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Review

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The bidirectional relationship between fatty liver disease and COVID-19

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Abstract

COVID-19 and nonalcoholic fatty liver disease (NAFLD) have emerged as global pandemics affecting millions of people worldwide over the past three years. NAFLD is particularly prevalent in individuals with metabolic comorbidities, such as diabetes and obesity, which have been strongly linked to a severe course of Sars-CoV-2 infection. Recently, due to the close association between metabolic abnormalities and NAFLD, the disease has been redefined as metabolic dysfunction-associated fatty liver disease (MAFLD). This review offers an overview of the biological and cellular mechanisms by which COVID-19 can cause liver damage, with a specific focus on the influence of fatty liver in these mechanisms. Additionally, it explores how fatty liver can exacerbate a COVID-19 infection and, conversely, if the presence of COVID-19 may accelerate the development and progression of fatty liver. Finally, the review examines the existing evidence suggesting that NAFLD or MAFLD independently contributes to a heightened severity of COVID-19, while also considering other factors such as age and metabolic comorbidities that may play a role in the disease's progression.

Keywords: MAFLD, NAFLD, fatty liver, COVID-19, SARS-CoV-2

INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has impacted a staggering number of individuals, surpassing 620 million people, and has resulted in more than 6.5 million deaths[1]. While COVID-19 is primarily characterized by respiratory symptoms, it has become evident that multiple organs, including the digestive system and liver, can be involved[2]. Additionally, individuals with pre-existing chronic conditions have been found to experience a more severe trajectory of COVID-19, resulting in hospitalization, the need for intensive care treatments, and increased mortality rates[3]. Notably, individuals with metabolic disorders such as obesity, diabetes, and/or metabolic syndrome have shown a higher susceptibility to severe manifestations of COVID-19 based on clinical observations and studies[4]. Liver steatosis, commonly found in patients with obesity, metabolic syndrome, or diabetes, has been recognized as an independent predictor of COVID-19 severity in some research studies[5].

nonalcoholic fatty liver disease (NAFLD) is a prevalent chronic liver condition, affecting approximately 25.2% of the worldwide population[6]. The occurrence of NAFLD differs among various regions, with the Middle East (32%), South America (31%), Asia (27%), the United States (24%), and Europe (23%) reporting the highest prevalence rates, while Africa has the lowest estimated prevalence at 14%. Interestingly, NAFLD has also been identified among adolescents, with prevalence ranging from 3% to 18%[7]. NAFLD is characterized by the accumulation of fat droplets in the liver, affecting at least 5% of hepatocytes, in patients who do not consume excessive amounts of alcohol (defined as daily alcohol intake of ≥ 30 g for men and ≥ 20 g for women)[8].

In recent years, a new term, "metabolic dysfunction-associated fatty liver disease (MAFLD)", has been proposed to underline the metabolic mechanisms leading to hepatic fat accumulation. This terminology change was endorsed by international expert consensus[9]. The diagnosis of MAFLD is based on evidence of liver fat accumulation through histology, imaging, or blood biomarkers, along with the presence of either overweight/obesity, type 2 diabetes mellitus, or two or more metabolic risk factors in lean/normal weight individuals. It should be noted that patients meeting the criteria for MAFLD diagnosis may also have other factors contributing to fatty liver, such as viral infections, alcohol misuse, autoimmune hepatitis, or drug-induced liver injury (DILI)[10]. The ongoing debate regarding nomenclature has yet to be definitively resolved[11], so studies investigating the influence of liver steatosis on COVID-19 severity encompass patients categorized under both MAFLD and NAFLD definitions. Given the lack of consensus among researchers, this review includes studies that consider both MAFLD and NAFLD in their analysis.

The objective of this narrative review is to present a comprehensive overview of the close relationship between liver steatosis and COVID-19. We primarily focus this review on two aspects: the biological interplay between COVID-19 and liver cells, and the clinical implications of liver steatosis in COVID-19, particularly in terms of prognosis and the risk of complications.

METHODS

The biological interplay section delves into the intricate mechanisms by which COVID-19 affects liver cells. It explores the interactions between the virus and liver tissues, shedding light on the pathophysiological processes that lead to liver damage. The purpose of this section is to enhance comprehension of the fundamental biological mechanisms involved in COVID-19-mediated liver injury.

Moving on to the clinical implications, the review examines the influence of liver steatosis on COVID-19 disease. It explores the correlation between liver steatosis and the extent of COVID-19 severity, prognosis, and likelihood of developing complications. By synthesizing available evidence, the review aims to elucidate

the clinical significance of liver steatosis in COVID-19 disease.

Overall, this narrative review seeks to consolidate the existing knowledge on the interplay between liver steatosis and COVID-19. By addressing both the biological and clinical aspects, it aims to provide valuable insights into the implications of liver steatosis in COVID-19 disease, contributing to a better understanding of this complex interaction.

We focused on examining the interplay between SARS-CoV-2 and liver steatosis (NAFLD/MAFLD). To address this, we conducted a thorough literature review to address two key questions: (1) is there a biological mechanism that can explain the association between the two? and (2) does this association increase the risk of progressive clinical outcomes in patients?

To begin, we provide an overview of the biological and cellular mechanisms that have been recognized as triggered by SARS-CoV-2 infection, particularly in the liver. Moreover, we investigate the potential influence or impact of fatty liver disease on these mechanisms. By examining the existing literature, we aim to shed light on the potential interplay between SARS-CoV-2 and liver steatosis at a cellular level.

Furthermore, we investigate whether NAFLD or MAFLD may serve as significant prognostic factors in COVID-19, specifically in terms of the risk of severe disease and death. To accomplish this, we conducted a literature search using the PubMed Database with specificsearch terms, including "NAFLD", "MAFLD", "fatty liver", "liver steatosis", "COVID-19", and "SARS-CoV-2". We included studies published in English between November 2019 and November 2022, encompassing basic science studies, clinical studies, meta-analyses, and reviews. For our narrative review, we included relevant papers that provided compelling data and theories either supporting or challenging the hypothesis that fatty liver disease acts as a risk factor for a more severe course of COVID-19.

Overall, our review aims to provide a comprehensive analysis of the association between liver steatosis and SARS-CoV-2. It specifically emphasizes the fundamental biological mechanisms involved and the potential implications for clinical outcomes in COVID-19 patients.

SARS-COV-2 BIOLOGICAL AND CELLULAR MECHANISMS OF DAMAGE

SARS-CoV-2 virus and liver

To gain a better understanding of the association between SARS-CoV-2 and potential liver damage, it is crucial to examine the characteristics of this pathogenic microorganism. SARS-CoV-2, belonging to the Coronaviridae family and Coronavirinae subfamily, shows a strong phylogenetic correlation with Betacoronaviruses like SARS-CoV and MERS-CoV. Similar to other coronaviruses, SARS-CoV-2 possesses a positive single-stranded RNA [(+)ssRNA] genome of approximately 30kb, enclosed in a viral envelope[12,13].

The entry of the virus into host cells relies on the Spike (S) protein, which is a transmembrane protein consisting of two distinct subunits: S1, housing the receptor binding domains (RBD), and S2, responsible for membrane fusion[14,15]. When the S protein binds to its target receptor, the angiotensin-converting enzyme 2 (ACE2), host cell proteases such as transmembrane serine protease 2 (TMPRSS2), furin, and cathepsin L cleave the S2 subunit, facilitating viral entry into the cell[16,17] [Figure 1].

Once inside the cell cytoplasm, the viral genome, which is uncoated, is initially translated into polyproteins (pp1a and pp1ab). These polyproteins generate 16 non-structural proteins (nsp1-16) that assemble to form viral replicase-transcriptase complexes (RTCs)[15,18]. The virus then replicates its own genome, likely within

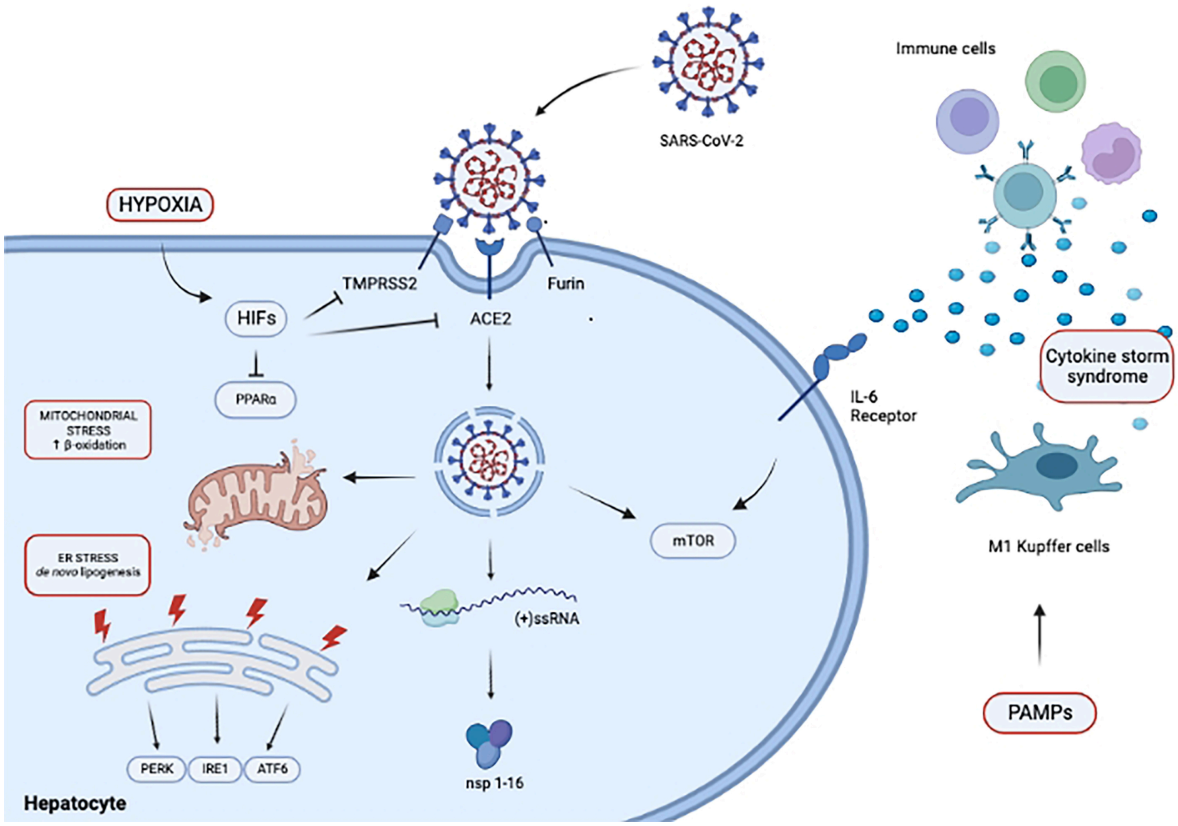

Figure 1. Mechanisms of liver damage by SARS-CoV-2 virus. SARS-CoV-2 can directly cause hepatic cytotoxicity by infecting hepatocytes. The consequent endoplasmic reticulum stress and mitochondrial stress contribute to steatosis. The hypoxic conditions arising from COVID-19 determine the activation of hypoxia-inducible factors (HIFs), exacerbating NAFLD. COVID-19 infection and PAMPs derived from the intestine cause hyperactivation of the immune system, leading to the cytokine storm syndrome, which worsens the pre-existent inflammatory state of NAFLD patients. SARS-CoV-2 can activate mTOR both directly and indirectly through the release of IL-6 during the cytokine storm syndrome. NAFLD: nonalcoholic fatty liver disease.

double-membrane vesicles (DMVs). Subsequently, new virions can be assembled and released from host cells to propagate the infection[13].

ACE2 is well-known as the primary receptor for viral entry and plays a critical role in SARS-CoV-2 pathogenesis[19]. ACE2 is a dipeptidyl carboxypeptidase that plays a decisive role in the renin-angiotensin system, cleaving angiotensin I (Ang I) into the inactive nonapeptide form (Ang 1-9) and Ang II into the vasodilator heptapeptide Ang 1-7. Although ACE2 is primarily expressed in lung type II pneumocytes, which are the main targets of infection, this receptor is also widely distributed in several tissues such as the heart, kidneys, intestines, pancreas, muscular and nervous systems, and the liver[13,20]. Single Cell Portal data indicates that ACE2, TMPRSS2, and Furin are expressed in both cholangiocytes and hepatocytes, suggesting the possibility of viral entry and infection in liver cells[21]. Indeed, studies have demonstrated the capability of SARS-CoV-2 to infect different cell types, including Huh7 human hepatocarcinoma cells and liver organoids derived from human stem cells, indicating the potential for direct infection of liver cells and consequent hepatic injury[21-23]. Additionally, the expression of the papain-like protease domain of the SARS-CoV-2 nsp3 has been shown to promote an inflammatory cascade, apoptosis, and oxidative stress in various polarized epithelial cells, including Caco-2 intestinal and HepG2 hepatoma cells[24].

Furthermore, clinical evidence indicates elevated levels of alanine and aspartate serum transaminases (ALT and AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase, and hypoalbuminemia in individuals with COVID-19, providing support for the occurrence of hepatocyte and cholangiocyte injury[25,26]. Individuals with pre-existing liver conditions, such as NAFLD, seem to have a higher vulnerability to SARS-CoV-2 infection, leading to more severe outcomes[27]. Interestingly, an increase in the expression of the ACE2 receptor has been noticed in NAFLD cases, liver fibrosis, and obese individuals with non-alcoholic steatohepatitis (NASH), indicating a possible connection to the advancement of the viral disease[28-30].

SARS-CoV-2 can directly cause hepatic cytotoxicity by infecting hepatocytes. The consequent endoplasmic reticulum stress and mitochondrial stress contribute to steatosis. The hypoxic conditions arising from COVID-19 determine the activation of hypoxia-inducible factors (HIFs), exacerbating NAFLD. COVID-19 infection and PAMPs derived from the intestine cause hyperactivation of the immune system, leading to the cytokine storm syndrome, which worsens the pre-existent inflammatory state of NAFLD patients. SARS-CoV-2 can activate mTOR both directly and indirectly through the release of IL-6 during the cytokine storm syndrome.

Sars-CoV-2 infection and altered Insulin homeostasis

Insulin resistance (IR) plays a significant role in the pathogenesis and progression of NAFLD/MAFLD. However, the literature exploring the association between COVID-19 and IR is limited, and the hypothetical effects of SARS-CoV-2 on insulin secretion remain unknown[31]. Nonetheless, it is well-established that ACE2 receptors, including those present in the pancreas, are widely distributed in various tissues and organs. Consequently, the virus could potentially inflict direct damage to pancreatic beta-cells and disrupt glucose metabolism[32]. The overexpression of pancreatic ACE2 receptors caused by IR creates a predisposing condition for SARS-CoV-2 infection. Furthermore, the hyperactivation of the immune response triggered by COVID-19 can exacerbate the pre-existing inflammatory state in individuals with obesity and diabetes[33]. The chronic activation of the pro-inflammatory NF-kB pathway in diabetic patients plays a significant role in increasing their vulnerability to SARS-CoV-2 infection[34]. Indeed, COVID-19 infection leads to immune system dysregulation and increased expression of inflammatory pathways, particularly NF-kB, which induces the production of cytokines resulting in cytokine storm syndrome (CSS)[35]. NF-kB also influences the polarization of macrophages into the M1 phenotype and has an impact on the expression of genes associated with the production of IL1β, IL6, TNFα, COX2, and IL12[36]. Furthermore, hyperinsulinemia may induce a pro-inflammatory profile in dendritic cells (DCs), stimulate advanced glycosylation end products (AGEs), and promote their maturation, although the underlying mechanisms of these processes are not well understood[37]. Elevated glucose levels in diabetic patients inhibit neutrophil functions such as chemotaxis, phagocytosis, and intracellular killing, thereby increasing their vulnerability to viral infections[38]. Concurrently, IR hampers anti-inflammatory pathways by reducing phosphoinositide 3-kinase activity and impairing the effects of nitric oxide (NO)[39]. Kulcsar *et al.* demonstrated in a diabetic mouse model infected with MERS-CoV that there was a low expression of CD4+ T cells, macrophages, IL6, IL12b, TNFα, and Arg1, but high levels of IL17a, indicating immune response dysregulation[40]. Similarly, the complex interplay between COVID-19 and diabetes may lead to deregulation of the immune response, resulting in more severe outcomes.

BIDIRECTIONAL LINK BETWEEN NAFLD/NASH AND SARS-COV-2 INFECTION

Clinical evidence

Several risk factors linked with more severe COVID-19 disease were identified a few months after the outbreak began. Severe COVID-19 disease is defined based on specific criteria, including hypoxemia, mean low oxygen saturation (< 93% at rest) or arterial partial pressure of oxygen/fraction of inspired oxygen (P/F

ratio) ≤ 300 mmHg, respiratory distress or respiratory failure requiring mechanical ventilation, shock, or the need for intensive care unit treatment due to organ failure. The mortality rate for severe COVID-19 is significantly high, ranging from 20% to above 30%[41].

Numerous studies and meta-analyses have provided evidence linking severe COVID-19 disease with certain risk factors. These include older age[42], male sex[43,44], and various comorbidities such as obesity[43-45], type 2 diabetes[46,47], cardiovascular disease[46,48], and hypertension[49]. The presence of obesity and diabetes, for instance, has been demonstrated to triple and sextuple the likelihood of severe illness, respectively[45,46]. Given the prevalence of these comorbidities in the general population, particularly in Western countries, their impact on COVID-19 disease is even more significant. In the heavily affected New York urban area during the first wave of COVID-19, the prevalence of obesity and diabetes reached 41.7% and 33.8%, respectively[50].

Although NAFLD is commonly observed in individuals with metabolic syndrome, particularly those who are obese or have diabetes[51], its independent role as a risk factor for severe COVID-19 disease remains a topic of debate. Interestingly, a meta-analysis of autopsy data from 116 COVID-19 patients revealed a higher prevalence of steatosis and fibrosis compared to the general population. Hepatic steatosis and fibrosis were found in 55% and 36% of patients, respectively[52]. In a retrospective study by Wang *et al.*, in the overall cohort, there was no significant association found between NAFLD and the severity of COVID-19[53]. However, a subgroup analysis based on body mass index (BMI) revealed that among patients with a normal BMI (18.5-24 kg/m^2), those with NAFLD were more prone to experiencing severe symptoms compared to those without NAFLD (adjusted hazard ratio [HR] = 3.26, 95% confidence interval [CI]: 1.17-9.04, $P = 0.023$). Interestingly, this association was not observed in patients with low (< 18.5 kg/m^2) or high (≥ 24 kg/m^2) BMI.

The debate extends beyond whether NAFLD/MAFLD could serve as a risk factor for SARS-CoV-2 infection incidence or severity, as it also questions whether COVID-19 infection could trigger the onset or exacerbation of metabolic chronic liver disease. These questions remain unanswered definitively. However, in the following paragraph, we will provide a comprehensive summary of the available evidence that may contribute to resolving these issues.

Clinical observations have shown that COVID-19 infection can lead to elevated levels of liver enzymes, including ALT, AST, and GGT[54]. A cohort study involving 202 participants revealed that COVID-19-related liver damage can range from mild to moderate, with a higher frequency of hepatocellular pattern compared to cholestatic pattern[55]. Cai *et al.* reported an association between elevated serum liver enzyme levels and the progression to severe pneumonia[56]. The occurrence of abnormal liver function tests and liver injury during acute COVID-19 infection is more common in patients with NAFLD.

In a retrospective study by Huang *et al.*, which included 280 COVID-19 patients, 86 of whom were diagnosed with NAFLD using the Hepatic Steatosis Index (HSI), NAFLD patients exhibited higher ALT levels both on admission and during hospitalization compared to control patients (40.7% *vs.* 10.8%; $P < 0.001$ and 65.1% *vs.* 38.7%; $P < 0.001$, respectively)[57]. However, no complications such as death or liver failure occurred during hospitalization, and the clinical outcomes between NAFLD and non-NAFLD patients were similar in this study. This evidence highlights a strong interaction between the chronic inflammatory pathway of NAFLD and the acute inflammatory response of COVID-19[58].

Numerous studies have consistently shown that patients with pre-existing chronic liver diseases, regardless of the underlying cause, experience greater severity and higher mortality rates from COVID-19[59]. In a recent meta-analysis by Nagarajan *et al.*, the risk of severe COVID-19 disease and death was found to be twice as high among patients with chronic liver diseases compared to those without such conditions. Further subgroup analysis highlighted liver cirrhosis, MAFLD, and NAFLD as the main types of chronic liver diseases associated with severe COVID-19 disease (pooled odds ratio [OR]: 3.06, 3.20, 5.60, respectively)[60]. The connection between NAFLD/MAFLD and the cytokine storm associated with COVID-19 further supports this strong association observed in various clinical studies.

In a cohort study conducted by Gao *et al.*, involving non-diabetic patients, 65 cases with MAFLD and 65 controls without MAFLD were included. They found that the presence of MAFLD, diagnosed by CT scan, was associated with a 4-fold increased risk of severe COVID-19 requiring intensive care[61]. In a study by Younossi *et al.*, the outcomes of COVID-19 were examined in a cohort of 553 hospitalized patients with a documented history of NAFLD determined through imaging or liver biopsy. Upon admission, NAFLD patients displayed more pronounced respiratory symptoms, higher body temperature, and elevated levels of AST and ALT in comparison to non-NAFLD patients. The NAFLD group also had a higher proportion of patients requiring mechanical ventilation, intensive care, and longer hospital stays. However, no significant difference was observed in the mortality rate between the two groups[62]. Interestingly, FIB-4 index, along with obesity, hypoxemia, and older age, was identified as an independent predictor of mortality in this cohort.

Targher *et al.* evaluated 310 COVID-19 patients, including 94 with MAFLD, and found that among MAFLD patients, the severity of COVID-19 disease was higher in those with intermediate (1.3-2.67) or high (> 2.67) FIB-4 index values, independent of sex, obesity, and diabetes (adjusted OR: 2.59 and 4.04, respectively)[63]. Similarly, Yao et al. conducted a study that included 86 young patients (median age of 43.5 years) with COVID-19 and NAFLD. The diagnosis of NAFLD involved the application of the Hepatic Steatosis Index (HSI), whereas the severity of liver fibrosis was assessed using the NAFLD fibrosis score (NFS) (44.2% of NAFLD patients had advanced fibrosis). The results of the univariate analysis revealed that obesity (BMI ≥ 28 kg/m^2) (OR 5.53, 95%CI: 1.37-22.26, $P = 0.01$), diabetes (OR 9.85, 95%CI: 2.28-42.58, $P < 0.01$), and advanced liver fibrosis (OR 19.15, 95%CI: 2.34-156.54, $P < 0.01$) were associated with a more severe outcome[64]. Similar findings were recently reported by Vázquez-Medina et al. in a cohort of 359 hospitalized COVID-19 patients. Among the patients, 22% had NAFLD and 61% had MAFLD. After adjusting for sex, age, and comorbidities (diabetes, arterial hypertension, and obesity), the Cox regression models revealed that patients with NAFLD exhibited an elevated risk of requiring intubation (adjusted HR 2.15; $P = 0.02$). However, they did not face a higher risk of mortality unless advanced fibrosis (FIB-4 > 2.67) was present (adjusted HR 2.44; $P = 0.01$). On the other hand, patients with MAFLD had a higher risk of intubation (adjusted HR 2.79; $P = 0.002$) and death (adjusted HR 1.75; $P = 0.02$), and this risk was further increased by the presence of advanced fibrosis[65].

The interpretation of the findings from these cohort studies has been controversial, as many authors have raised concerns about the heterogeneity of ethnicity, the prevalence and diagnostic criteria of NAFLD, the variations in the standard of care for COVID-19 infection across different countries, and the differences between the diagnostic criteria of NAFLD and MAFLD[66]. Furthermore, it is still debated whether the severe course of COVID-19 disease is directly linked to NAFLD/MAFLD or indirectly associated with the various comorbidities commonly found in patients with NAFLD and MAFLD.

Several meta-analyses have been conducted in the past two years to address these concerns [Table 1]. Tao *et al.* performed a meta-analysis that included seven studies from China, USA, Israel, Qatar, and the UK, involving 2,141 COVID-19 patients[67]. The pooled prevalence of underlying MAFLD was found to be 36%. The diagnosis of MAFLD was made according to the new consensus criteria[10]. According to the findings of the meta-analysis, individuals with MAFLD exhibited a notably increased risk of severe COVID-19 (pooled OR = 1.8, 95%CI: 1.5-2.1, $P < 0.01$). However, no heightened risk of mortality was observed among this population (pooled OR = 0.97, 95%CI: 0.69-1.36, $P = 0.85$). Another study by Lu *et al.* included six studies with 1,293 patients, all from China. The pooled prevalence of MAFLD was 31%, although the diagnostic criteria for MAFLD were not fully described. The study found that MAFLD increased the risk of severe COVID-19 disease severity by 2.93-fold (95%CI: 1.87-4.60, $P = 0.16$)[68].

Hegyi *et al.* conducted a study that included nine studies from USA, China, and Israel, with a homogeneous definition of MAFLD[71]. However, the diagnosis of NAFLD varied across the studies, using different methods such as his > 36 or ICD codes. The results showed that both MAFLD and NAFLD were associated with an increased risk of severe COVID-19 disease, with OR of 2.61 and 5.22, respectively.

In a meta-analysis conducted by Sachdeva *et al.*, eight studies involving 8,142 COVID-positive patients were included. Among these patients, 833 were diagnosed with NAFLD using computed tomography (CT) or abdominal ultrasound (US) and according to an internal expert consensus statement. The analysis revealed that NAFLD was linked to a higher risk of severe COVID-19, including hospitalization and ICU admission. This association remained significant even after adjusting for obesity as a confounding factor. The pooled odds ratio (OR) for severe COVID-19 in individuals with NAFLD, while accounting for obesity, was 2.36 (95%CI: 1.90-2.92, $P < 0.01$)[70] .

In another meta-analysis by Singh *et al.*, 14 studies with a total of 19,149 COVID-19 patients were included, including 1,851 NAFLD patients[69]. The diagnosis of NAFLD was confirmed through imaging using ultrasound (US) or computed tomography (CT), HSI, consensus definition of NAFLD, or the International Classification of Diseases (ICD) code. The findings from the included studies supported the association between NAFLD and severe COVID-19, as indicated by the reported ORs. After analyzing data from eight included studies, it was found that patients with NAFLD had a significantly higher adjusted OR for severe COVID-19 compared to those without NAFLD (OR: 2.60, 95%CI: 2.24-3.02, $P < 0.01$). Meta-regression analysis revealed that the risk of severe COVID-19 in NAFLD patients was not influenced by age ($P = 0.65$) or BMI ($P = 0.29$). Regarding ICU admission, the pooled OR based on data from two studies showed that patients with NAFLD had a higher likelihood of being admitted to the ICU compared to those without NAFLD (OR: 1.66, 95%CI: 1.26-2.20, $P < 0.01$) for patients with NAFLD compared to those without NAFLD, based on data from two studies, was 1.66 (95%CI: 1.26-2.20, $P < 0.001$). However, no significant difference in mortality was observed between patients with NAFLD and those without NAFLD.

In a recent meta-analysis, which included 18 studies with 22,056 patients, the presence of NAFLD was found to be significantly linked to a more severe form of COVID-19, as indicated by a pooled OR of 1.76[72]. Notably, this association retained its significance even after adjusting for various factors such as sex, age, smoking habits, diabetes, obesity, and hypertension. Interestingly, subgroup analysis based on age demonstrated that the association between NAFLD and severe COVID-19 was consistent among younger patients (< 60 years) with a pooled OR of 2.08 (95%CI: 1.33-3.27), but not among older patients (> 60 years) with a pooled OR of 1.37 (95%CI: 0.97-1.93)[72]. These results suggest that NAFLD may have a prognostic impact on COVID-19 disease, particularly in young patients. However, in older patients, other comorbidities might outweigh NAFLD as prognostic factors.

Table 1. Characteristics of Metanalysis that explored the association between NAFLD/MAFLD and severe COVID-19 or Mortality

Paper	Countries	Gender (male)^	Age*	Cohort size *COVID-19 +*	NAFLD prevalence	MAFLD prevalence	NAFLD diagnosis	MAFLD diagnosis	Risk factor for	
									Severe COVID-19	Mortality
Tao *et al.*[67]	China, USA, Israel, Qatar, and the UK	28% - 84%	44 - 63	2141	n/a	36% 95%CI:23-49%	n/a	consensus diagnostic criteria of MAFLD	**MAFLD** pOR = 1.8 (95%CI: 1.5 - 2.1)	MAFLD pOR = 0.97 (95%CI: 0.7 - 1.3)
Pan *et al.*[68]	China	25% - 74%	42 - 47	1293	n/a	31% 95%CI:28-35%	n/a	consensus diagnostic criteria of MAFLD	**MAFLD** pOR = 2.9 (95%CI: 1.8 - 4.6)	n/a
Singh *et al.*[69]	China, Europe, and USA	n/a	40.9 - 70.3	19149	1851 (9,6%)	n/a	Imaging-based (US or CT) or HSI or consensus definition of NAFLD or ICD	n/a	**NAFLD** pOR = 2.6 (95%CI: 2.2 - 3.0)	NAFLD pOR = 1.01 (95%CI: 0.6 - 1.6)
Sachdeva *et al.*[70]	USA, China, and Israel	28%-74%	n/a	8142	833 (10,2%)	n/a	Imaging-based (US or CT) or consensus definition of NAFLD	n/a	**NAFLD** pOR = 2.3 (95%CI: 1.9 - 2.9)	n/a
Hegyi *et al.*[71]	USA, China, and Israel	27%-64%	42 - 63	NAFLD comparison 7635 MAFLD comparison 948	592 (7,7%)	329 (34,7%)	different methods across studies (HIS > 36 or ICD codes)	consensus diagnostic criteria of MAFLD	**MAFLD** pOR = 2.6 (95%CI: 1.7 - 3.9) **NAFLD** pOR = 5.2 (95%CI: 1.9 - 14.3)	n/a
Wang *et al.*[72]	China, Europe, and USA	n/a	n/a	22056	n/a	n/a	n/a	n/a	**NAFLD** pOR = 1.7 (95%CI: 1.2 - 2.5)	n/a

pOR: pooled odds ratio; 95%CI: 95% Confidence Interval; n/a: not available; MAFLD: Metabolic dysfunction-associated fatty liver disease; NAFLD: nonalcoholic fatty liver disease. *Mean age range in studies included in metanalysis; ^male sex prevalence range in studies included in metanalysis.

Despite the studies mentioned above suggesting NAFLD/MAFLD as a risk factor for severe COVID-19, conflicting data exist in the literature, leading to the ongoing debate within the hepatology field[73].

During the first wave of COVID-19, Forlano *et al.* conducted a study involving a cohort of 193 patients from the UK and did not find any association between NAFLD and severe outcomes of COVID-19 disease[73]. Interestingly, in this cohort, NAFLD patients exhibited higher levels of C-reactive protein than non-NAFLD patients, potentially indicating an augmented COVID-19-related inflammatory response in individuals with NAFLD.

Mushtaq *et al.* examined a cohort of 589 patients, among whom 320 (54.3%) were found to have NAFLD based on HSI. However, the presence of NAFLD did not emerge as an independent predictor of increased

mortality, disease severity upon presentation, or disease progression. Instead, older age (> 50 years) stood out as the sole independent predictor of mortality, while age (> 50 years) and overweight (BMI > 25 kg/m^2) were the only two significant and independent predictors of disease progression (including mechanical ventilation, intensive care, and the development of ARDS). Notably, the presence of NAFLD emerged as an independent predictor solely for the occurrence of mild-to-moderate liver injury[74].

Furthermore, a recent Mendelian randomization analysis was conducted to further investigate a possible causal relationship between NAFLD and severe COVID-19 disease. The analysis revealed that NAFLD, ALT, grade of steatosis, and fibrosis stage were not associated with severe COVID-19. However, BMI, waist circumference, and hip circumference showed significant and independent associations with severe COVID-19 disease[75].

Possible mechanistic nexus between NAFLD/MAFLD-related hepatic damage and SARS-CoV-2 infection

Therefore, it is crucial to further investigate the mechanisms of COVID-19-mediated hepatic damage. SARS-CoV-2 can directly cause cytotoxicity in the liver by infecting hepatocytes that express the ACE2 receptor. In fact, liver abnormalities such as endoplasmic reticulum dilatation, mitochondrial stress, and apoptosis have been observed in COVID-19 patients[76]. This mitochondrial stress leads to impairment in beta-oxidation, resulting in lipid accumulation and the development of microvesicular steatosis.

Considering that steatosis is a hallmark of NAFLD/MAFLD, SARS-CoV-2 infection may exacerbate the metabolic profile of patients with these conditions[13].

Notably, it is well-established that endoplasmic reticulum (ER) stress can contribute to hepatic steatosis through various mechanisms, such as the induction of de novo lipogenesis, disruption of very low-density lipoprotein (VLDL) secretion, and impairment of insulin signaling[77]. Coronavirus proteins, including the S protein, have been shown to induce ER stress. This occurs when viral proteins accumulate within the ER, leading to the disruption of its normal folding capacity and triggering the unfolded protein response (UPR). The UPR activates key stress factors, such as transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1) and PKR-like ER kinase (PERK)[78]. Moreover, SARS-CoV-infected cells increase the expression of ER stress-associated genes (GRP94 and GRP78)[79].

The mammalian target of rapamycin (mTOR) pathway is another potential mechanism linking COVID-19 with NAFLD/MAFLD. Previous in vitro studies on Huh7 cells infected with MERS-CoV showed direct activation of mTOR[80]. Additionally, interleukin-6 (IL-6), a major inflammatory factor released during the cytokine storm syndrome caused by SARS-CoV-2 infection, can indirectly activate the mTOR pathway[81]. Considering that insulin also triggers the mTOR pathway in the liver, hyperactivation of mTOR activity in patients with metabolic diseases could lead to worse outcomes in COVID-19[13].

Hypoxia is another mechanism that may connect COVID-19 with NAFLD/MAFLD. SARS-CoV-2 primarily affects the respiratory system, impairing gas exchange and leading to acute respiratory distress syndrome (ARDS) and systemic hypoxemia in severe cases[82]. Hypoxia triggers the activation of transcription factors known as hypoxia-inducible factors (HIFs) at the cellular level[83]. Current evidence suggests that HIF signaling can result in altered metabolic conditions. Specifically, studies have shown that upregulation of HIF-2α suppresses peroxisome proliferator-activated receptor alpha (PPARα) in the liver, exacerbating NAFLD[84]. Conversely, HIF-1α inhibits the expression of TMPRSS2 and ACE2, indicating that hypoxic conditions may impair viral infection[82].

Liver steatosis, particularly NASH, is characterized by hepatic inflammation and innate immune activation, which play an essential role in initiating and perpetuating the inflammatory state within the liver[85,86]. Similarly, COVID-19 infection induces a significant release of cytokines that can impact various organs, including the liver[25]. Following infection, pathogenic T cells become activated, leading to the production of inflammatory mediators such as IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF), which further activate inflammatory monocytes. This cascade results in the generation of a large quantity of pro-inflammatory factors, contributing to cytokine storm syndrome (CSS)[87]. Notably, IL-6 plays a pivotal role in the initiation and progression of CSS in COVID-19 patients, and elevated levels of IL-6 have been observed in individuals with metabolic conditions such as diabetes, obesity, and NAFLD[86,88].

Furthermore, resident macrophages in the liver, known as Kupffer cells, can modulate the inflammatory response. These macrophages can be classified into two sub-phenotypes: M1, which promotes pro-inflammatory responses, and M2, which exhibits anti-inflammatory functions. In patients with MAFLD, there is a predominance of M1 polarization and a suppression of M2 polarization, which may contribute to the progression of COVID-19 infection[89]. Individuals with pre-existing liver diseases are more susceptible to experiencing gastrointestinal symptoms following SARS-CoV-2 infection[89]. Given that the small intestine expresses a high level of ACE2 receptors, the virus can infect the gut, potentially leading to the release of pathogen-associated molecular patterns (PAMPs) into the portal vein of the liver. Consequently, the hyperactivation of the immune response triggered by PAMPs can contribute to the development of CSS[87]. Finally, gut dysbiosis, characterized by alterations in the microbiome and the translocation of microorganisms into the portal circulation in NAFLD/NASH patients, may represent an additional risk factor for the outcome and progression of COVID-19[87].

DISCUSSION

In recent years, clinical practice has revealed that patients with metabolic comorbidities, including obesity, diabetes, and metabolic syndrome, face a higher risk of severe SARS-CoV-2 infection. Fatty liver disease has been proposed as one of the key factors contributing to this association. It is now well-established that the ACE2 receptor, which facilitates viral entry into cells, is widely expressed in various organs and tissues, including the liver[13]. Notably, cases of NAFLD/MAFLD often exhibit overexpression of the ACE2 receptor, potentially enabling direct infection of hepatic cells by SARS-CoV-2 and causing liver damage. Furthermore, the presence of comorbidities can increase the susceptibility of NAFLD/MAFLD patients to SARS-CoV-2 infection. Increased insulin resistance leads to the upregulation of pancreatic ACE2 receptors and impairs neutrophil functions, thereby enhancing vulnerability to viral infection[38].

Although a clear causal relationship between NAFLD/MAFLD and the development of COVID-19 has yet to be established, clinical observations suggest that patients with pre-existing metabolic conditions are more prone to SARS-CoV-2 infection. Moreover, COVID-19 may exacerbate patients' underlying metabolic disorders, potentially promoting the progression of NAFLD to NASH in the long term, although the underlying mechanism remains unclear[90]. Consistently, SARS-CoV-2 has been found to induce mitochondrial and endoplasmic reticulum stress, leading to lipid accumulation and steatosis, thereby exacerbating the metabolic profile of NAFLD patients[13]. In vitro experiments have demonstrated that SARS-CoV-2 can directly and indirectly activate the mTOR pathway, which in turn promotes de novo lipogenesis[80]. These findings indicate that COVID-19 may act as a risk factor for exacerbation and progression of NAFLD/MAFLD.

Fatty liver disease may also contribute to the systemic inflammation triggered by SARS-CoV-2 infection. In NAFLD patients, an excess of free fatty acids enters the liver and activates Kupffer cells, resulting in a shift

from anti-inflammatory M2 polarization to pro-inflammatory M1 polarization and increased production of pro-inflammatory cytokines[89]. Concurrently, COVID-19 triggers a substantial release of pro-inflammatory factors, with IL-6 playing a crucial role[87]. Hence, it is reasonable to speculate that systemic inflammation significantly contributes to the intensified hepatic inflammatory condition observed in NAFLD/MAFLD patients experiencing severe COVID-19 outcomes.

From a clinical standpoint, the studies and meta-analyses discussed in this review present contradictory findings regarding the relationship between NAFLD/MAFLD and the onset of severe COVID-19. In fact, the relationship between NAFLD/MAFLD and severe COVID-19 disease remains a topic of debate in the literature due to several potential biases, conflicting results and a lack of prospective cohort studies. One potential bias arises from the varying definitions of "fatty liver disease" used in the reviewed studies. Some studies refer to MAFLD, others to NAFLD, and many consider both conditions, leading to inconsistencies. Additionally, the diagnosis and assessment of disease severity rely on various methods, such as non-invasive scores (HIS, FIB4, NFS), imaging-based diagnosis (ultrasound or CT), or liver biopsy, further contributing to potential biases among included studies. These biases likely contribute to the significant heterogeneity observed regarding the prevalence of NAFLD and MAFLD in different studies. For instance, the prevalence of NAFLD ranged from 5.5% to 38%, while MAFLD prevalence ranged from 28% to 50% among the studies included in the meta-analysis by Hegyi *et al.*[71]. In fact, one of the main distinctions between patients with MAFLD and NAFLD is the presence of an additional underlying cause for chronic liver disease, such as alcohol consumption or chronic viral infections. This difference in etiology can readily explain the varying prevalence of these two conditions observed in studies, and it may also contribute to the contrasting prognostic impact of NAFLD and MAFLD in COVID-19-related illness. Moreover, it has been demonstrated that alcohol consumption has significantly increased during the pandemic, potentially further influencing the disparities in susceptibility to severe COVID-19 between NAFLD and MAFLD[91].

CONCLUSION

In conclusion, the relationship between NAFLD/MAFLD and COVID-19 has garnered significant attention in recent research. Accumulating evidence suggests that individuals with NAFLD/MAFLD are at an increased risk of developing severe forms of COVID-19, leading to worse clinical outcomes. The underlying mechanisms linking these two conditions involve multiple pathways, including the dysregulation of the renin-angiotensin-aldosterone system, increased expression of ACE2 receptors in the liver, enhanced systemic inflammation, and polarization shift of hepatic macrophages from anti-inflammatory M2 to pro-inflammatory M1 phenotype. Moreover, the interaction between SARS-CoV-2 and the liver can induce endoplasmic reticulum stress, mitochondrial dysfunction, and the activation of pro-inflammatory pathways, further contributing to liver injury and inflammation.

It is important to acknowledge the limitations and potential biases in the existing studies investigating the relationship between NAFLD/MAFLD and COVID-19. Metabolic dysregulation, a hallmark of NAFLD/MAFLD, also plays a significant role in the susceptibility to and severity of COVID-19. The presence of obesity, insulin resistance, and type 2 diabetes, which are often linked to NAFLD/MAFLD, are recognized risk factors for severe COVID-19. Therefore, it is crucial to give thorough consideration and appropriately account for these factors in the analyses. Furthermore, variations in the definitions and diagnostic criteria of fatty liver disease, as well as the diverse methods used to assess disease severity, introduce heterogeneity in the reported associations.

Despite these limitations, the available evidence from meta-analyses consistently supports the notion that NAFLD/MAFLD is an independent risk factor for the development of severe COVID-19. The pooled OR

reported in these meta-analyses indicate a significantly higher risk of adverse outcomes, including the need for intensive care and/or mechanical ventilation, and extended hospital stays, among individuals with NAFLD/MAFLD. However, it is important to note that no significant association between fatty liver disease and COVID-19 mortality has been documented to date.

Considering the growing body of research, it is imperative to conduct further studies to elucidate the underlying mechanisms.

DECLARATIONS

Author's contribution

Conception or design: Liguori A, Calvez V, Miele L
Extracted data: Liguori A, Calvez V, Sciarra A, D'Ambrosio F
Acquisition, analysis, or interpretation of data: Liguori A, Calvez V, Sciarra A, D'Ambrosio F
Created the figure of the manuscript with https://app.biorender.com/biorender-templates: D'Ambrosio F
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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

Not applicable.

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