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REVIEW

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COVID-19 and non-alcoholic fatty liver disease: Two intersecting pandemics

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Abstract

Background: Initial evidence from China suggests that most vulnerable subjects to COVID-19 infection suffer from pre-existing illness, including metabolic abnormalities. The pandemic characteristics and high-lethality rate of COVID-19 infection have raised concerns about interactions between virus pathobiology and components of the metabolic syndrome.

Methods: We harmonized the information from the recent existing literature on COVID-19 acute pandemic and mechanisms of damage in non-alcoholic fatty liver disease (NAFLD), as an example of chronic (non-communicable) metabolic pandemic.

Results: COVID-19-infected patients are more fragile with underlying metabolic illness, including hypertension, cardiovascular disease, type 2 diabetes, chronic lung diseases (e.g. asthma, chronic obstructive pulmonary disease and emphysema) and metabolic syndrome. During metabolic abnormalities, expansion of metabolically active fat ('overfat condition') parallels chronic inflammatory changes, development of insulin resistance and accumulation of fat in configuring NAFLD. The deleterious interplay of inflammatory pathways chronically active in NAFLD and acutely in COVID-19-infected patients, can explain liver damage in a subgroup of patients and might condition a worse outcome in metabolically compromised NAFLD patients. In a subgroup of patients with NAFLD, the underlying liver fibrosis might represent an additional and independent risk factor for severe COVID-19 illness, irrespective of metabolic comorbidities.

Conclusions: NAFLD can play a role in the outcome of COVID-19 illness due to frequent association with comorbidities. Initial evidences suggest that increased liver fibrosis in NAFLD might affect COVID-19 outcome. In addition, long-term monitoring of post-COVID-19 NAFLD patients is advisable, to document further deterioration of liver damage. Further studies are required in this field.

KEYWORDS
fatty liver, mitochondria, nitrosative stress, oxidative stress, SARS-CoV-2

1 | INTRODUCTION

The global acute pandemic of severe acute respiratory syndrome (SARS) caused by the coronavirus SARS-CoV-2 (COVID-19, *Sarbecovirus* subgenus, *Betacoronavirus* genus, *Coronaviridae* family) has suddenly become a major threat to public health.[1,2] Since late 2019, more than 3.6 million confirmed cases, more than 250,000 deaths in 213 countries at a world level (at May 5, 2020), and a huge burden of care have been recorded.[3]

Although many subjects remain asymptomatic,[4] the most frequent and critical clinical presentation of COVID-19 is the respiratory involvement, ranging from mild respiratory symptoms to severe pneumonia. However, the infection by SARS-CoV-2 virus represents a systemic disease,[5] which can lead to myocardial injury,[6,7] heart failure,[6] vascular inflammation, myocarditis, cardiac arrhythmias,[7] hypoxic encephalopathy,[8] multi-organ failure and ultimately death.[9]

In the first phase of the COVID-19 disease, the pathogenic properties depend on binding of spike viral proteins to angiotensin I converting enzyme 2 (ACE2) receptors,[10-12] which allow the virus to enter the target cells.[13] Receptors are expressed in the epithelia of the upper respiratory tract (nasopharynx) as major site of replication and, in the human lung, in alveolar epithelial cells (type II) and ciliated cells.[11,14,15] ACE2 receptor expression also occur in vascular endothelium, in the brush border of intestinal enterocytes[11,16] and in cholangiocytes.[11,17] Thus, the symptomatic involvement of the gastrointestinal tract is possible with COVID-19.[18-21] A recent USA report describes a clinically evident gastrointestinal involvement in 61% of COVID-19-positive subjects.[22] The presence of ACE2 receptors in the glandular cells of gastric, duodenal and distal enterocytes may result in malabsorption, unbalanced intestinal secretion and activation of the enteric nervous system, leading to gastrointestinal symptoms.[23,24]

The liver can also become a target of COVID-19 infection, although major liver damage is uncommon.[25-28] SARS-Cov-2 might affect the liver by direct (i.e. viral translocation from the gut to the liver) or indirect mechanisms (ie systemic inflammation, liver ischaemia and hypoxia, effects on pre-existing liver diseases, drug-related liver injury) and represents a new challenge for hepatologists.[28] Notably, non-alcoholic fatty liver disease (NAFLD) is a chronic dysmetabolic pandemic which has become the most common liver disease in the world, with a prevalence rate of 30% in the Western population.[29,30] Moreover, NAFLD does not stands on its own but it is usually associated as 'fellow traveller' with a constellation of risk factors, metabolic syndrome and illness (Figure 1).[31] Along with this view, the acronym NAFLD has been recently re-visited by coining the acronym MAFLD ('metabolic dysfunction-associated fatty liver disease').[32] NAFLD/MAFLD can therefore affect the final outcome in COVID-19-infected patients.[33-36] In addition, the liver itself has increased susceptibility to drugs in conditions of chronic injury.[37-39] In this context, the presence of inflammatory pathways (in particular those involving cytokines) present either in NAFLD[40-42] and COVID-19-infected patients [43-46] could increase liver inflammation or be a marker of metabolic risk factors further aggravating the clinical outcome.

Because of the pandemic characteristics and high-lethality rate of SARS-CoV-2 infection, precise knowledge of the virus behaviour and of risk factors predisposing to COVID-19 onset and progression has a key role in the near future to anticipate virus-related events worldwide. In the analysis of Wang et al, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease and cerebrovascular disease (OR 2.29-5.97) were independent risk factors associated with COVID-19-infected patients.[47] Furthermore, a recent analysis of 1999 hospitalised COVID-19-infected patients in New York showed that BMI > 40 kg/m^2 is one of the strongest predictor of hospitalisation (OR 6.2) and is exceeded only by age ≥ 75 years (OR 66.8) and age 65-74 years (OR 10.9).[48] Finally, a study on 202 consecutive patients with confirmed COVID-19 identified NAFLD as independently associated with COVID-19 progression.[49]

We discuss here the ongoing interaction of two different pandemic conditions: the recent, acute COVID-19 outbreak and the chronic NAFLD as part of an even wider set of metabolic disorders. During COVID-19 infection, the underlying NAFLD could pave the way to more severe hepatic and metabolically associated complications and become another prognostic marker of viral disease.

2 | COVID-19 AND NAFLD

In the liver, ACE2 receptors are mainly expressed in cholangiocytes (60% of cells) and in endothelial cells, rather than in hepatocytes (only 3% of cells) or Kupffer cells (where ACE2 receptors are absent).[17,50,51] Major factors involved in SARS-CoV-2 infection and liver damage are depicted in Figure 2.

In Chinese patients, the prevalence of acute liver injury during COVID-19 disease was 15.4%.[52] However, an involvement of the liver has been reported in about 60% of cases,[53] and the risk of liver dysfunction seems to increase in older age.[54]

Ji et al[49] reported on 202 COVID-19-infected patients and NAFLD status. Liver abnormalities were 50% on admission and 75% during hospitalization, manifesting as hepatocellular pattern (only 3% with ductular or mixed pattern); 33% of the patients had persistent abnormal liver function from admission to last follow-up. COVID-19 progression was associated with male sex, age > 60 years, higher BMI, underlying comorbidity and NAFLD. In this study, univariate and multivariate logistic regression analyses indicated NAFLD as an

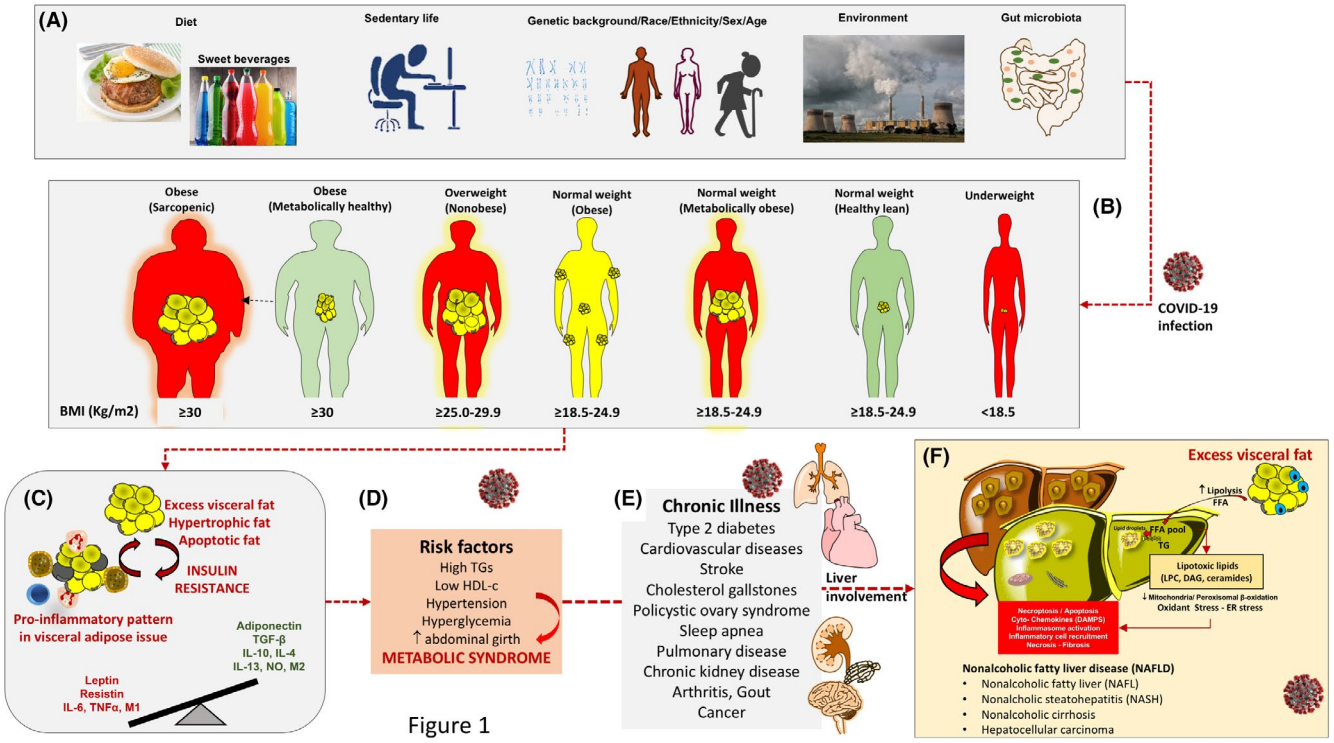

Figure 1

FIGURE 1 Sequences of pathophysiological mechanisms predisposing to metabolic illness and liver steatosis. Rationale to explain multi-organ and liver damage during COVID-19 infection. (A) Initial role of wrong lifestyles (hypercaloric, unbalanced, fructose- and refined carbohydrate-enriched diet, sedentary behaviour), on a genetic/racial, ethnical and environmental background. Changes in intestinal microbiota can also govern additional metabolic changes due to biotransformation of foods, local inflammatory changes, increased intestinal permeability[112] to bacterial products (ie lypopolisaccharides). (B) Expansion of visceral fat may occur in different phenotypes, independently of simple body weight (encompassing the term 'adiposity' or 'overfat'). The three subtypes at risk include normal weight but metabolically obese subjects (characterized by high visceral adiposity, ie about % overfat, normal lean mass, propensity to develop metabolic abnormalities),[87,113] overweight individuals and obese sarcopaenic subjects (high visceral adiposity, decreased lean mass, likely several metabolic abnormalities). The subtype «normal weight obese» has increased (>30%) fat mass (not necessarily visceral adiposity), a normal lean mass, without metabolic abnormalities. Overfat conditions (in red) are predisposing to chronic metabolic inflammation, compromised immunity, increased risk of chronic disease and infections (including viral infections). Underweight, underfat individuals also share the same risk for chronic inflammation, compromised immunity, increased risk of chronic disease and infections. (C) The metabolically active vicious circle originates from the excess visceral fat with production of inflammatory molecules. In lean individuals or metabolically healthy subjects, anti-inflammatory cytokines (transforming growth factor beta (TGF-β), interleukin 10 (IL-10), IL-4, IL-13, nitric oxide (NO)) activate M2 macrophage- and inhibit neutrophil-mediated inflammation. T lymphocytes, neutrophils, B1 and B2 cells, NK cells and innate lymphoid cells also populate the fat tissue.[95] Hypertrophic or apoptotic adipocytes (in grey) in obese individuals can secrete pro-inflammatory molecules (leptin, resistin, IL-6 and tumour necrosis factor-α) that activate a pro-inflammatory M1 macrophage.[114] The pro-inflammatory metabolic status is a factor promoting insulin resistance, as well as defective immune response (poor T cell and macrophage function). (D) Further progression of the chronic pro-inflammatory status and insulin resistance paves the way to several metabolic risk factors contributing to the metabolic syndrome. (E) Chronic illness can follow with established risk factors. (F) Non-alcoholic fatty liver disease (NAFLD) and the spectrum of liver abnormalities are the consequence of the accumulated metabolic abnormalities. Excess lipolysis during insulin resistance will increase the influx of free fatty acids (FFA), synthesis of triglycerides, enrichment of FFA pool with lipotoxic products (lysophosphatidylcholine (LPC); diacylglycerol (DAG); ceramides). Products mediate endoplasmic reticulum (ER) stress, oxidant stress and activation of the inflammasome (multiprotein cytoplasmic complex that responds to damage-associated molecular patterns (DAMPs), as part of the innate immunity response).[38,39,90,115] Abbreviations: BMI, body mass index

independent risk factor for COVID-19 progression (OR 6.4; 95% CI 1.5-31.2). NAFLD was also associated with higher likelihood of abnormal liver function from admission to discharge, and longer viral shedding time.

The risk of severe COVID-19 presentation increases by the coexistence of obesity and NAFLD,[55] pointing to a specific and additional role for pathogenic mechanisms involved in NAFLD onset and progression.

NAFLD has also been previously linked with increased risk of recurrent bacterial infections,[56] and with increased 30-day all-cause mortality in patients with community-acquired pneumonia.[57]

A meta-analysis examined 313 severe group cases and 1167 non-severe group cases with respect to liver disease in patients with COVID-19. Patients with previous liver disease were not at increased risk of disease progression (OR: 0.67,

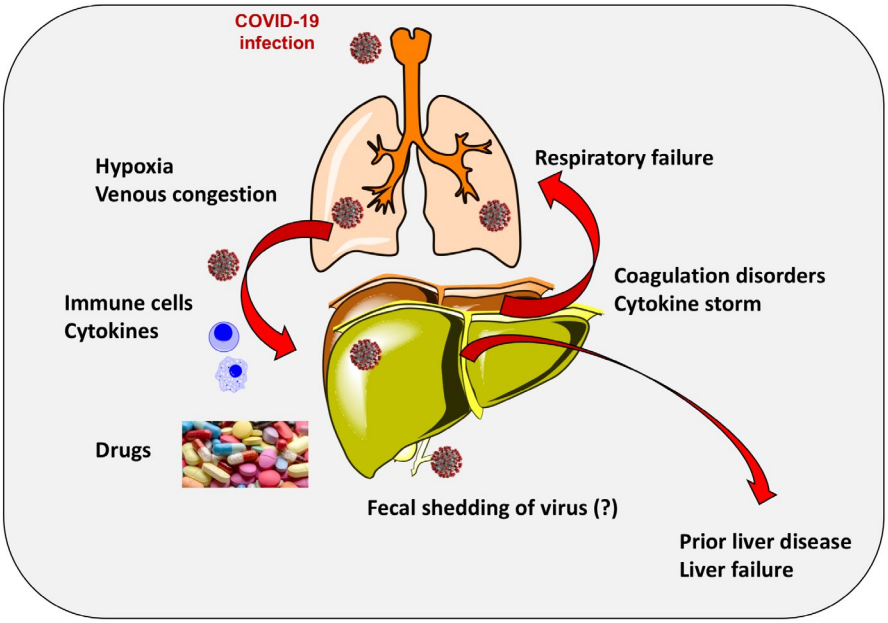

FIGURE 2 Major factors involved in COVID-19 infection and liver damage. Factors include lung involvement leading to hypoxia and venous congestion with liver stasis, role of immune cells and cytokines, drug-induced liver damage and addition of coagulation disorders and cytokine storm. A prior liver disease might exaggerate the damage from ongoing COVID-19 infection. Non-alcoholic fatty liver disease might represent per se a condition of intrinsic frailty (due to ongoing lipotoxicity, chronic inflammatory status, insulin resistance, oxidant stress, immune response), or be a marker of additional coexisting metabolic disorders which will aggravate the clinical course of COVID-19

95% CI: 0.30-1.49, $P = .326$).[47] Limitations in this survey, however, include the poor number of available cases, different severity definitions, underlying coexisting illness and unspecified liver diseases. On the other hand, in a series of 310 patients with COVID-19 and NAFLD, the presence of intermediate or high FIB-4 scores greatly and independently increased the risk of a severe progression of the COVID-19 disease.[58] Patients with NAFLD show a different risk since they are exposed to a significant metabolic risk. Several mechanisms of damage could link COVID-19 to liver and require attention (Figure 2).

a. A direct cytopathic viral damage is a possibility. SARS-CoV-2 in gut lumen could translocate to the liver via portal flow and induce a direct damage due to active viral replication in hepatic cells through ACE2 receptors.[59] This effect is not necessarily linked to increased liver SARS-CoV-2 uptake, since NAFLD/MAFLD is not associated with changes in expression of liver genes implicated in SARS-CoV-2 infection. A study did not find significant differences in human liver biopsies comparing gene expression of four proteins: angiotensin-converting enzyme 2, cellular protease Transmembrane Protease Serine 2, phosphatidylinositol 3-phosphate 5-kinase, and cathepsin L protein (genes ACE2, TMPRSS2, PIKfyve and CTSL, respectively).[60] Thus, a role for the hepatic innate immunity populations in increasing the likelihood of symptomatic COVID-19 infections (see below) is possible.[61]
b. Hepatocellular hypoxia in chronic liver diseases in COVID-19-infected patients might lead to increased expression of ACE2 receptors,[51] and hypoxia-inducible factors (HIFs), a family of transcription factors activated by hypoxia. Such changes might further aggravate metabolic diseases such as NAFLD,[62] aggravating NAFLD progression.[54,63] From a clinical point of view, specific abnormalities of bile duct chemistry are rare in COVID-19-infected patients[9] and, thus, the ACE2-mediated liver injury could be mainly secondary to the localization of these receptors in the endothelial cells[17] and NAFLD progression might include exaggerated production of ROS and NO derivatives,[64] inflammatory pathways leading to cellular crosstalk with Kupffer cells[65] and HIF-2α upregulation,[66] through suppression of fatty acid β-oxidation and induction of lipogenesis in the liver via PPARα.[63] This hypothesis is partly supported by liver histology from patients deceased due to severe COVID-19, reporting moderate microvesicular steatosis and mild lobular and portal activity, possibly due to a direct effect of SARS-CoV-2 infection or to drug-induced liver injury (DILI).[67]
c. Dysregulated systemic and hepatic innate immunity.[44,68] ACE2 receptors in enterocytes [69] would predispose to viral translocation to the liver with potentials for viral circulation via the reticular system.[70] The innate immune cellular cluster in the liver would be activated with inflammatory and changes due to cytokine production (Figure 3). Patients with severe COVID-19 infection display elevation of inflammatory biomarkers such as C-reactive protein

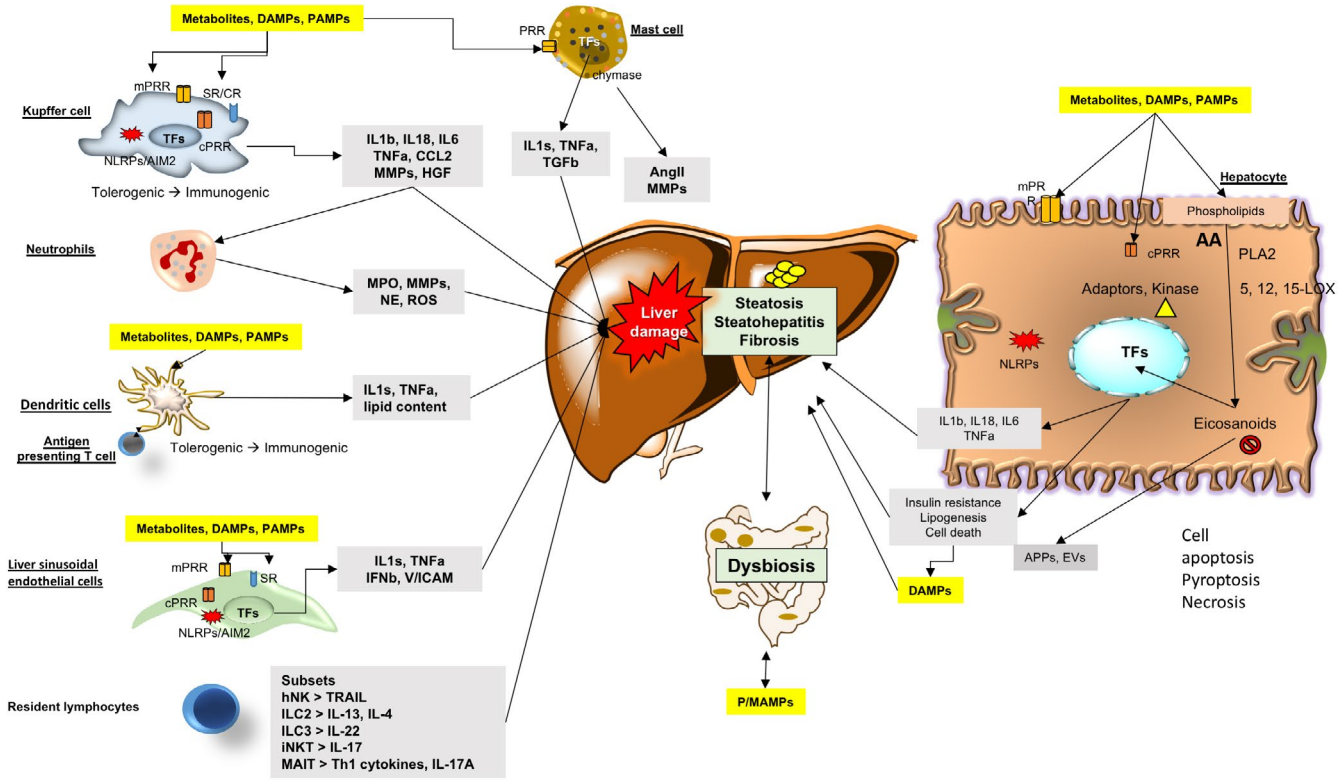

FIGURE 3 Population of innate immune cells playing a role in progression of NAFLD. Immune cells include mast cells (MC), Kupffer cells (KC), neutrophils, dendritic cells (DC), liver sinusoidal endothelial cells (LSEC), resident innate-like lymphocytes (ILC) and hepatocytes. Kupffer cells, neutrophils, dendritic cells, liver sinusoidal endothelial cells and hepatocytes detect the presence of gut-derived P/MAMPs (microbe-associated molecular pattern molecules), endogenous DAMPs (damage-associated molecular pattern Molecules), PAMPs (pathogen-associated molecular pattern molecules) and excessive metabolites via PRRs (pattern recognition receptor), leading to the increased release of pro-inflammatory cytokines and chemokines. In liver sinusoidal endothelial cells, stressor-induced upregulation of expression of adhesion molecules plus chemokines, stimulate recruitment of neutrophils and monocytes to the liver. Activated neutrophils initiate liver damage mainly by releasing enzymes and ROS (reactive oxygen species). Activated dendritic cells also present antigens to T cells with initiation of adaptive responses. Kupffer cells and hepatocytes regulate release and endocytosis of APPs (acute-phase protein), thus extending their innate immune function to extrahepatic organs. Kupffer cells, mast cells and hepatocytes increase expression of other factors MMPs (matrix metalloprotease), Ang II (angiotensin II), TGF (transforming growth factor) and HGF (hepatic growth factor) to stimulate HSC (hepatic stellate cell) activation and liver fibrosis. Innate immune signals also mediate metabolic changes (e.g. lipogenesis and insulin resistance) and cell apoptosis, pyroptosis or necrosis in hepatocytes. KCs and LESCs express high levels of SR (scavenger receptor), which clears circulating molecules and organisms. SR plays a key role in the innate immune response. Innate-like lymphocytes, including NKs (natural killer cell), ILCs (innate lymphoid cell), iNKTs (invariant natural killer T cell) and MAITs (mucosal-associated invariant T cell), also generate multiple cytokines and influence their local microenvironment of the liver. ILC are fundamental cell that transit from an immune-tolerant state (a condition in which they produce interleukin (IL-10), transforming growth factor (TGF-β), etc) to an immune-active phenotype (producing IL-1s, TNF-α, etc). ILC form the first line of defence against invading organisms and environmental challenges through pattern recognition receptor (PRR) ligation and activation of complement receptors (CRs) or scavenger receptors (SRs). Together, these events result in liver steatosis, inflammation and fibrosis and lead to NASH and advanced complications. Abbreviations: CCL2, C-C motif chemokine 2; TF, transcriptional factor; Th1, T helper 1 (Adapted from Cai et al[68,116] and Jenne & Kubes[117])

(CRP), serum ferritin, LDH, D-dimer and interleukin (IL-6, IL-2).[71] IL-6, in particular, appears as a key factor in the onset and progression of the 'cytokine storm' described in COVID-19-infected patients,[54] and increased IL-6 levels have been reported in subjects with NAFLD.[40,72] IL-6 plays an important role in the 'cytokine storm' of COVID-19-infected patients.[54] Increased IL-6 levels occur in NAFLD[40,72] and could represent a marker or mediator of related atherosclerosis[72] and comorbidities often found in COVID-19-infected patients. The cytokine MCP-1 is often increased in COVID-19-infected patients[45] and acts as a further hit for steatohepatitis.[73]

d. Drug-induced liver injury (DILI): initial clinical guidelines recommended antiviral agents for COVID-19, with some of them, including lopinavir/ritonavir, remdesivir, chloroquine, tocilizumab, and uminefovir, Chinese traditional medicine, being potentially hepatotoxic in some patients (and a few have subsequently already been proven to be ineffective). The presence of underlying metabolic abnormalities and NAFLD might facilitate DILI.[49,74]

e. Reactivation of pre-existing liver disease: patients with pre-existing chronic liver disease may be more susceptible to liver damage from SARS-CoV-2.[75] Biological drugs like tocilizumab and baricitinib might also cause HBV re-activation and thus lead to liver function deterioration. On the other hand, it is still unknown whether SARS-CoV-2 infection exacerbates cholestasis in those with underlying cholestatic liver diseases. Such pathways might aggravate NAFLD.
f. Hepatic lipid metabolism. Lipid production and lipid breakdown in the liver provide lipid species which negatively regulate the underlying status of chronic metabolic inflammation. Basic and clinical research suggest that the complex network of factors acting within the liver can drive innate immune activation. This pathway directly triggers and amplifies hepatic inflammation and affects the development of hepatic fibrosis in NAFLD/NASH.[76]

Although there is no direct evidence that, in the acute phase of the disease, a major liver damage occurs more frequently in COVID-19-infected patients with pre-existing NAFLD, the common pathogenic mechanisms involved in COVID-19 and NAFLD could generate, in COVID-19-infected patients, an increased risk of NAFLD progression to steatohepatitis in the long term.[77] Thus, in these patients, a close follow-up aimed at explore the long-term outcomes of liver injury is needed.

3 | NAFLD, VIRUS AND METABOLIC ALTERATIONS

Studies from China confirm that most vulnerable subjects to COVID-19 infection suffer from pre-existing illness that includes hypertension, cardiovascular disease, diabetes, chronic lung disease (e.g. asthma, chronic obstructive pulmonary disease, and emphysema), cancer and chronic inflammation.[9,34,78,79]

Several of such conditions, alone or in combination, predispose or are associated with metabolic changes of the liver, namely NAFLD. Although there is a hope for more specific therapies in COVID-19 infection, including vaccines,[80] a rational approach against future outbreaks must include preventive measures such as lifestyle changes to decrease the burden of chronic metabolic disorders, adiposity and associated pro-inflammatory status while preserving an healthy immune response.[81,82]

This conclusion is supported by emerging relationships between COVID-19 outcomes and frequent metabolic abnormalities which coexist with NAFLD.

Diabetes mellitus has been described as an additional risk to the progression of COVID-19,[34,47] probably also due to the presence of an 'overfat' condition (see below), low-grade chronic inflammation, insulin resistance, obesity[38,83-85] and a dysregulation of ACE2.[61] Of note, the ACE2 is also expressed in the endocrine pancreas. Thereby, COVID-19 might facilitate a status of insulin resistance and impaired insulin secretion.[86]

Independently from diabetes, the presence of an 'overfat' condition (i.e., excess body fat that impairs health[87]) has developed as a pandemic worldwide and can occur in obesity, overweight and even normal weight subjects with excess fat involving the liver as well in terms of steatosis (Figure 1). Several abnormalities can cluster together with overfat, that is overweight, obesity, chronic 'metabolic' inflammation and insulin resistance, eventually configuring the metabolic syndrome (MetS).[9,88,89]

Excess body fat can impair immunity, as confirmed by the higher incidence of both autoimmune and immune diseases.[90] A defective immune response (mainly of T lymphocytes and macrophages) with underlying adiposity will compromise the immune system to increase the risk of infections, and chronic respiratory diseases.[91,92] Notably, the overfat condition appears to be a risk factor in infectious viral diseases.[93,94] In particular, overfat might negatively affect immune function and host defence mechanisms,[95] while the response to viral and bacterial hits becomes defective in overfat hosts.[93,95-97]

Lastly, illness, such as asthma, chronic obstructive pulmonary disease, emphysema and cancer, can be further associated with the overfat condition [9,78,79]). Thus, whether the overfat condition represents an additional negative factor during COVID-19 infection requires attention.

MetS, on the other hand, is a frequent and important underlying condition in patients developing infections, and MetS components (combined with liver steatosis) might further deteriorate with infections.[9,34,78,79] Major contributing risk factors for MetS include overweight and obesity.[98-109] In this case, individuals have increased morbidity in response to COVID-19 infection.[110,111]

4 | CONCLUSIONS AND FUTURE PERSPECTIVES

The pandemic characteristics and high-lethality rate of SARS-CoV-2 infection have raised concerns about mechanisms of injury in patients at risk. Initial evidence from China indicated that the subjects most vulnerable to COVID-19 suffer from pre-existing illness. COVID-19 acute pandemic often develops in patients with major metabolic abnormalities, including fatty liver disease, which is part of a chronic pandemic together with body fat accumulation. During metabolic abnormalities, the expansion of metabolically active fat ('overfat condition') parallels chronic inflammatory changes,[9,34,78,79] the development of

insulin resistance and, in the liver, the accumulation of fat and, possibly, an underlying fibrosis. In this context, the deleterious interplay of the complex inflammatory pathways chronically present in NAFLD can be acutely boosted in the setting of COVID-19, magnifying liver injury and deteriorating outcome in metabolically compromised populations. Thus, NAFLD should be considered as prognostic indicator during COVID-19 and, on the other hand, close long-term monitoring of patients with NAFLD who experienced COVID-19 might be needed.

Finally, a further challenge in the diagnosis and treatment of patients with NAFLD is to reduce the vulnerability from non-communicable diseases, increasing the individual resilience to future outbreaks.

CONFLICT OF INTEREST

None declared.

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