bradley *et al* [17], 2020	United States	14	74, 42-84	M 6, F 8	7 partial and 7 complete	5 obesity, 8 hypertension, 4 heart failure, 8 CKD	NR	Congestion	10 congestion, 9 steatosis, 1 toxic or metabolic disease, 4 centrilobular necrosis, 3 periportal inflammation	None	12 respiratory failure in COVID-19, 2 cardiovascula-r failure	NR	All hospit-alized	2 positive and 1 negative PCR-test, 11 not tested. 14 negative IHC and TEM

Bryce *et al* [18], 2020	United States	92	NR	NR	Complete	28 fatty liver disease	NR	NR	8 cirrhosis, 57 early organizing thrombi in portal venules and terminal hepatic venules, 41 congestion with some cases showing hemophago-cytosis	None	NR	NR	NR	No search
Bösmüller *et al*[19], 2020	Germany	4	72, 59-79	M 3, F 1	Complete-no brain	2 HIV, 2 hypertension	3 NR 1 with normal values	1 hepato-spleno-megaly and 1 yellowish surface	Case 1: congestion and activation of Kupffer cells. Case 2: macrophages activation with signs hemophago-cytosis	None	1 respiratory failure in COVID-19, 3 MOF	1 had a MOF and was intubated, 1 was treated with meropenem, 1 was treated with ECMO	3 hospit-alized and 1 home death	Negative PCR-test
Bugra *et al* [20], 2021	Turkey	100	55, 7-98	M 80, F 20	Partial	NR	NR	NR	84 inflam-mation, 54 steatosis, 19 glycogen-isation, 9 centilobulary necrosis, 18 autolysis, 45 congestion, 7 endotheliitis, 1 cirrhosis, 2 fibrin thrombosis, 2 bridging necrosis, 1 granulo-matous inflam-mation, 23 cholestasis	CD3+ in portal space	74 respiratory failure in COVID-19 and 26 NR	NR	25 hospit-alized, 55 home dead, 6 falling from height, 5 car accidents and 9 NR	No search
Chornenkyy *et al*[21], 2021	United States	8	58, 18-81	M 3, F 5	Complete	2 chronic liver disease (1 HCV and 1 autoimmune hepatitis), 6 obesity, 4 hypertension	Peak AST: 146 (20-1470) and ALT: 214 (10-9961)	Yellowish surface and congestion	3 periportal fibrosis, 2 necrosis, 5 inflam-mation, 7 portal inflam-	NR	NR	NR	All hospit-alized	4 positive and 4 negative PCR-test

								mation, 6 congestion, 4 steatosis, 6 acute hepatitis					
Danics *et al* [22], 2021	Hungary	100	75, 40-102	M 50, F 50	Complete	36 obesity, 6 liver diseases, 85 hypertension	41 elevated AST values and 27 elevated ALT values	Average weight 1544 g (range 520-3046 g)	63 steatosis, 43 portal fibrosis, 4 cirrhosis, 11 centrolobular necrosis, 87 congestion, 52 hepato-cellular cholestasis	None	NR	NR	All hospit-alized	No search
Del Nonno *et al*[23], 2021	Italy	3	69, 63-76	M 2, F 1	Complete	NR	Admission AST: 63 (31-128) and ALT: 41 (19-84)	NR	All cases showed steatosis, portal inflam-mation, portal fibrosis, focal lobular inflam-mation, zonal necrosis and congestion	IHC: CD8+ in portal inflam-mation, CD34 positive staining in the portal tract vasculature and sinusoids, Perl's staining for iron demonstrate-d iron deposits into hepatocytes	All respiratory failure in COVID-19	1 NR, one with immunosup-pressor (tocilizumab) and one with antibiotics + morphine. All had O_2 therapy (1 CPAP and 2 venturi mask)	All hospit-alized	Negative PCR-test and IHC detection (nucleo-capsid and nucleo-protein)
Edler *et al* [24], 2020	Germany	80	79, 52-96	M 46, F 34	Complete	6 obesity, 4 cirrhosis	NR	NR	Congestion	None	76 respiratory failure in COVID-19, 1 pericardial tamponade, 1 sepsis and 2 cardiovascula-r failure	17 with NIV	51 hospit-alized, 13 in nursing care homes, 12 home deaths, 1 in a hotel and 3 NR	No search
Elsoukkary *et al*[25], 2020	United States	32	68, 30-100	M 22, F 10	Partial	17 hypertension, 12 obesity	AST: 567 (18-6000) and ALT: 387 (12-4885)	NR	9 steatosis, 6 portal inflam-mation, 3 bridging fibrosis and/or cirrhosis	None	NR	19 hydroxy-chloroquine and antibiotics, 9 only antibiotics	All hospit-alized	No search
Evert *et al*	Germany	8	62, 44-73	M 4, F 4	Complete	7 obesity, 1	NR	NR	7 cholestasis,	None	8 MOF	All did NIV,	All hospit-	3 positive

[26], 2021						liver cirrhosis, 5 hypertension			7 single-cell necrosis, 5 fatty degeneration with 2 showing marked steatosis, 2 mild fibrosis, 1 cirrhosis			dialysis and antibiotics. 5 had ECMO	alized	PCR-test
Falasca *et al* [27], 2020	Italy	22	68, 27-92	M 15, F 7	Complete	1 obesity	NR	Congestion	11 inflam-mation, 10 congestion, 12 steatosis	None	All respiratory failure in COVID-19	NR	All hospit-alized	No search
Fassan *et al* [28], 2020	Italy	26	82, 61-97	M 14, F 11	Complete	5 obesity, 1 HCV-related cirrhosis	NR	NR	1 cirrhosis, 22 congestion, 5 centrilobular parenchymal atrophy, 2 fibrosis, 5 sinusoidal diffuse microthromb-i, 3 portal vein thrombosis, 2 centroacinar necrosis, 26 activation of Kupffer cells, 1 portal inflam-mation, 9 steatosis	None	NR	NR	NR	Negative ISH
Greuel *et al* [29], 2021	Germany	6	35, 26-46	M 3 F 3	Complete	1 obesity, 2 right cardiac insufficiency, 1 Ewing sarcoma	4 elevated AST and ALT values	NR	1 severe cholestasis, 1 focal ischemic damage 2 steatosis	None	3 MOF, 1 acute mesenteric ischemia, 1 cardiovascula-r failure, 1 hemorrhagic shock	5 had ECMO and NIV	All hospit-alized	Negative PCR-test
Grosse *et al* [30], 2020	Austria	14	82, 55-94	M 9, F 5	Complete	1 liver cirrhosis, 8 hypertension	Admission AST: 49 (12-98) and ALT: 25 (7-87)	NR	13 steatosis, 14 congestion, 12 portal lymphoid infiltration, 4 portal fibrosis	None	2 bronchopneu-monia, 12 NR	12 had antibiotics	All hospit-alized	No search
Hanley *et al*	United	10	73, 52-79	M 7, F 3	Complete	5 obesity, 4	NR	Average	7 steatosis, 3	None	NR	4 NIV	All hospit-	3 positive

[31], 2020	Kingdom					hypertension		weight 1432 g (range 1012-2466) and 3 hepato-megaly	cirrhosis or bridging fibrosis				alized	PCR-test (e gene)
Hirayama *et al*[32], 2021	United Kingdom	19	71, 42-94	M 11, F 8	Complete	5 obesity, 8 hypertension	NR	NR	12 steatosis, 5 congestion, 4 cirrhosis, 3 portal inflammation	None	NR	NR	All hospit-alized	No search
Hooper *et al* [33], 2021	United States-Brazil	135	61	M 80, F 55	36 core-biopsy and 99 partial	34 obesity, 5 liver disease, 86 hypertension	NR	NR	41 necrosis, 37 steatosis, 19 inflam-mation, 7 fibrosis, 6 congestion, 5 cirrhosis, 3 cholestasis	None	101 respiratory failure in COVID-19, 6 cardiovascula -r failure, 28 NR	NR	All hospit-alized	No search
Ihlow *et al* [34], 2021	Germany	1	88	F	Complete	None	Peak AST: 1690 and ALT: 1632	Subtotal liver dystrophy	Necrosis, cirrhosis, portal inflammation	IHC for ACE2, TMPESS2 and cathepsin L: strong membranous signals in intrahepatic bile duct epithelium	Acute liver failure	Antibiotics	Hospitalized	ISH positive in the bile duct epithelium and positive PCR-test
Lacy *et al* [35], 2020	United States	1	58	F	Complete	Obesity	NR	Weight 1990 g	Steatosis and congestion	None	Respiratory failure in COVID-19	NR	Home death	No search
Lagana *et al* [36], 2020	United States	40	70, 66-80	M 28, F 12	NR	2 chronic liver disease, 1 alcohol-related cirrhosis, 1 liver transplant with acute rejection and 1 with anti-HBV core antibody positivity	*n* = 33 Admission AST: 63 (43-92) and ALT: 32 (19 - 55). Peak AST: 102 (54-294) and ALT: 68 (32-258)	2 fibrosis and 1 had abscesses, 37 with steatosis and congestion	20 lobular necroinflam-mation, 20 portal inflam-mation, 10 lobular apoptosis, 30 steatosis, 32 congestion, 16 centrilobular necrosis, 15 cholestasis	None	NR	22 steroids, 19 hydroxy-chloroquine, and 6 received tocilizumab	All hospit-alized	11 positive and 9 negative PCR-test
Lax *et al*[37], 2020	Austria	11	82, 75-91	M 8, F 3	Partial	2 obesity, 9 hypertension, 1 Hodgkin lymphoma	AST: 66 (17-189) and ALT: 41 (19-98)	NR	11 steatosis, 8 congestion, 7 necrosis, 10 Kupffer cell	None	Pulmonary arterial thrombosis	2 NIV, 9 AIRVO and 9 had antibiotics	All hospit-alized	No search

						and 1 bladder carcinoma			proliferation, 6 portal fibrosis, 8 inflammation, 8 ductular proliferation					
Malik *et al* [38], 2021	India	1	31	F	Complete	None	NR	Congestion	Congestion, mild chronic inflammatory infiltrate in some portal tract, and occasional lymphocytic aggregate adjacent to central vein	None	Respiratory failure in COVID-19	None	Hospitalized	Positive PCR-test
Menter *et al* [39], 2020	Switzerland	21	76, 53-96	M 17, F 4	17 complete and 4 partial	2 chronic liver disease, 21 hypertension, 6 obesity	*n* = 10 AST: 67.2 (22-214)	NR	7 steatosis, 5 necrosis, 3 ASH/NASH	None	Respiratory failure in COVID-19	NR	All hospitalized	No search
Nunes *et al* [40], 2021	South Africa	75	60, 49-68	M 29, F 46	Core- biopsy	41 hypertension, 20 HIV	NR	NR	33 portal inflammation, 24 steatosis, 40 sinusoidal inflammation, 10 lobular hepatitis, 9 Kupffer cell activation, 11 spotty necrosis, 4 confluent necrosis, 6 fibrosis, 26 congestion, 7 fibrin-platelet thrombi	None	NR	NR	All hospitalized	No search
Oprinca[41], 2020	Romania	3	59, 27-79	M 3	1 complete and 2 partial	1 choledochal preampular intraluminal obstruction	NR	Case 1: choledochal preampullary intraluminal obstruction, case 2: normal, case 3: hepatomegaly and cirrhosis	Case 1: congestion, steatosis, periportal fibrosis and portal inflammation, case 2: nothing, case 3:	None	2 respiratory failure in COVID-19, 1 shock hemorrhagic	Case 1: antibiotics, corticosteroids and assisted oxygenation. Case 2: none (home death). Case 3: none	2 hospitalized, 1 NR	No search

								bridging fibrosis and portal inflammation					
Rapkiewicz *et al*[42], 2020	United States	7	NR, 44-65	M 3, F 4	Complete	5 obesity and 7 hypertension	NR	NR	6 steatosis, 1 cirrhosis, 6 platelet-fibrin microthromb-i in sinusoids, 2 necrosis	None	Cardiovascular failure	5 azithro-mycina and hydroxy-chloroquine and O_2 NIV	5 hospit-alized, 2 home deaths	No search
Remmelink *et al*[43], 2020	Belgium	17	72, 62-77	M 12, F 5	Complete	2 cirrhosis, 1 liver transplant, 10 hypertension	NR	5 hepato-megaly	7 congestion, 1 steato-necrosis, 10 steatosis, 1 cholestasis, 3 chronic hepatitis, 2 cirrhosis, 1 centro-obular necrosis	None	9 respiratory failure in COVID-19, 7 MOF and 1 NR	11 had mechanical ventilation	All hospit-alized	14 positive and 3 negative PCR-test
Ren *et al*[44], 2021	China	1	53	F	Complete	None	Admission AST: 27 and ALT: 24. Peak AST: 83 and ALT: 93	Normal	Nothing remarkable	None	Respiratory failure with bacterial infection	She treated herself at home with Chinese herb medicine. In hospital intensive oxygen and supportive measurement-s, extensive antibiotics and antiviral	Hospitalized	Positive PCR-test
Schmit *et al* [45], 2020	Belgium	14	63, 50-83	M 10, F 4	Complete	1 HIV, 1 non-alcoholic steatohep-atitis, 1 HCV-hepatitis, 6 obesity	Admission AST: 54 (15-188) and ALT: 30 (7-62). Peak AST: 2610 (15-24176) and ALT: 854 (10-7245)	Average weight 1988 g (range 1280-3220 g). 8 cases yellowish appearance 6 nutmeg appearance, 2 indurated consistency, 1 hepato-cellular carcinoma, 1 normal	11 centrilobular necrosis, 9 steatosis, 8 lobular inflam-mation, 12 portal inflam-mation, 4 fibrosis, 5 bile duct proliferation, 5 cholestasis, 5 iron overload	None	13 NR and 1 acute mesenteric ischemia	8 hydroxy-chloroquine and antibiotics, 4 with antibiotics, 2 with hydroxy-chloroquine	All hospit-alized	No search
Schweitzer *et*	Switzerland	1	50	M	Complete	HIV	NR	Reduced	Steatosis and	None	Respiratory	None	Home death	No search

al[46], 2020							consistency	liver dystrophy		failure in COVID-19			
Shishido-Hara *et al* [47], 2021	Japan	1	75	M	Complete	None	NR	Normal	Portal inflammation	None	Severe hemorrhage	Anti-viral therapy, antibiotics, O_2 therapy	Hospitalized	No search
Sonzogni *et al* [48], 2020	Italy	48	71, 32-86	M 22, F 8	30 partial and 18 complete - no brain	7 obesity	47 elevated values	NR	24 lobular inflammation, 32 portal inflammation, 18 confluent necrosis 18, 26 steatosis, 48 vascular thrombosis (35 portal, 13 sinusoidal), 37 fibrosis	None	NR	NR	All hospitalized	No search
Suess *et al* [49], 2020	Switzerland	1	59	M	Complete	None	NR	NR	Steatosis and some single necrotic hepatocytes	None	Respiratory failure in COVID-19	NR	Home death	No search
Tehrani *et al* [50], 2022	Iran	5	71, 55-85	M 3, F 2	Partial	None	AST: 275 (106-528) and ALT: 392 (168-978)	NR	Congestion, hepatocytes mildly expanding and bile plugs	None	4 respiratory failure in COVID-19 and 1 cardiovascular failure	1 hydroxychloroquine and antibiotics, 2 with hydroxychloroquine and anti-viral therapy, 1 only anti-viral therapy, 1 anti-viral therapy + antibiotics	All hospitalized	No search
Tian *et al*[51], 2020	China	4	73, 59-81	M 3, F 1	Core-biopsy	1 cirrhosis and 1 hypertension	AST: 36,4 (30-48.8) and ALT: 16 (11-25.5)	NR	Case 1: congestion, glycogen accumulation and focal steatosis, case 2: regenerative nodules and fibrous bands, lobular inflammation	None	Respiratory failure in COVID-19	Antibiotics, antiviral therapy assisted oxygenation	All hospitalized	1 positive and 2 negative PCR-test, 1 was not tested

									and Kupffer cell activation, cases 3: Kupffer cell activation, case 4: periportal and centrilobular necrosis					
Varga *et al* [52], 2020	Switzerland	1	58	F	NR	Obesity and hypertension	NR	NR	Endotheliitis and necrosis	None	MOF	Dialysis	Hospitalized	No search
Wang *et al* [53], 2020	China	2	50 and 79	M 1, F 1	Core-biopsy	NR	Case 1 peak ALT and AST of 70 U/L and 111 U/L, respectively. Case 2 peak ALT and AST of 76 and 236 U/L	NR	Case 1: apoptotic hepatocytes, steatosis, lobular inflammation, portal inflammation, case 2: apoptotic bodies, steatosis, portal inflammation	IHC: case 1 increased CD68 + cells in hepatic sinusoids and infrequent CD4+. Case 2: many CD68+ cells in sinusoids	1 respiratory failure in COVID-19 and 1 septic shock	Both had antiviral therapy and antibiotics	All hospitalized	2 positive TEM (viral particles exist without membrane-bound vesicles)
Wang *et al* [54], 2020	China	1	75	F	Core-biopsy	Chronic cardiac insufficiency, hypertension	Elevated AST and ALT values	NR	Necrosis, activated histiocytes, occasional apoptotic hepatocytes, steatosis and cholestasis	None	MOF	NR	Hospitalized	Negative ISH
Xu *et al*[55], 2020	China	1	50	M	Core-biopsy	NR	NR	NR	Steatosis	None	Respiratory failure in COVID-19	Antibiotics, antiviral therapy and oxygenation	Hospitalized	No search
Yadav *et al* [56], 2022	India	21	61, 25-84	M 15, F 6	Complete	6 obesity, 1 hepatitis B, 1 multiple myeloma	Admission AST: 95.4 (18.9-760.4) and ALT: 52,1 (13,2-229,2). Peak AST: 162,6 (19,8-760,4) and ALT: 75 (21.8-229.2)	NR	20 portal inflammation, 17 steatosis, 9 lobular inflammation, 1 fibrosis, 1 vascular thrombosis, 1 necrosis	None	10 MOF, 1 multiple injuries, 6 septic shock, 3 cardiovascular failure, 1 respiratory failure in COVID-19	11 treated with antibiotics, 7 antibiotics and antiviral therapy	All hospitalized	11 positive, 9 negative PCR-test, 1 not tested

Youd *et al* [57], 2020	United Kingdom	9	72, 33-88	M 4, F 5	Complete	3 obesity	NR	4 congestion, 1 steatosis and 4 normal	NR	None	Respiratory failure in COVID-19	NR	9 deaths in community settings	No search
Zhao *et al* [58], 2020	United States	17	65, 44-85	M 10, F 7	Complete	5 hyperlipidemia, 1 cirrhosis	12 elevated AST and ALT values. Peak AST: 1903 (24-13592) and ALT 1059 (13-6136)	Weight 17694 g (1000-2600 g)	12 platelet-fibrin microthrombi, 5 histiocyte activation, 12 steatosis, 5 lobular inflammation, 8 portal inflammation, 10 necrosis	CD68 stain confirmed histiocytic hyperplasia	NR	NR	All hospitalized	5 positive IHC (spike protein) in the histiocytes in the portal tracts. Negative IHC in endothelial cells and hepatocytes

F: Female; Male: M; HCV: Hepatitis C virus; NIV: Non-invasive ventilation; ECMO: Extracorporeal membrane oxygenation; COVID-19: Coronavirus disease 2019; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ISH: *In situ* hybridization; MOF: Multi-organ failure; PCR: Polymerase chain reaction; TEM: Transmission electron microscopy; NR: Not reported; IHC: Immunohistochemistry.

to 3220 g.

Microscopic results

Microscopic results were described in 983 (99%) cases. The two most frequent findings were congestion, in 420 cases, and steatosis, in 409 cases. Four cases were described as normal. All findings are described in Table 3.

Cause of death

Cause of death was reported for 440 (44%) cases. The most frequent cause of death was respiratory failure in COVID-19, seen in 355 (81%) cases, followed by multi-organ failure in 33 cases, cardiovascular failure in 22, pulmonary thrombosis in 11, and sepsis in 8. The remaining 11 cases died respectively of hemorrhagic shock (3 cases), acute liver failure (2 cases), acute mesenteric ischemia (2 cases), bronchopneumonia (2 cases), and one case each of cardiac tamponade and multiple injuries.

Virus search

The search for the presence of SARS-CoV-2 was performed in only 162 (16%) cases. Of these 105 were tested by real-time reverse-transcription polymerase chain reaction (RT-PCR) and found positive in 53 cases, 34 cases were tested by immunohistochemistry (IHC) and all found negative, 28 were tested by *in situ* hybridization (ISH) and found negative in all cases, and lastly, 16 were tested by transmission electron microscopy and found positive in 2 cases.

Table 2 Laboratory findings

Laboratory findings	Mean (UI/L)	Range (UI/L)
Admission values (n = 53)		
AST	58	12-760
ALT	34	7-229
Peak values (n = 64)		
AST	868	15-24176
ALT	509	10-9961
Non specified		
AST (n = 61)	202	17-6000
ALT (n = 51)	209	11-4885

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

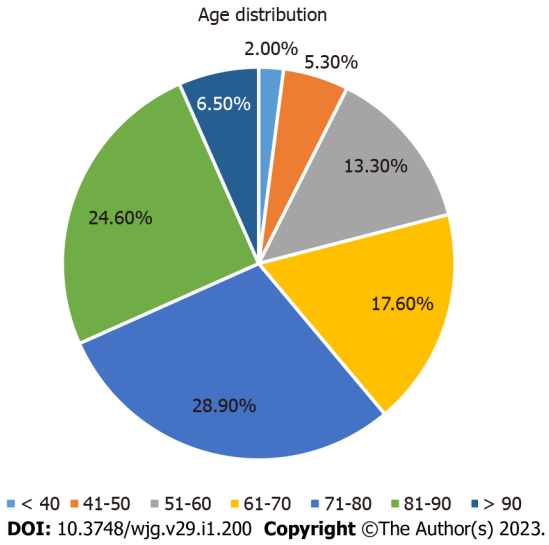
Table 3 Microscopic findings

Microscopic findings	*n* (%)
Hepatic necrosis	190 (19)
Hepatic inflammation	190 (19)
Portal inflammation	178 (18)
Fibrosis	149 (15)
Microthrombi	121 (12)
Cholestasis	114 (11)
Hemophagocytosis	51 (5)
Bile plugs	2 (0.2)
Endotheliitis	7 (0.7)
Autolysis	20 (2)
Iron overload	5 (0.5)
Other (abscess, ductal proliferation and granulomatosis)	15 (1.5)

DISCUSSION

A total of 994 autopsy cases of COVID-19 patients with liver assessment were found in the literature. As expected, more than half of the deceased were males and age distribution was highly variable, with a predominance of subjects in the age group 60-90 (71.1%).

Pre-existing liver disease was rare (6%-literature data shows a frequency of 2%-11%), with only 16.2% of the cases presenting obesity (BMI > 30 kg/m^2)[7]. Obesity, in association with diabetes and hypertension, is a prominent risk factor for severe disease and could predispose to nonalcoholic fatty liver disease (NAFLD), a metabolic syndrome which is known to suppress the pro-inflammatory M1 macrophages favoring the progression of virus infection[2,8,11]. NAFLD seems to be identified with a higher prevalence in patients with severe COVID-19 and predisposes to higher liver enzymes at admission and at discharge[59]. To date the fact that pre-existing liver disease is an independent risk factor for poor outcome is still debated; for some authors patients with liver diseases are not over-represented in hospital casuistry[4,60-62], while for others the presence of a pre-exiting illness is index of a greater probability of a bad outcome[7,63-65]. This does not count in the case of cirrhosis, seen in only 1% in this review, which is known to be an important predictor of mortality, with a mortality rate of 31%[2,61]. It appears that in the case of cirrhosis those who survive the first insult have a re-admission rate in hospital similar to those with cirrhosis, but without COVID-19, indicating that beyond the acute phase SARS-CoV-2 does not change the natural history of the disease[4]. There are currently few data regarding the mortality rate associated with alcohol liver disease as an independent risk factor, mainly related to the difficulties of correlating liver damage or elevation of liver enzymes to alcohol



DOI: 10.3748/wjg.v29.i1.200

Figure 1 Age distribution.

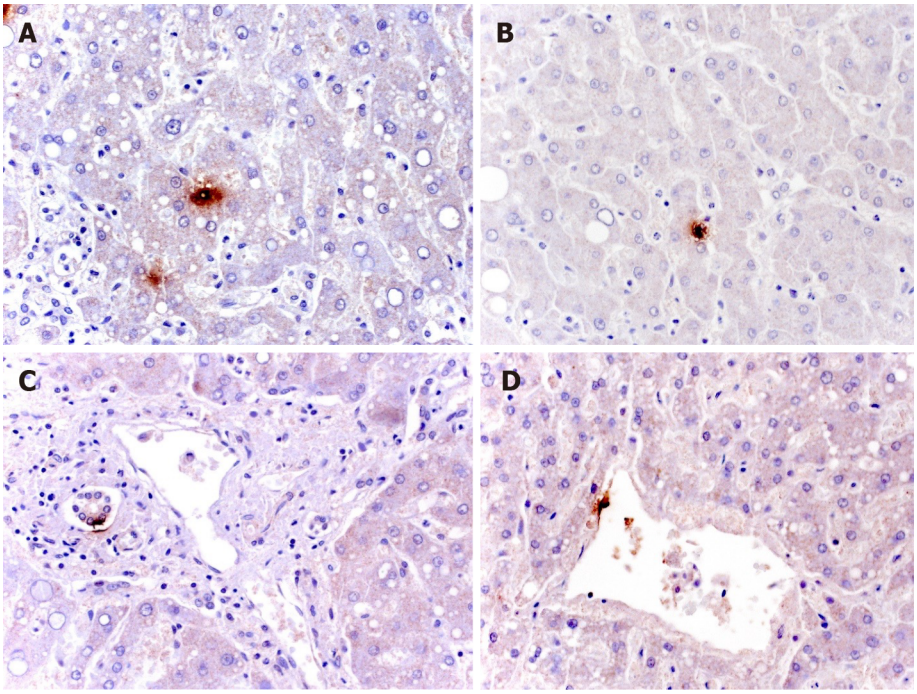
consumption. To date, it seems that alcohol liver disease increases the mortality risk by 1.8 fold[61].

Laboratory findings have not been collected in a homogeneous way, with 27 papers not reporting any data, 5 reporting AST and ALT values at admission, and 8 reporting the maximum values during hospitalization, and 4 reports for AST and 5 papers for ALT described the laboratory values without specifying the timing of the sampling. Abnormal values, without specifying the laboratory values, were described in 5 articles. From literature data it appears that liver enzyme abnormalities have a wide range, occurring in 14%-76% of the cases[4,5,7,11,66]. This great range, as Marjot *et al*[4] pointed out, could be attributed to different limits of the definition of normal values. It is still debated whether elevated liver enzymes are associated with a greater risk of mortality, because patients with worst outcomes tend to be monitored in intensive care units, while those with mild symptoms are not strictly monitored. Thus, the use of abnormal laboratory findings at admission as a predictor of poor outcome is still not sure. Liver enzyme elevation mainly affects AST and ALT, indicating hepatocellular damage rather than cholestatic, despite a greater expression of ACE2 receptor in cholangiocytes[3]. As the study of Wong *et al*[67] pointed out, the odd ratio of elevated AST and ALT levels in COVID-19 patients is 3.4 and 2.5, respectively.

Due to the presence of such fragmented laboratory data, it is difficult to draw conclusions about the trend of laboratory values during hospitalization, although some authors have found a tendency of increased values during hospitalization, in particular in those in critical conditions[9,11,12,68,69]. Whether enzyme elevation is induced directly by the virus or because of the inflammation, congestion, or medications is still not clear. Certainly, many of the drugs used in COVID-19 positive patients turn out to be hepatotoxic such as hydroxychloroquine and antivirals such as ritonavir, lopinavir, and remdesivir[8,66]. The meta-analysis by Wong *et al*[67] and Cai *et al*[66] suggests that liver injury is higher in studies with high usage of lopinavir/ritonavir, despite that their hepatotoxic role is still to be described in patients without pre-existing liver disease, while there was no evidence of a higher risk of liver injury for those treated with antibiotics, nonsteroidal anti-inflammatory drugs, ribavirin, herbal medications, and interferon.

The literature review highlighted the presence of a great discrepancy in the autopsy protocols, with only half of the autopsies performed as complete (full autopsies), while the other half as partial. Macroscopic evaluation of the liver was not frequent, while microscopic assessment was present in almost every case (99%). As expected, congestion and steatosis were the most frequent findings. The congestion can be traced back to the presence in these patients of cardiovascular dysfunction due to the massive inflammation and cytokine storm linked to the infection. The presence of steatosis needs a more complex analysis; lipid accumulation due to SARS-CoV-2 has to be differentiated from pre-existing modifications, typical of patient with metabolic syndrome. COVID-19 lipid accumulation can be explained because of the cytopathic effect of the coronavirus, which induces endoplasmatic stress and lipogenesis[2]. Transcriptomic profiling of COVID-19 patients by Wanner *et al*[5] demonstrated an upregulation of cellular processes involved in lipid/cholesterol synthesis. Furthermore, corticosteroid therapy, widely used in the treatment of COVID-19, is known to be associated with steatosis or glycogenosis[2].

Hepatic necrosis and inflammation can be multifactorial; they can be induced by a cytopathic direct effect of the virus, because of inflammatory storm or hypoxic hepatitis, or may be drug induced. These hepatic changes are the third most frequent finding in liver autopsies of COVID-19 patients[70]. Differentiating the different causes from a pathological point of view is impossible, also in consideration of



DOI: 10.3748/wjg.v29.i1.200

Figure 2 Immunohistochemical staining for severe acute respiratory syndrome coronavirus 2 in liver tissue. A and B: Spot localization of virus in samples of initial hepatic necrosis and in Kupffer cells; C and D: Spot localization of isolated ductular and endothelial cells (mouse, GeneTex GTX632604, 1A9 clone, 1:100).

the fact that they can overlap one another. In addition, patients with pre-existing liver diseases, such as chronic liver disease, have an increased risk of drug-induced hepatic damage, therefore in those patients the use of hepatotoxic treatments should be weighted. Liver damage in critically ill patients is known and is linked to the so-called hypoxic hepatitis, which is caused by underlying cardiac dysfunction and respiratory failure that decrease the blood flow and oxygenation inducing cellular stress. Moreover, damage could even be mediated by reperfusion, which promotes the production of reactive oxygen species, leading to damage. This process can be highlighted in some cases as a picture of endotheliitis[2,3,11]. Massive inflammation is common in COVID-19 patients and macrophage activation is evidenced by the presence of hemophagocytosis in liver tissue.

Unlike what is reported by Marjot *et al*[4], the frequency of thrombotic phenomena of the hepatic vascular tree is lower, with 12% of cases instead of 29%. As Kleiner[70] noted, death could occur long after the acute phase of liver damage, so the histological changes do not always represent a reliable image of what happened in acute damage, but are the result of damage and reparative modifications. Therefore, to better understand the acute damage, it could be of help to perform a liver biopsy in patients with liver damage. Obviously, it is understood that the execution of such an invasive examination is not a priority in the treatment of these patients, but it could be performed in those cases where the hepatic injury dominates the clinical picture.

Despite the presence of hepatic injury, the presence of SARS-CoV-2 in the liver has been sought infrequently (16% of the cases). Most studies have exploited the RT-PCR to search for the viral genome, but only a few have applied other techniques (IHC, ISH, and transmission electron microscopy) to identify the cells in which the viral proteins were expressed (Figure 2A and B). It is not surprising that by using RT-PCR a greater number of cases resulted positive, because this type of analysis uses a homogenized tissue, which also contains vessels and immunity cells. However, the few available data allow us to confirm the fact that the virus can be found mainly in Kupffer cells, endothelial cells of centrolobulare veins, and cholangiocytes (Figure 2C and D). Note that Wanner *et al*[5] demonstrated that, when comparing the levels of SARS-CoV-2 RNA copies per cell between airway samples and autopsy livers biopsies, the levels of RNA show similar ranges, but with lower median RNA in liver specimens.

CONCLUSION

Postmortem investigations remain the gold standard to investigate the effects of SARS-CoV-2 in different organs and apparatuses. It is well known that the absence of postmortem investigations in the first wave of the pandemic has failed to provide a valuable contribution to the correct management and

treatment of patients. On the other hand, the execution of clinical and forensic autopsies has disclosed several important aspects of the disease, clarifying morphological and virologic features and promoting unexplored therapeutic approaches and new frontiers of research[71-74]. Despite the limited number of performed autopsies worldwide, to date there is no doubt that the liver is a target for the virus, despite minimal viral receptor expression. However, liver damage is not always directly linked to the action of the virus, but can be secondary to inflammation or even simply caused by the therapy administered during hospitalization. Therefore, it is important to monitor patients who use hepatotoxic drugs, to avoid worsening of the liver functions, which can affect the patient's outcome.

ARTICLE HIGHLIGHTS

Research background

Hepatic histologic manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are far to be completely investigated. Many authors demonstrated the presence of angiotensin converting enzyme 2 receptor in the liver as well as transmembrane serine protease 2.

Research motivation

Liver injury was demonstrated in 14%-53% of cases of patients with SARS-CoV-2 infection. In the first wave of the pandemic few autopsies were performed and only few authors can provide a wide casistic. Authors started to study the histologic manifestations of coronavirus disease 2019 (COVID-19) in the lungs, heart, and liver, too.

Research objectives

The objectives of the study were to summarize the biochemical and histological changes in the liver and to promote the leading role of autopsy in the pandemic.

Research methods

Authors provide a systematic review focusing on autopsy studies of COVID-19 deaths and in particular on liver pathology.

Research results

Forty-six articles corresponding to the inclusion criteria were included, with only 994 autopsy cases of COVID-19 patients. Congestion and steatosis were the main histopathological findings, followed by hepatic necrosis, hepatic and portal inflammation, and fibrosis. The most frequent cause of death was respiratory failure, pulmonary thrombosis, and sepsis. Acute liver failure was indicated as the cause of death in two cases.

Research conclusions

The review of the literature highlighted the presence of a great discrepancy in the autopsy protocols, with only half of the autopsies performed as complete (full autopsies), while the other half as partial. Macroscopic and microscopic evaluation of the liver was not always performed or described. Despite the presence of hepatic injury, the presence of SARS-CoV-2 in the liver has been sought infrequently (16% of the cases).

Research perspectives

Much more effort needs to be addressed to completely investigate liver toxicity from COVID-19. Autopsies had a leading role during the pandemic and were important to understand the physiopathology of SARS-CoV-2 infection and should be always considered to improve scientific research.

FOOTNOTES

Author contributions: Zanon M and D'Errico S contributed to the writing and conceptualization; Neri M and Pizzolitto S contributed to the formal analysis and investigation; Radaelli D and Concato M contributed to the data curation; Peruch M contributed to the supervision.

Conflict-of-interest statement: The authors declare no conflict of interest for this article.

PRISMA 2009 Checklist statement: The review followed the PRISMA 2009 checklist statement.

Country/Territory of origin: Italy

ORCID number: Martina Zanon 0000-0002-8970-9133; Margherita Neri 0000-0002-6459-1669; Davide Radaelli 0000-0002-7053-6463; Monica Concato 0000-0003-1026-3106; Michela Peruch 0000-0001-8863-7126; Stefano D'Errico 0000-0003-3689-0001.

S-Editor: Zhang H
L-Editor: Wang TQ
P-Editor: Zhang H

REFERENCES

1 **Sun J**, Aghemo A, Forner A, Valenti L. COVID-19 and liver disease. *Liver Int* 2020; **40**: 1278-1281 [PMID: 32251539 DOI: 10.1111/liv.14470]
2 **Nardo AD**, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. *Liver Int* 2021; **41**: 20-32 [PMID: 33190346 DOI: 10.1111/liv.1473]
3 **Yang RX**, Zheng RD, Fan JG. Etiology and management of liver injury in patients with COVID-19. *World J Gastroenterol* 2020; **26**: 4753-4762 [PMID: 32921955 DOI: 10.3748/wjg.v26.i32.4753]
4 **Marjot T**, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, Barnes E. COVID-19 and liver disease: mechanistic and clinical perspectives. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 348-364 [PMID: 33692570 DOI: 10.1038/s41575-021-00426-4]
5 **Wanner N**, Andrieux G, Badia-I-Mompel P, Edler C, Pfefferle S, Lindenmeyer MT, Schmidt-Lauber C, Czogalla J, Wong MN, Okabayashi Y, Braun F, Lütgehetmann M, Meister E, Lu S, Noriega MLM, Günther T, Grundhoff A, Fischer N, Bräuninger H, Lindner D, Westermann D, Haas F, Roedl K, Kluge S, Addo MM, Huber S, Lohse AW, Reiser J, Ondruschka B, Sperhake JP, Saez-Rodriguez J, Boerries M, Hayek SS, Aepfelbacher M, Scaturro P, Puelles VG, Huber TB. Molecular consequences of SARS-CoV-2 liver tropism. *Nat Metab* 2022; **4**: 310-319 [PMID: 35347318 DOI: 10.1038/s42255-022-00552-6]
6 **Pirisi M**, Rigamonti C, D'Alfonso S, Nebuloni M, Fanni D, Gerosa C, Orrù G, Venanzi Rullo E, Pavone P, Faa G, Saba L, Boldorini R. Liver infection and COVID-19: the electron microscopy proof and revision of the literature. *Eur Rev Med Pharmacol Sci* 2021; **25**: 2146-2151 [PMID: 33660834 DOI: 10.26355/eurrev_202102_25120]
7 **Warner FJ**, Rajapaksha H, Shackel N, Herath CB. ACE2: from protection of liver disease to propagation of COVID-19. *Clin Sci (Lond)* 2020; **134**: 3137-3158 [PMID: 33284956 DOI: 10.1042/CS20201268]
8 **Jothimani D**, Venugopal R, Abedin MF, Kaliamoorthy I, Rela M. COVID-19 and the liver. *J Hepatol* 2020; **73**: 1231-1240 [PMID: 32553666 DOI: 10.1016/j.jhep.2020.06.006]
9 **Mohammed A**, Paranji N, Chen PH, Niu B. COVID-19 in Chronic Liver Disease and Liver Transplantation: A Clinical Review. *J Clin Gastroenterol* 2021; **55**: 187-194 [PMID: 33394628 DOI: 10.1097/MCG.0000000000001481]
10 **Lizardo-Thiebaud MJ**, Cervantes-Alvarez E, Limon-de la Rosa N, Tejeda-Dominguez F, Palacios-Jimenez M, Méndez-Guerrero O, Delaye-Martinez M, Rodriguez-Alvarez F, Romero-Morales B, Liu WH, Huang CA, Kershenobich D, Navarro-Alvarez N. Direct or Collateral Liver Damage in SARS-CoV-2-Infected Patients. *Semin Liver Dis* 2020; **40**: 321-330 [PMID: 32886936 DOI: 10.1055/s-0040-1715108]
11 **Parker GA**, Picut CA. Liver immunobiology. *Toxicol Pathol* 2005; **33**: 52-62 [PMID: 15805056 DOI: 10.1080/01926230590522365]
12 **Gracia-Ramos AE**, Jaquez-Quintana JO, Contreras-Omaña R, Auron M. Liver dysfunction and SARS-CoV-2 infection. *World J Gastroenterol* 2021; **27**: 3951-3970 [PMID: 34326607 DOI: 10.3748/wjg.v27.i26.3951]
13 **Fiel MI**, El Jamal SM, Paniz-Mondolfi A, Gordon RE, Reidy J, Bandovic J, Advani R, Kilaru S, Pourmand K, Ward S, Thung SN, Schiano T. Findings of Hepatic Severe Acute Respiratory Syndrome Coronavirus-2 Infection. *Cell Mol Gastroenterol Hepatol* 2021; **11**: 763-770 [PMID: 32992052 DOI: 10.1016/j.jcmgh.2020.09.015]
14 **Aguiar D**, Lobrinus JA, Schibler M, Fracasso T, Lardi C. Inside the lungs of COVID-19 disease. *Int J Legal Med* 2020; **134**: 1271-1274 [PMID: 32458044 DOI: 10.1007/s00414-020-02318-9]
15 **Arslan MN**, Büyük Y, Ziyade N, Elgörmüş N, Şirin G, Çoban İ, Gökşen ME, Daş T, Akçay A. COVID-19 autopsies of Istanbul. *Ir J Med Sci* 2022; **191**: 529-541 [PMID: 33755916 DOI: 10.1007/s11845-021-02602-6]
16 **Barton LM**, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 Autopsies, Oklahoma, USA. *Am J Clin Pathol* 2020; **153**: 725-733 [PMID: 32275742 DOI: 10.1093/ajcp/aqaa062]
17 **Beigmohammadi MT**, Jahanbin B, Safaei M, Amoozadeh L, Khoshavi M, Mehrtash V, Jafarzadeh B, Abdollahi A. Pathological Findings of Postmortem Biopsies From Lung, Heart, and Liver of 7 Deceased COVID-19 Patients. *Int J Surg Pathol* 2021; **29**: 135-145 [PMID: 32552178 DOI: 10.1177/1066896920935195]
18 **Bradley BT**, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N, Marshall DA. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020; **396**: 320-332 [PMID: 32682491 DOI: 10.1016/S0140-6736(20)31305-2]
19 **Bryce C**, Grimes Z, Pujadas E, Ahuja S, Beasley MB, Albrecht R, Hernandez T, Stock A, Zhao Z, AlRasheed MR, Chen J, Li L, Wang D, Corben A, Haines GK 3rd, Westra WH, Umphlett M, Gordon RE, Reidy J, Petersen B, Salem F, Fiel MI, El Jamal SM, Tsankova NM, Houldsworth J, Mussa Z, Veremis B, Sordillo E, Gitman MR, Nowak M, Brody R, Harpaz N,

Merad M, Gnjatic S, Liu WC, Schotsaert M, Miorin L, Aydillo Gomez TA, Ramos-Lopez I, Garcia-Sastre A, Donnelly R, Seigler P, Keys C, Cameron J, Moultrie I, Washington KL, Treatman J, Sebra R, Jhang J, Firpo A, Lednicky J, Paniz-Mondolfi A, Cordon-Cardo C, Fowkes ME. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. *Mod Pathol* 2021; **34**: 1456-1467 [PMID: 33795830 DOI: 10.1038/s41379-021-00793-y]

20 **Bösmüller H**, Traxler S, Bitzer M, Häberle H, Raiser W, Nann D, Frauenfeld L, Vogelsberg A, Klingel K, Fend F. The evolution of pulmonary pathology in fatal COVID-19 disease: an autopsy study with clinical correlation. *Virchows Arch* 2020; **477**: 349-357 [PMID: 32607684 DOI: 10.1007/s00428-020-02881-x]

21 **Bugra A**, Das T, Arslan MN, Ziyade N, Buyuk Y. Postmortem pathological changes in extrapulmonary organs in SARS-CoV-2 rt-PCR-positive cases: a single-center experience. *Ir J Med Sci* 2022; **191**: 81-91 [PMID: 33963513 DOI: 10.1007/s11845-021-02638-8]

22 **Chornenkyy Y**, Mejia-Bautista M, Brucal M, Blanke T, Dittmann D, Yeldandi A, Boike JR, Lomasney JW, Nayar R, Jennings LJ, Pezhouh MK. Liver Pathology and SARS-CoV-2 Detection in Formalin-Fixed Tissue of Patients With COVID-19. *Am J Clin Pathol* 2021; **155**: 802-814 [PMID: 33914058 DOI: 10.1093/ajcp/aqab009]

23 **Danics K**, Pesti A, Törő K, Kiss-Dala N, Szlávik J, Lakatos B, Radnai A, Balázs T, Bacskai M, Dobi D, Várkonyi T, Glasz T, Lotz G, Kiss A, Schaff Z, Vályi-Nagy I. A COVID-19-association-dependent categorization of death causes in 100 autopsy cases. *Geroscience* 2021; **43**: 2265-2287 [PMID: 34510338 DOI: 10.1007/s11357-021-00451-w]

24 **Del Nonno F**, Nardacci R, Colombo D, Visco-Comandini U, Cicalini S, Antinori A, Marchioni L, D'Offizi G, Piacentini M, Falasca L. Hepatic Failure in COVID-19: Is Iron Overload the Dangerous Trigger? *Cells* 2021; **10** [PMID: 34064487 DOI: 10.3390/cells10051103]

25 **Edler C**, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, Klein A, Langenwalder F, Lütgehetmann M, Meißner K, Püschel K, Schädler J, Steurer S, Mushumba H, Sperhake JP. Dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int J Legal Med* 2020; **134**: 1275-1284 [PMID: 32500199 DOI: 10.1007/s00414-020-02317-w]

26 **Elsoukkary SS**, Mostyka M, Dillard A, Berman DR, Ma LX, Chadburn A, Yantiss RK, Jessurun J, Seshan SV, Borczuk AC, Salvatore SP. Autopsy Findings in 32 Patients with COVID-19: A Single-Institution Experience. *Pathobiology* 2021; **88**: 56-68 [PMID: 32942274 DOI: 10.1159/000511325]

27 **Evert K**, Dienemann T, Brochhausen C, Lunz D, Lubnow M, Ritzka M, Keil F, Trummer M, Scheiter A, Salzberger B, Reischl U, Boor P, Gessner A, Jantsch J, Calvisi DF, Evert M, Schmidt B, Simon M. Autopsy findings after long-term treatment of COVID-19 patients with microbiological correlation. *Virchows Arch* 2021; **479**: 97-108 [PMID: 33471172 DOI: 10.1007/s00428-020-03014-0]

28 **Falasca L**, Nardacci R, Colombo D, Lalle E, Di Caro A, Nicastri E, Antinori A, Petrosillo N, Marchioni L, Biava G, D'Offizi G, Palmieri F, Goletti D, Zumla A, Ippolito G, Piacentini M, Del Nonno F. Postmortem Findings in Italian Patients With COVID-19: A Descriptive Full Autopsy Study of Cases With and Without Comorbidities. *J Infect Dis* 2020; **222**: 1807-1815 [PMID: 32914853 DOI: 10.1093/infdis/jiaa578]

29 **Fassan M**, Mescoli C, Sbaraglia M, Guzzardo V, Russo FP, Fabris R, Trevenzoli M, Pelizzaro F, Cattelan AM, Basso C, Navalesi P, Farinati F, Vettor R, Dei Tos AP. Liver histopathology in COVID-19 patients: A mono-Institutional series of liver biopsies and autopsy specimens. *Pathol Res Pract* 2021; **221**: 153451 [PMID: 33932720 DOI: 10.1016/j.prp.2021.153451]

30 **Greuel S**, Ihlow J, Dragomir MP, Streit S, Corman VM, Haberbosch L, Winkler D, Meinhardt J, Aschman T, Schneider J, Trotsyuk I, Kunze CA, Maurer L, Radbruch H, Heppner FL, Horst D, Elezkurtaj S. COVID-19: Autopsy findings in six patients between 26 and 46 years of age. *Int J Infect Dis* 2021; **108**: 274-281 [PMID: 34089883 DOI: 10.1016/j.ijid.2021.05.069]

31 **Grosse C**, Grosse A, Salzer HJF, Dünser MW, Motz R, Langer R. Analysis of cardiopulmonary findings in COVID-19 fatalities: High incidence of pulmonary artery thrombi and acute suppurative bronchopneumonia. *Cardiovasc Pathol* 2020; **49**: 107263 [PMID: 32784110 DOI: 10.1016/j.carpath.2020.107263]

32 **Hanley B**, Naresh KN, Roufosse C, Nicholson AG, Weir J, Cooke GS, Thursz M, Manousou P, Corbett R, Goldin R, Al-Sarraj S, Abdolrasouli A, Swann OC, Baillon L, Penn R, Barclay WS, Viola P, Osborn M. Histopathological findings and viral tropism in UK patients with severe fatal COVID-19: a post-mortem study. *Lancet Microbe* 2020; **1**: e245-e253 [PMID: 32844161 DOI: 10.1016/S2666-5247(20)30115-4]

33 **Hirayama Y**, Daniels NF, Evans S, Clarke D, Purvis S, Oliver C, Woodmansey S, Staniforth J, Soilleux EJ. High Prevalence of Pre-Existing Liver Abnormalities Identified Via Autopsies in COVID-19: Identification of a New Silent Risk Factor? *Diagnostics (Basel)* 2021; **11** [PMID: 34574044 DOI: 10.3390/diagnostics11091703]

34 **Hooper JE**, Padera RF, Dolhnikoff M, da Silva LFF, Duarte-Neto AN, Kapp ME, Lacy JM, Mauad T, Saldiva PHN, Rapkiewicz AV, Wolf DA, Felix JC, Benson P, Shanes E, Gawelek KL, Marshall DA, McDonald MM, Muller W, Priemer DS, Solomon IH, Zak T, Bhattacharjee MB, Fu L, Gilbert AR, Harper HL, Litovsky S, Lomasney J, Mount SL, Reilly S, Sekulic M, Steffensen TS, Threlkeld KJ, Zhao B, Williamson AK. A Postmortem Portrait of the Coronavirus Disease 2019 (COVID-19) Pandemic: A Large Multi-institutional Autopsy Survey Study. *Arch Pathol Lab Med* 2021; **145**: 529-535 [PMID: 33449998 DOI: 10.5858/arpa.2020-0786-SA]

35 **Ihlow J**, Seelhoff A, Corman VM, Gruber AD, Dökel S, Meinhardt J, Radbruch H, Späth-Schwalbe E, Elezkurtaj S, Horst D, Herbst H. COVID-19: a fatal case of acute liver failure associated with SARS-CoV-2 infection in pre-existing liver cirrhosis. *BMC Infect Dis* 2021; **21**: 901 [PMID: 34479499 DOI: 10.1186/s12879-021-06605-7]

36 **Lacy JM**, Brooks EG, Akers J, Armstrong D, Decker L, Gonzalez A, Humphrey W, Mayer R, Miller M, Perez C, Arango JAR, Sathyavagiswaran L, Stroh W, Utley S. COVID-19: Postmortem Diagnostic and Biosafety Considerations. *Am J Forensic Med Pathol* 2020; **41**: 143-151 [PMID: 32379077 DOI: 10.1097/PAF.0000000000000567]

37 **Lagana SM**, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, Del Portillo A, De Michele S, de Gonzalez AK, Saqi A, Khairallah P, Chong AM, Park H, Uhlemann AC, Lefkowitch JH, Verna EC. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol* 2020; **33**: 2147-2155 [PMID: 32792598 DOI: 10.1038/s41379-020-00649-x]

38 **Lax SF**, Skok K, Zechner P, Kessler HH, Kaufmann N, Koelblinger C, Vander K, Bargfrieder U, Trauner M. Pulmonary

Arterial Thrombosis in COVID-19 With Fatal Outcome : Results From a Prospective, Single-Center, Clinicopathologic Case Series. *Ann Intern Med* 2020; **173**: 350-361 [PMID: 32422076 DOI: 10.7326/M20-2566]

39 **Malik Y**, Singh K, Yadav S, Vashist YK, Garg A, Kumar S, Sharma G. COVID-19: Asymptomatic Carrier: An Autopsy Case Report. *Int J Appl Basic Med Res* 2021; **11**: 120-124 [PMID: 33912436 DOI: 10.4103/ijabmr.IJABMR_579_20]

40 **Menter T**, Haslbauer JD, Nienhold R, Savic S, Hopfer H, Deigendesch N, Frank S, Turek D, Willi N, Pargger H, Bassetti S, Leuppi JD, Cathomas G, Tolnay M, Mertz KD, Tzankov A. Postmortem examination of COVID-19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings in lungs and other organs suggesting vascular dysfunction. *Histopathology* 2020; **77**: 198-209 [PMID: 32364264 DOI: 10.1111/his.14134]

41 **Nunes MC**, Hale MJ, Mahtab S, Mabena FC, Dludlu N, Baillie VL, Thwala BN, Els T, du Plessis J, Laubscher M, Mckenzie S, Mtshali S, Menezes C, Serafin N, van Blydenstein S, Tsitsi M, Dulisse B, Madhi SA. Clinical characteristics and histopathology of COVID-19 related deaths in South African adults. *PLoS One* 2022; **17**: e0262179 [PMID: 35051205 DOI: 10.1371/journal.pone.0262179]

42 **Oprinca GC**, Muja LA. Postmortem examination of three SARS-CoV-2-positive autopsies including histopathologic and immunohistochemical analysis. *Int J Legal Med* 2021; **135**: 329-339 [PMID: 32851474 DOI: 10.1007/s00414-020-02406-w]

43 **Rapkiewicz AV**, Mai X, Carsons SE, Pittaluga S, Kleiner DE, Berger JS, Thomas S, Adler NM, Charytan DM, Gasmi B, Hochman JS, Reynolds HR. Megakaryocytes and platelet-fibrin thrombi characterize multi-organ thrombosis at autopsy in COVID-19: A case series. *EClinicalMedicine* 2020; **24**: 100434 [PMID: 32766543 DOI: 10.1016/j.eclinm.2020.100434]

44 **Remmelink M**, De Mendonça R, D'Haene N, De Clercq S, Verocq C, Lebrun L, Lavis P, Racu ML, Trépant AL, Maris C, Rorive S, Goffard JC, De Witte O, Peluso L, Vincent JL, Decaestecker C, Taccone FS, Salmon I. Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients. *Crit Care* 2020; **24**: 495 [PMID: 32787909 DOI: 10.1186/s13054-020-03218-5]

45 **Ren L**, Liu Q, Wang R, Chen R, Ao Q, Wang X, Zhang J, Deng F, Feng Y, Wang G, Zhou Y, Li L, Liu L. Clinicopathologic Features of COVID-19: A Case Report and Value of Forensic Autopsy in Studying SARS-CoV-2 Infection. *Am J Forensic Med Pathol* 2021; **42**: 164-169 [PMID: 33464756 DOI: 10.1097/PAF.0000000000000644]

46 **Schmit G**, Lelotte J, Vanhaebost J, Horsmans Y, Van Bockstal M, Baldin P. The Liver in COVID-19-Related Death: Protagonist or Innocent Bystander? *Pathobiology* 2021; **88**: 88-94 [PMID: 33108789 DOI: 10.1159/000512008]

47 **Schweitzer W**, Ruder T, Baumeister R, Bolliger S, Thali M, Meixner E, Ampanozi G. Implications for forensic death investigations from first Swiss post-mortem CT in a case of non-hospital treatment with COVID-19. *Forensic Imaging* 2020; **21**: 200378 [DOI: 10.1016/j.fri.2020.200378]

48 **Shishido-Hara Y**, Furukawa K, Nishio M, Honda K, Tando S, Yaoi T, Kawamoto M, Maehara Y, Nakaya T, Itoh K. An autopsy case of COVID-19 with a sudden death: Clinico-pathological comparison. *Clin Case Rep* 2022; **10**: e5961 [PMID: 35702618 DOI: 10.1002/ccr3.5961]

49 **Sonzogni A**, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, Morotti D, Zerbi P, Carsana L, Rossi R, Lauri E, Pellegrinelli A, Nebuloni M. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. *Liver Int* 2020; **40**: 2110-2116 [PMID: 32654359 DOI: 10.1111/liv.14601]

50 **Suess C**, Hausmann R. Gross and histopathological pulmonary findings in a COVID-19 associated death during self-isolation. *Int J Legal Med* 2020; **134**: 1285-1290 [PMID: 32504146 DOI: 10.1007/s00414-020-02319-8]

51 **Shirazi Tehrani A**, Tabatabaei Mirakabad FS, Abdollahifar MA, Mollazadehghomi S, Darabi S, Forozesh M, Rezaei-Tavirani M, Mahmoudiasl GR, Ahrabi B, Azimzadeh Z, Allah Abbaszadeh H. Severe Acute Respiratory Syndrome Coronavirus 2 Induces Hepatocyte Cell Death, Active Autophagosome Formation and Caspase 3 Up-Regulation in Postmortem Cases: Stereological and Molecular Study. *Tohoku J Exp Med* 2022; **256**: 309-319 [PMID: 35321977 DOI: 10.1620/tjem.2022.J007]

52 **Tian S**, Xiong Y, Liu H, Niu L, Guo J, Liao M, Xiao SY. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol* 2020; **33**: 1007-1014 [PMID: 32291399 DOI: 10.1038/s41379-020-0536-x]

53 **Varga Z**, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417-1418 [PMID: 32325026 DOI: 10.1016/S0140-6736(20)30937-5]

54 **Wang Y**, Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; **73**: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]

55 **Wang XX**, Shao C, Huang XJ, Sun L, Meng LJ, Liu H, Zhang SJ, Li HJ, Lv FD. Histopathological features of multiorgan percutaneous tissue core biopsy in patients with COVID-19. *J Clin Pathol* 2021; **74**: 522-527 [PMID: 32848014 DOI: 10.1136/jclinpath-2020-206623]

56 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

57 **Yadav J**, Goel G, Purwar S, Saigal S, Tandon A, Joshi A, Patel B, Js S, S M, Singh J, Shankar P, Arora A, Singh S. Clinical, Virological, and Pathological Profile of Patients Who Died of COVID-19: An Autopsy-Based Study From India. *Cureus* 2022; **14**: e23538 [PMID: 35494966 DOI: 10.7759/cureus.23538]

58 **Youd E**, Moore L. COVID-19 autopsy in people who died in community settings: the first series. *J Clin Pathol* 2020; **73**: 840-844 [PMID: 32605920 DOI: 10.1136/jclinpath-2020-206710]

59 **Zhao CL**, Rapkiewicz A, Maghsoodi-Deerwester M, Gupta M, Cao W, Palaia T, Zhou J, Ram B, Vo D, Rafiee B, Hossein-Zadeh Z, Dabiri B, Hanna I. Pathological findings in the postmortem liver of patients with coronavirus disease 2019 (COVID-19). *Hum Pathol* 2021; **109**: 59-68 [PMID: 33307078 DOI: 10.1016/j.humpath.2020.11.015]

60 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]

61 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research

Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

62 **Marjot T**, Moon AM, Cook JA, Abd-Elsalam S, Aloman C, Armstrong MJ, Pose E, Brenner EJ, Cargill T, Catana MA, Dhanasekaran R, Eshraghian A, García-Juárez I, Gill US, Jones PD, Kennedy J, Marshall A, Matthews C, Mells G, Mercer C, Perumalswami PV, Avitabile E, Qi X, Su F, Ufere NN, Wong YJ, Zheng MH, Barnes E, Barritt AS 4th, Webb GJ. Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study. *J Hepatol* 2021; **74**: 567-577 [PMID: 33035628 DOI: 10.1016/j.jhep.2020.09.024]

63 **Wang X**, Fang X, Cai Z, Wu X, Gao X, Min J, Wang F. Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis. *Research (Wash D C)* 2020; **2020**: 2402961 [PMID: 32377638 DOI: 10.34133/2020/2402961]

64 **Vila-Corcoles A**, Satue-Gracia E, Vila-Rovira A, de Diego-Cabanes C, Forcadell-Peris MJ, Hospital-Guardiola I, Ochoa-Gondar O, Basora-Gallisa J. COVID19-related and all-cause mortality risk among middle-aged and older adults across the first epidemic wave of SARS-COV-2 infection: a population-based cohort stuJune 2020.dy in Southern Catalonia, Spain, March-. *BMC Public Health* 2021; **21**: 1795 [PMID: 34615512 DOI: 10.1186/s12889-021-11879-2]

65 **Dorjee K**, Kim H, Bonomo E, Dolma R. Prevalence and predictors of death and severe disease in patients hospitalized due to COVID-19: A comprehensive systematic review and meta-analysis of 77 studies and 38,000 patients. *PLoS One* 2020; **15**: e0243191 [PMID: 33284825 DOI: 10.1371/journal.pone.0243191]

66 **Cai Q**, Huang D, Yu H, Zhu Z, Xia Z, Su Y, Li Z, Zhou G, Gou J, Qu J, Sun Y, Liu Y, He Q, Chen J, Liu L, Xu L. COVID-19: Abnormal liver function tests. *J Hepatol* 2020; **73**: 566-574 [PMID: 32298767 DOI: 10.1016/j.jhep.2020.04.006]

67 **Wong YJ**, Tan M, Zheng Q, Li JW, Kumar R, Fock KM, Teo EK, Ang TL. A systematic review and meta-analysis of the COVID-19 associated liver injury. *Ann Hepatol* 2020; **19**: 627-634 [PMID: 32882393 DOI: 10.1016/j.aohep.2020.08.064]

68 **Wu Y**, Li H, Guo X, Yoshida EM, Mendez-Sanchez N, Levi Sandri GB, Teschke R, Romeiro FG, Shukla A, Qi X. Incidence, risk factors, and prognosis of abnormal liver biochemical tests in COVID-19 patients: a systematic review and meta-analysis. *Hepatol Int* 2020; **14**: 621-637 [PMID: 32710250 DOI: 10.1007/s12072-020-10074-6]

69 **Barnes E**. Infection of liver hepatocytes with SARS-CoV-2. *Nat Metab* 2022; **4**: 301-302 [PMID: 35347317 DOI: 10.1038/s42255-022-00554-4]

70 **Kleiner DE**. Liver Biopsy Shines a Light on COVID-19-Related Liver Injury. *Cell Mol Gastroenterol Hepatol* 2021; **11**: 881-882 [PMID: 33144089 DOI: 10.1016/j.jcmgh.2020.10.003]

71 **D'Errico S**, Zanon M, Montanaro M, Radaelli D, Sessa F, Di Mizio G, Montana A, Corrao S, Salerno M, Pomara C. More than Pneumonia: Distinctive Features of SARS-Cov-2 Infection. From Autopsy Findings to Clinical Implications: A Systematic Review. *Microorganisms* 2020; **8** [PMID: 33114061 DOI: 10.3390/microorganisms8111642]

72 **Macor P**, Durigutto P, Mangogna A, Bussani R, D'Errico S, Zanon M, Pozzi N, Meroni P, Tedesco F. Multi-organ complement deposition in COVID-19 patients. *medRxiv* 2021 [PMID: 33442701 DOI: 10.3390/biomedicines9081003]

73 **Cipolloni L**, Sessa F, Bertozzi G, Baldari B, Cantatore S, Testi R, D'Errico S, Di Mizio G, Asmundo A, Castorina S, Salerno M, Pomara C. Preliminary Post-Mortem COVID-19 Evidence of Endothelial Injury and Factor VIII Hyperexpression. *Diagnostics (Basel)* 2020; **10** [PMID: 32784826 DOI: 10.3390/diagnostics10080575]

74 **Frisoni P**, Neri M, D'Errico S, Alfieri L, Bonuccelli D, Cingolani M, Di Paolo M, Gaudio RM, Lestani M, Marti M, Martelloni M, Moreschi C, Santurro A, Scopetti M, Turriziani O, Zanon M, Scendoni R, Frati P, Fineschi V. Cytokine storm and histopathological findings in 60 cases of COVID-19-related death: from viral load research to immunohistochemical quantification of major players IL-1β, IL-6, IL-15 and TNF-α. *Forensic Sci Med Pathol* 2022; **18**: 4-19 [PMID: 34463916 DOI: 10.1007/s12024-021-00414-9]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com