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Liver involvement in patients with COVID-19 infection: A comprehensive overview of diagnostic imaging features

Ippolito D *et al*. What's important to know

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Abstract

During the first wave of the pandemic, coronavirus disease 2019 (COVID-19) infection has been considered mainly as a pulmonary infection. However, different clinical and radiological manifestations were observed over time, including involvement of abdominal organs. Nowadays, liver is considered one of the main affected abdominal organs. Hepatic involvement may be caused by either a direct damage by the virus or an indirect damage related to COVID-19 induced thrombosis or to the use of different drugs. After clinical assessment, radiology plays a key role in the evaluation of liver involvement. Ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) may be used to evaluate liver involvement. US is widely available and it is considered the first-line technique to assess liver involvement in COVID-19 infection, in particular liver steatosis and thrombosis. CT and MRI are used as second- and third-line techniques, respectively, considering their higher sensitivity and specificity compared to US for assessment of both parenchyma and vascularization. This review aims to the spectrum of COVID-19 Liver involvement and the most common imaging features of COVID-19 Liver damage.

Key Words: Liver; Fatty liver; Hepatomegaly; Hepatic infarction; Liver diseases; Liver failure; Biliary tract diseases; COVID-19; SARS-CoV-2; Infection; X-Ray computed tomography; Magnetic resonance imaging; Ultrasonography

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Core Tip: Coronavirus disease 2019 (COVID-19) infection has an impact not only on lung involvement but also in other systems, in particular the gastrointestinal one, with a special focus on the liver. Hepatocytes express the receptor of angiotensin-converting enzyme which is the main door of the entrance of severe acute respiratory syndrome coronavirus 2. Consequently, different mechanisms can lead to different hepatic scenarios, such as hepatomegaly, steatosis, steatohepatitis, and drug-induced liver injury. As for lung involvement, the infection can lead to hepatic vascular involvement, especially portal vein thrombosis. Finally, it has been demonstrated a possible biliary involvement in COVID-19 patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, named coronavirus disease 2019 (COVID-19), represents an epoch-making global healthcare crisis, with 603711760 confirmed cases and 6484136 deaths caused to date worldwide[1].

Although the lung represents the most affected organ, COVID-19 may present as a multiorgan disease. Clinical manifestations may vary from flu-like symptoms, such as fever, dry cough, myalgia, and fatigue, often coupled with hypo-/anosmia and ageusia[2-4], to more severe conditions with dyspnea and respiratory impairment requiring admission to intensive care unit (ICU) and advanced respiratory assistance[5]. A severe course of the disease has been reported in 5%-22 % of COVID-19 patients[3,5].

In this scenario we focused our attention on hepatic manifestations of COVID-19 infection. Hepatic involvement in patients with COVID-19 infection is not negligible. Liver damage can occur in different ways, ranging from hepatomegaly, acute hepatitis, steatosis and steatohepatitis, portal vein thrombosis (PVT) and liver infarction, biliary and gallbladder involvement, up to drug-induced liver injury, with chronic liver disease that needs further long-term studies to be understood (Figure 1).

In this review, we aim to describe the spectrum of COVID-19 Liver involvement and the most common imaging features of COVID-19 Liver damage with a descriptive correlation to the underlying pathogenesis.

IMAGING TECHNIQUES

The standard radiological approach for liver assessment (*i.e.*, anatomy, focal liver lesions, or diffuse diseases) has been widely described and does acknowledge the use of ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Technical advances in liver imaging have also been conducted over the last decades, with lots of research on quantitative and functional assessments in different liver pathologies[6].

US

Brightness-mode (B-mode) transabdominal US generally represents the first-line approach in patients with suspected liver disease[7]. US is widely available, non-invasive, low cost, safe, ionizing radiation-free[6] and can be performed bedside, particularly in ICU or isolated patients. Anatomical and vascular imaging and lesion detection are feasible, although limited by the field of view and dependent on operator experience[7].

During the last decades, different US developments have been introduced, including elastography, contrast-enhanced US (CEUS), and novel doppler techniques[6-9].

Moreover, an advanced multiparametric US approach for the evaluation of the liver could be an option, particularly for long-term follow-up of COVID-19 patients. The multiparametric US includes elastography, share wave dispersion, and attenuation imaging. The evaluation by the 2D-shear wave elastography technique allows quantification of the increase in liver stiffness related to the evolution toward fibrosis, but it can be altered in the inflammatory early stages (*e.g.*, steatohepatitis)[10]. Shear-wave dispersion is a measure of liver viscosity that is changed during inflammatory processes in the liver. Finally, hepatic attenuation imaging is a useful tool for quantifying steatosis.

Elastography enables the assessment of liver fibrosis[6]. Usually, a quantitative assessment of liver stiffness is obtained by applying an external force by means either of a US-induced focused impulse (point shear wave elastography) or a mechanically induced impulse (transient elastography)[7]. More recent developments of US elastography include a volumetric assessment of liver stiffness and its real-time variations. Clinical use of US elastography is mainly limited by cutoff values for fibrosis staging that vary across US systems from different vendors[6].

CEUS is accepted as a second-line imaging modality for the characterization of focal liver lesions after inconclusive baseline US, and its cost-effectiveness is higher compared to CT or MRI[6,7,11]. CEUS interpretation is similar to CT and MRI, relying on the similar post-contrast phases (arterial, portal-venous, delayed), vascular architecture, and phase-specific enhancement of the lesion compared with the adjacent liver parenchyma[7]. CEUS is useful for lesion detection and characterization in several clinical settings, without the use of ionizing radiations and with higher temporal resolution compared to CT or MRI[6].

It can be useful in non-oncologic non-cirrhotic patients[6,9], for the assessment of incidental focal lesions, in cirrhotic patients, allowing characterization of contrast enhancement patterns of hepatocellular carcinoma (HCC) with good sensitivity and specificity[6], and in oncologic patients, providing higher sensitivity compared to the standard US for liver metastases detection and indeterminate CT or MRI lesions characterization[12]. CEUS can also be used to guide, in real-time, both focal lesions procedures[7,8] and locoregional ablative therapies, as well as for treatment response assessment[13,14]. According to the latest guidelines[14], US contrast agents can be safely administered in various applications, with minimal risks to patients. The reported rate of anaphylactoid-type reactions is extremely rare (0.014%).

Among novel third-generation doppler developments, US manufacturers have introduced techniques such as superb microvascular imaging (SMI) that has improved the sensitivity and accuracy of Doppler US in the assessment of hepatic vascular anatomy[9] and the detection of liver tumors vascularity with a safe, inexpensive, and readily available modality[6]. SMI is based on an adaptive algorithm that separates low flow signals from overlaying tissue motion artifacts; thereby SMI allows visualization of microscopic vessels (either native or within lesions), with no need for contrast agents injection[9].

CT

CT represents the mainstay technique for liver imaging, with the majority of acquisitions performed with multiphase acquisition protocols, and standardized assessment based on size and density measurements. Due to its wide availability, CT is generally preferred to MRI in daily clinical practice, despite its overall lower sensitivity. Moreover, reproducibility and high temporal and spatial resolutions allow its employment in both standard and emergency settings[6,15-17].

Contrast-enhanced CT allows the characterization of liver lesions deemed indeterminate on US in non-oncologic and non-cirrhotic patients. In cirrhosis, while the US remains the standard technique for follow-up, contrast-enhanced CT and MRI are the

currently recommended techniques for the characterization of US-detected nodules, diagnosis and post-treatment follow-up of HCC[6,18]. In oncologic patients, CT is generally used for staging and follow-up. Accurate timing of image acquisition during the various dynamic phases is critical to enable accurate determination of liver lesion characteristics and enhancement features[11]. In these scenarios, CT acquired during the portal-venous phase is the most common study performed in oncologic patients[6], but its main limitation is the detection and characterization of small hypoattenuating lesions and lesion detection in the background of liver steatosis[6,19]. On the other hand, multiphase scans (arterial, portal-venous, and delayed phases) are generally used in cirrhotic patients, for focal liver lesions characterization, and in trauma patients[6,8].

More advanced and emerging techniques include perfusion CT, dual-energy CT (DECT) and photon-counting detector CT (PCD-CT)[6,17].

DECT is based on CT data acquisition by using X-rays generated at two different energy spectra; therefore, allowing for superior materials discrimination and characterization. Images are obtained either with dual-source, ultra-fast kV switching, or sandwich detector[6,16]. Then, DECT data post-processing generates several types of images: monochromatic image reconstructions, useful to improve iodine contrast visualization; attenuation maps of different elements according to their atomic number, including iodine, calcium, and water[6]. Moreover, the possibility of generating virtual unenhanced (VUE) images may help reduce radiation dose exposure. DECT improves the delineation of hypo- and hypervascular liver lesions by increasing the lesion to parenchyma contrast. Given the possibility of material decomposition, DECT can also allow distinguishing contrast from calcifications, and noninvasively quantifying fat, iron, and other moieties, compensating for the high cost and examination time length of MRI and invasiveness of biopsy[6,16,17]. However, DECT is affected by some shortcomings, including technical limitations (limited field-of-view, reduced spectral separation depending on vendor or scanner) and software challenges (lack of enough research comparing vendors and scanners' variability on VUE and iodine attenuation values)[16].

PCD-CT is the most recent promising technique but nowadays is still mainly limited to preclinical or small *in vivo* studies in volunteers. More clinical and validation research is therefore needed over a longer time[6].

MRI

MRI is fundamental in the workup of patients with liver diseases[6,17,20] and has been addressed as the preferred imaging modality for the characterization of equivocal focal lesions detected by other imaging modalities[17]. Along with appropriate clinical information, MRI can also allow a definitive diagnosis, avoiding in most cases invasive procedures such as biopsy[21].

A proper dedicated MRI liver protocol requires to be short, comprehensive, standardized, and reproducible[6,17,21]. Pre-contrast MRI, given its higher contrast resolution compared to CT, provides information about tissue and lesion composition (*i.e.*, solid or liquid; iron, fat, glycogen, blood products) and lesions cellularity, either neoplastic or inflammatory[6,11,17,22]. Diffusion-weighted imaging (DWI) has been reported to improve the detection and characterization of focal liver lesions, also allowing differentiation of cysts from solid masses. Moreover, by combining hyperintensity on high b-value DWI (hypercellular lesions) with dynamic multiphasic studies, improvement in lesions detection and characterization (in particular for tumors < 2 cm) can be achieved[11].

Contrast-enhanced MRI represents a relevant component of any liver MRI protocol. It provides reliable information about focal lesions characterization, vascular and biliary anatomy, and more recently organ function[17,20,21]. Both gadolinium-based extracellular (ECA) and hepatobiliary (HBA) contrast agents can be used for multiphase imaging[6,17,21]. Morphologic and vascular-related information are obtained with ECA and HBA through the dynamic study[21].

Moreover, HBA provides the ability to acquire images in the HBA phase, offering information about hepatocytes uptake and excretion in the biliary system[6,11,20,21]. Therefore, HBA may provide functional information[21]. Indeed, lesions, or abnormalities

without hepatocytes or with non-functioning hepatocytes, appear as hypointense compared to the surrounding liver parenchyma[20]. Among reported HBA advantages, it is worth mentioning higher lesion conspicuity with increased sensitivity in lesion detection, and improved lesion characterization with increased ability in the differential diagnosis.

One of the most used advanced MRI techniques useful to detect and characterize focal or diffuse liver disease is DWI. Highly cellular tissues or those with cellular swelling exhibit lower diffusion coefficients, and these aspects can be useful for the evaluation of liver diseases[22].

The evaluation of the biliary tree can be easily made using highly weighted T2 sequences in different planes. In this setting, magnetic resonance cholangiopancreatography (MRCP) is nowadays considered the reference standard for noninvasive biliary evaluation. Thanks to the improvement of MRI techniques, it is now possible to acquire 3D images that can be reformatted in every plane of space by post-processing techniques[23].

LIVER DISEASE INVOLVEMENT

COVID-19 liver injury is defined as any liver involvement that occurs during the course of COVID-19, whether there is a known history of liver disease or not[24]. The presence of liver damage from a laboratory point of view is very common: an increase in liver enzymes is described in around 40% of patients[24], it is greater with severe COVID-19 and at the same time a predictor of adverse events[25,26].

SARS-CoV-2 primarily infects respiratory epithelial cells *via* angiotensin-converting enzyme 2 (ACE2). ACE2 is also expressed at high levels in the endothelium layer of tiny blood arteries and cholangiocytes in the liver and at a low level in hepatocytes. Furthermore, the SARS-CoV-2 virus may use the gut-liver route *via* the hepatic reticular system to reach the liver[25]. Finally, other organ systems and drugs have a significant influence on the liver. As a result, the causative mechanisms of liver damage in COVID-19 infection are many, including direct cytotoxicity caused by active SARS-CoV-2

replication, immune-mediated liver injury, vascular impairment caused by coagulopathy, endothelium, or cardiac congestion, hypoxic changes caused by respiratory failure, drug-induced liver injury, and exacerbation of the underlying chronic liver disease[25] (Figure 1 and Table 1).

Hepatomegaly and steatosis

COVID-19 causes twice as much liver damage at the cellular level. First, hepatocellular damage occurs, resulting in mild steatosis, lobular and portal inflammation, and areas of apoptosis and necrosis. This type of damage raises aspartate aminotransferase (AST) and alanine transaminase (ALT) levels. Later on, the damage is direct to cholangiocytes, with bile duct damage and increase in gamma-glutamyl transferase (GGT) and bilirubin[27].

When there is a clinical suspicion of liver involvement in COVID-19, bedside US is the first imaging technique used in the diagnostic workup. A quick and targeted bedside US may be critical in referring selected patients to second-level imaging techniques, to reduce unnecessary exams and diagnostic delays. US can detect morphological or structural changes in the liver: the most encountered findings in COVID-19 patients are hepatomegaly[28,29] and steatosis[29,30].

According to Abdelmohsen *et al*[28], the most common morphological change in the liver in critically ill COVID-19 patients is hepatomegaly (about 55% of patients), which is also consistent with autopsies in COVID-19 patients[29-31]. Spogis *et al*[29] found hepatomegaly associated with gallbladder wall thickening and decreased echogenicity (*i.e.* signs of acute hepatitis) in 33% of COVID-19 patients with elevated liver cytolysis indices (> 10-fold). Hepatomegaly is usually identified subjectively during imaging: the "qualitative criteria" include the inferior extension of the right lobe to the lower pole of the right kidney and the rounding of the hepatic inferior border. Otherwise, the quantitative criteria are based on the length of the right liver lobe, with a cutoff of 16.5 cm[31].

On the other side, the most common liver structural change associated with COVID-19 is the presence of hepatic steatosis[28,29] (Figure 2). Coagulation activation can produce

hepatic steatosis, and this could be a unique mechanism that leads to both thrombosis and steatosis that are common findings in COVID-19 patients[32]. US B-mode is the most used technique for diagnosing and classifying hepatic steatosis[33], particularly in the moderate or severely affected liver. It has an overall sensitivity and specificity of 85% and 93%, respectively[33]. However, the detection of moderate degree of steatosis remains poor, with about 60% sensitivity[34]. B-mode US imaging is mostly used to analyze the liver qualitatively, searching for characteristic markers of steatosis (*i.e.* hyperechoic liver in comparison to the spleen or neighboring kidney)[29]. US findings can be confirmed on abdominal CT. According to Lei *et al*[35], the most common CT abnormalities in COVID-19 patients include diffuse hypoattenuation of the liver (26%) – more common in severe patients (59%) – and the CT-quantified liver/spleen attenuation that can predict prognosis in COVID-19 patients[35,36]. Furthermore, because the liver is partially included in every chest CT, liver data from chest CT scans performed in many COVID-19 patients can be easily retrieved.

Using a multiparametric US approach Radzina *et al*[30] evaluated 90 patients affected with COVID-19 in the previous 3-9 mo demonstrating how liver elasticity, viscosity, and steatosis are altered after COVID-19 and that these alterations well correlate with liver enzyme abnormalities, even better than CT or MRI findings.

Other consequences of chronic liver disease, such as nonalcoholic fatty liver disease (NAFLD), must be considered in addition to COVID-19-induced liver damage[37]. Obesity and other components of metabolic syndrome have been linked to COVID-19 severity. The impact of NAFLD in COVID-19 patients is controversial in the literature[37]. In a meta-analysis of 1851 patients, Singh *et al*[38] found that, while there was an increase in the course severity of COVID-19 with a 2.60 odds ratio (OR), the adjusted OR (aOR) for mortality risk was 1.01; however, these data should be considered with caution due to the significant heterogeneity among the included studies. Interestingly, Ghoneim *et al*[39] analyzed 8885 patients with common comorbidities known to be linked with COVID-19 and found out that the cumulative incidence of disease was higher if metabolic syndrome was the primary diagnosis (OR 7.0). COVID-19 patients who were African Americans

(aOR 7.45), hypertensive (aOR 2.53), obese (aOR 2.20), diabetic (aOR 1.41), hyperlipidemic (aOR 1.70) or had non-alcoholic steatohepatitis (NASH) (aOR 4.93) had a higher aOR. These findings demonstrated that, among all concomitant metabolic disorders, NASH had the strongest connection with COVID-19. In support of these data, Roca-Fernández *et al*[40] analyzed 41791 people who underwent MRI for assessment of liver fat, liver fibro-inflammatory disease, and liver iron with proton density fat fraction calculation before February 2020 and found that people with fatty liver (> 10%) had a higher likelihood of testing positive (OR: 1.35), and people with obesity and fatty liver had a 5.14 times higher risk of hospitalization. Obese people who did not have a fatty liver did not have an increased risk (OR: 1.75). According to the findings, obese people with fatty liver disease are at a higher risk of COVID-19 infection and hospitalization.

To summarize, COVID-19 patients have a remarkable risk of liver damage, with the main morphologic and structural changes being hepatomegaly and steatosis, which have a significant impact on patients' prognosis and can be easily studied with US (Table 1). Epidemiologically, people with NAFLD/NASH appear to be at a higher risk of severe COVID-19 infection. However, it is unclear how much of this rise is due to hepatic steatosis or the presence of overlapping risk factors and comorbidities.

Acute hepatitis in COVID-19

Liver test abnormalities are frequently encountered in COVID-19 patients at admission, and their increase is associated with the severity of the disease[41,42]. In the majority of cases, COVID-19-induced hepatitis occurs as benign new transient hepatitis with gradual onset, elevated AST and ALT levels, and lack of any radiological HBA changes[29,42,43]. Occasionally, COVID-19-induced hepatitis may occur in otherwise asymptomatic patients as the sole manifestation of COVID-19 infection[44]. Liver damage in COVID-19-induced hepatitis may be the result of viral infection of hepatocytes or cholangiocytes, hypercoagulability with both microangiopathy and local thrombus formation, immune-mediated damage, systemic inflammation, or hypoxic hepatitis due to the respiratory disease[45-49]. Regarding the first mechanism, the virus enters the hepatocytes, and then

viral replication results in rupture of cells, generating elevated serum liver enzymes[48,50]. Thrombotic complications in COVID-19 patients are likely to occur due to a pro-coagulant effect or a progressive endothelial thrombo-inflammatory syndrome[49]. Interestingly, in a systematic review of pathology studies, hemodynamic compromise and thromboembolic disease in the liver were demonstrated in 48.3% and 39.4%, respectively, while liver microthrombi were not identified[48].

Radiological hallmarks of acute hepatitis in COVID-19 patients are encountered in approximately 8% of patients with mild-to-moderated liver test abnormalities, and the occurrence increases in patients with severe elevation of liver enzymes. Radiological hallmarks of COVID-19-induced hepatitis – particularly in the most severe cases – include thickening of the gallbladder wall, hepatomegaly, reduced echogenicity of the liver on the US or homogeneous/heterogeneous liver hypoattenuation on CT, and reduced Doppler signal in the hepatic artery[29,35,51]. Liver hypoattenuation is significantly more common in the most severe cases, with the decrease of the liver to spleen CT attenuation ratio being significantly correlated with the severity of pulmonary lesions and the overall COVID-19 severity[35] (Figure 3). A pathology-radiology correlation study demonstrated that the histological features in patients with sonographic changes included macrophage activation, centroacinar necrosis, granulocytic and histiocytic infiltrate, endothelial damage, and severe cholestasis[29,52]. Among these, macrophage activation was particularly interesting as it may represent the histopathologic correlate of a hyperinflammatory syndrome[29]. In a case of COVID-19-induced hepatitis being the sole symptom and without any other cause for liver damage, pathology demonstrated periportal and interstitial inflammation with predominantly lymphocytes, rare plasma cells, and neutrophils, hepatocyte rosette formation, apoptotic bodies, centrilobular congestion, and mildly increased portal and pericellular fibrosis[52] (Table 1).

Drug-induced liver injury

Drug-induced liver injury (DILI) is a liver dysfunction caused by drugs used as a treatment for COVID-19 disease. Therapeutic choices for COVID-19 have rapidly

expanded and changed over time with the increased understanding of the virus and the disease[53]. The various therapeutic treatments used over time included antiviral drugs, antibiotics, antimalarials, immunomodulator agents, antipyretic agents, adjunctive treatments, and several investigational treatments including convalescent plasma administration from COVID-19 recovered patients[54]. Different studies reported that liver injury in patients with COVID-19 infection could be a direct consequence of the administration of different drugs, such as antivirals and monoclonal antibodies, with most patients showing elevation of AST and ALT levels, and some also of bilirubin, lactate dehydrogenase, and C-reactive protein[55-59]. However, in most cases, elevated levels of AST and ALT do not lead to severe liver injury and the outcome is favorable[59].

The mechanisms underlying DILI in COVID-19 patients are not yet fully understood and they seem to vary depending on drug type[59,60]. A hepatocellular injury has been more often reported than cholestatic or mixed injury in COVID-19 patients with DILI[59]. On one hand, the drug-induced injury may lead to microvesicular steatosis as a result of drug interference with β-oxidation of fatty acids, mitochondrial respiration, or both which leads to the accumulation of non-esterified fatty acids which are subsequently converted into triglycerides[61,62]. On the other hand, there could be a downregulation of cytochromes p450 or CYPs family enzymes involved in oxidative biotransformation of many drugs, thus altering the metabolism of several COVID-19 drugs[60,61]. DILI could be enhanced by the production of reactive oxygen species by inflammatory cells, in addition to immune mechanisms shown in a small subset of DILI cases[63,64].

The radiological manifestations of DILI in COVID-19 patients are non-specific. One of the most frequent radiological signs of DILI is hepatic steatosis[65]. Hepatic steatosis is seen in the US as bright liver echo pattern with the markedly increased liver to kidney contrast, and on CT as a reduction of liver attenuation below 40 UH as an absolute value or liver attenuation reduced of more than 10 HU compared to the spleen[66]. MRI is the gold standard for detection and quantification of liver steatosis: new quantitative techniques are now available, and others are still being investigated also in US and CT[6]. DILI may occasionally lead to acute hepatitis and, therefore, radiological signs in these

cases include hepatomegaly with decreased parenchymal enhancement, periportal edema, gallbladder wall thickening, and ascites[29]. However, the role of traditional and new quantitative techniques for assessing hepatic steatosis and liver injury occurring as a manifestation of DILI in COVID-19 is poorly investigated, and it seems quite difficult to be analyzed: COVID-19 patients may have more commonly hepatic steatosis and liver injury not related to DILI and there are not specific signs allowing to differentiate between steatosis and liver injury caused by drugs or by other causes (*e.g.*, steatohepatitis, viral infection)[30] (Table 1).

PVT

The pandemic taught us the great impact of COVID-19 infection on the development of coagulation disorders, especially disseminated intravascular coagulation-like massive intravascular clot formation[67]. In this setting it has been partially explained that cytokines' cascade and endothelial damage can lead to the development of intravascular coagulation in the whole body, as reported by Cui *et al*[68]: critically ill patients showed a significantly higher incidence of thrombosis, up to 25%.

One of the most important visceral districts to consider in a setting of an altered vascular and endothelial environment is the portal vein, considering its importance in blood drainage from the gastrointestinal tract.

In non-cirrhotic patients, acute PVT may present with pain, even though the majority are found incidentally[69] (Figure 4). Different causes have been demonstrated as key roles in the development of PVT, with infection and inflammation being the most common. Rajani *et al*[70], reported that gastrointestinal inflammation accounts for about 14% of all causes of PVT. As for other viral and bacterial infections, COVID-19 can manifest with different gastrointestinal manifestations, including diarrhea, nausea, vomiting, and abdominal pain, which typically present after the respiratory symptoms (9 d *vs* 7.3 d)[71].

Even if it is well known that the inflammatory environment can lead to the development of micro- and macro-thrombosis, the current literature has not been focused

on the impact of PVT in COVID-19 patients. In fact, by searching medical databases, few studies were published regarding this topic, the majority being case reports.

A meta-analysis published in 2020[72] included 18 studies and reported that all COVID-19 patients were over 15 years old, and the majority were male (62%). The authors found a pooled prevalence of vascular thrombosis of 29.4%, one of the most representative signs in autoptic series. Similarly, Kheyrandish *et al*[73] (2021) reviewed all cases of PVT published in the literature, confirming the higher incidence in males during infection and in females after vaccination. Thrombocytopenia was the most common laboratory finding, followed by high D-Dimer values, and abnormal coagulation tests.

Radiology plays a key role in the diagnosis of PVT. The first imaging technique useful to determine portal vein patency is US, which can be performed at bedside, especially in critically ill or isolated patients. Acute PVT can manifest as the presence of heterogenous material in the portal vein lumen, which can be partial or complete[74]. Occasionally, the portal vein thrombus can be iso- or hypoechoic on US; in this setting, the use of color doppler can support the final diagnosis, showing the lack of flow in all or some parts of the portal vein lumen[75]. Nowadays, CT is the reference standard imaging technique to evaluate PVT and its extension, both intra-hepatic and into the whole mesenteric venous system. On the unenhanced images, a higher attenuation into the portal vein lumen, due to the fresh clot, can be appreciated. The injection of an intravenous iodinated contrast agent is necessary to evaluate the lack of enhancement in the lumen, more evident in the portal-venous phase. Liver enhancement can be inhomogeneous due to areas of hypervascularization during the arterial phase, then becoming homogenous in the portal-venous and delayed phases[74]. The portal trunk can be dilated, and, sometimes, it is possible to appreciate the enhancement of vein walls due to inflammatory response[76].

Due to the different imaging spectrums of COVID-19 infection, patients may undergo MRI of the upper abdomen. In these settings, acute PVT is represented by an inhomogeneous intraluminal area both on T1- and T2-weighted sequences. On T1-weighted sequences, PVT can manifest as hyperintense to the muscle if it is recent (acute),

while isointense if subacute. On T2-weighted sequences PVT can manifest with different grades of hyperintense signal according to the phase (acute or subacute). If MRI is performed also after intravenous injection of contrast agents, the appearance is superimposable to the above-mentioned CT scan (Table 1).

If the PVT is not treated, cavernous transformation can occur (Figure 5): the main portal venous trunk is not appreciable and the development of periportal venous collaterals can help the drainage of venous flow from the gastrointestinal tract to the liver. Considering that chronic PVT is not reported in any patients with COVID19 infection, its findings are out of the scope of the present review.

Biliary and gallbladder involvement

The development of biliary injury in patients with COVID-19 represents an important complication, associated with poor prognosis and clinical outcome[77]. Biliary involvement in patients with COVID-19 often demonstrates clinical and biochemical features similar to sclerosing cholangitis in critically ill patients (SSC-CIP), manifesting as increased cholestasis indexes (GGT and total bilirubin) in patients with prolonged admission to the ICU and no history of biliary or liver disease nor signs of mechanical obstruction[77,78]. Severe cholestasis has been reported in up to 27% of patients with COVID-19 admitted to the ICU[79]. The mechanism of the cholestatic injury in patients with COVID-19 is not completely understood and it is likely multifactorial, with direct viral damage due to the expression of ACE2 on cholangiocytes, immune or inflammatory damage associated with liver injury, toxic bile injury, and ischemic or hypoxic injury of the biliary epithelium[80]. Cholangiopathy has also been observed after chronic exposure to ketamine, a general anesthetic used for sedation of patients with COVID-19 and acute respiratory distress syndrome[81]. The prognosis of patients with SSC-CIP is poor, with mortality in up to 50% of cases due to the development of biliary complications and worsening of liver function[82]. Particularly, patients with pre-existing chronic liver disease have an increased risk of SSC-CIP and higher mortality during COVID-19 infection[83].

Imaging is important to guide the diagnosis of cholangiopathy in patients with COVID-19 in conjunction with laboratory markers and to exclude other causes of biliary obstruction. US and CT can be performed as first-line imaging examinations and can reveal the presence of bile duct dilatation with intrahepatic stones[84] (Figures 6 and 7). Heterogeneous enhancement of the liver parenchyma with periportal edema can also be observed on contrast-enhanced CT[85]. MRI with MRCP should be performed in patients with persistent cholestasis and elevated liver function tests to assess the extension of biliary damage. MRCP can demonstrate features of secondary sclerosing cholangitis characterized by multifocal biliary strictures alternated with dilated tracts, with a "beaded" appearance[79,85]. Biliary strictures can be complicated by biliary cast, presenting as intraductal filling detects on MRCP and T2-weighted images with corresponding linear hyperintensity on unenhanced T1W images. In a recent study by Ghafoor *et al*[86], MRCP findings associated with COVID-19 cholangiopathy included intrahepatic bile duct strictures associated with upstream dilatation in 58% of patients and the presence of biliary casts in 11.8% of cases (Figure 8). Peribiliary changes characterized by hyperintensity on T2W images and DWI restriction were reported in 70.6% of patients, while peribiliary enhancement was observed in 23.1% of cases[86]. Extrahepatic bile duct involvement is rare[86]. Other complications include sepsis with the possible development of hepatic abscesses and progressive liver disease with morphologic features of biliary cirrhosis. Endoscopic retrograde cholangiopancreatography can be performed to confirm the diagnosis of biliary strictures and stones in selected cases and allow treatment of biliary obstruction.

Acalculous cholecystitis has been reported as the most common gallbladder involvement in patients with COVID-19[87,88]. Despite the pathogenesis of acalculous cholecystitis in COVID-19 is still under investigation, the presence of SARS-Cov-2 virus was demonstrated in samples from the gallbladder wall, probably due to the presence of ACE2 receptors in the gallbladder[87]. Other possible causes include mechanical ventilation and prolonged total parenteral nutrition[89]. The US is the first-line imaging modality in patients with suspected acalculous cholecystitis and it may reveal thickened

gallbladder wall with peri-cholecystic fluid collection and gallbladder distension, in absence of gallstones. Contrast-enhanced CT may be performed in case of suspected complications, such as gallbladder perforation, fistula, or necrosis (*i.e.* gangrenous cholecystitis)[90]. CT findings include distended gallbladder with wall thickening, hyperenhancement of the gallbladder wall during postcontrast phases, and pericholecystic fluid[91] (Table 1).

Chronic findings

The current literature is lacking studies evaluating the chronic findings of COVID-19 on liver imaging. The type of hepatic chronic findings should be related to the sequelae of acute liver damage during COVID-19 infection after recovering from the acute disease. Severe liver cholestatic injury can progress into chronic liver disease with the development of cirrhosis, manifesting as abnormal liver morphology with associated imaging features of portal hypertension and ascites. On US, a prospective multiparametric assessment of post-COVID-19 patients observed increased liver stiffness and steatosis at 3-9 mo after COVID-19 compared to normal controls[30]. Complete PVT can progress to portal vein cavernoma if not promptly recanalized and resulting in chronic findings of noncirrhotic portal hypertension and risk of variceal bleeding[49].

Further studies are still needed to assess the evolution of hepatic findings and the possible long-term sequelae of liver damage in patients recovering from COVID-19.

CONCLUSION

Even if COVID-19 is extensively reported as a disease that mainly affects the lungs, the viral infection may cause an involvement of abdominal parenchymal organs and the gastrointestinal tract, increasing the risk of both acute and long-term health problems, especially of liver parenchyma. The liver damage may be caused by different mechanism, including direct hepatocytes involvement from the viral infection, indirect response to the systemic inflammatory status, or hepatotoxicity due to drugs used to manage the

infection. In this setting, the diagnostic imaging workup plays a crucial role for early detection of liver manifestations and assessment of long-term complications.

US should be considered as the main diagnostic option for the first evaluation of liver, biliary tree, and vascular district, in patients with abdominal symptoms, or with altered blood test, while abdominal contrast enhanced CT seems to be the most useful diagnostic tool for the overall abdominal assessment offering useful information regarding not only the liver itself, but also other parenchymal organs and vascular system. Finally, MRI should be considered the tool that better clarifies liver alterations in patients with COVID infection deemed indeterminate on US and CT.

It's important to underline that the main limitation in this field should be still considered the difficulty to understand the main COVID-19 pathological mechanisms and their related consequences. Further studies should be more focused on the evaluation of COVID-19 patients, in particular those with liver involvement, to quickly address the diagnosis and the best management possible.

A comprehensive knowledge of COVID-19 hepatic involvement assessed through the different diagnostic imaging modalities can help clinicians in addressing the correct treatment and long-term management of the disease.

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