






MINI-REVIEW

COVID-19, adaptative immune response and metabolic-associated liver disease

Luca Miele^{1,2}  | Cecilia Napodano^{1,2}  | Alfredo Cesario³ | Antonio De Magistris¹ | Krizia Pocino² | Umberto Basile⁴  | Gian L. Rapaccini^{1,2} | Antonio Gasbarrini^{1,2}  | Antonio Grieco^{1,2} 

¹Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A.Gemelli IRCCS, Rome, Italy

²Dipartimento di Medicina e Chirurgia Traslazionale, Scuola di Medicina e Chirurgia, Università Cattolica del Sacro Cuore, Rome, Italy

³Open Innovation Manager, Scientific Directorate, Fondazione Policlinico Universitario A.Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

⁴Dipartimento di Scienze di laboratorio e infettivologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Correspondence

Miele, MD, PhD, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Gemelli IRCCS, Università Cattolica del S. Cuore, 8, Largo Gemelli, 00168 Rome, Italy.
Email: luca.miele@policlinicogemelli.it; luca.miele@unicatt.it

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Abstract

Metabolic diseases are associated with a higher risk of a severer coronavirus disease 2019 (COVID-19) course, since fatty liver is commonly associated with metabolic disorders, fatty liver itself is considered as a major contributor to low-grade inflammation in obesity and diabetes. Recently a comprehensive term, metabolic (dysfunction) associated fatty liver disease (MAFLD), has been proposed. The hepatic inflammatory status observed in MAFLD patients is amplified in presence of severe acute respiratory syndrome coronavirus 2 infection. Intestinal dysbiosis is a powerful activator of inflammatory mediator production of liver macrophages. The intestinal microbiome plays a key role in MAFLD progression, which results in non-alcoholic steatohepatitis and liver fibrosis. Therefore, patients with metabolic disorders and COVID-19 can have a worse outcome of COVID-19. This literature review attempts to disentangle the mechanistic link of MAFLD from COVID-19 complexity and to improve knowledge on its pathophysiology.

KEYWORDS

COVID-19, liver function tests, immune response, MAFLD

1 | INTRODUCTION

In December 2019, an outbreak of the novel coronavirus disease 2019 (COVID-19) was reported in Wuhan, Hubei Province, China, which rapidly spread to other areas and countries. On 11 March 2020, the WHO declared COVID-19 a pandemic. The novel coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) for its capacity to cause severe acute respiratory syndrome and was isolated from the respiratory samples of patients

with pneumonia as shown by sequence analysis of the virus genome obtained.^{1,2}

In the majority of patients, infections are mild, but in some individuals, with advanced age or underlying medical comorbidities (obesity, hypertension, diabetes, cardiovascular disease, chronic lung disease and cancer) the virus causes atypical interstitial pneumonia progressing to acute lung injury requiring respiratory support.^{3,4}

The onset of COVID-19 presents mainly with fever, cough and dyspnoea, and some patients can progress to acute respiratory distress syndrome (ARDS) and septic shock. In addition to respiratory symptoms, digestive system involvement such as nausea, vomiting and diarrhoea have also been reported.⁵ Potential risk factors for

Luca Miele and Cecilia Napodano have equally contributed.

severe COVID-19 are age (>65 years), chronic lung disease, asthma, cardiovascular disease, inflammatory bowel disease (IBD), kidney failure, metabolic diseases, such as type 2 diabetes mellitus (T2DM), obesity, immunodeficiency and liver disease.⁶

Abnormalities in the distribution of biochemical inflammation markers are present in patients with COVID-19, which would lead to cataloging COVID-19 as a systemic pathology.⁷

Some COVID-19 patients present different degrees of liver injury with elevated serum transaminase and lactate dehydrogenase concentrations and hypoalbuminaemia,⁸ which suggests a relationship between coronavirus infection and liver injury.⁷

1.1 | Liver injury in COVID-19

Liver enzyme abnormalities are common in COVID-19 patients. Increased liver enzymes were observed more commonly in males and in severe COVID-19 case,⁹ aspartate aminotransferase and alanine aminotransferase are considerably elevated, and bilirubin is slightly elevated.¹⁰ Current knowledge about liver injury caused by coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2) suggests that it may be a result of direct virus-induced cytopathic effects and/or immunopathology induced by overshooting inflammatory responses.^{11,12} There are several potential contributors to elevated liver enzyme levels in COVID-19 such as immune-mediated inflammatory response, drug-induced liver injury, hepatic congestion and extra-hepatic release of transaminases,¹³ or a possible direct infection of hepatocytes.¹⁴ Patients with liver enzyme abnormalities have lower albumin levels, decreased circulating CD4+ T cells and B lymphocytes, higher GGT and alveolar-arterial PO₂ difference.¹⁰

Although alterations in liver biochemistries are common in hospitalized patients with COVID-19, not all studies show that abnormal liver biochemistries represent a worse course of the disease¹⁵; therefore, it is still unclear whether they have prognostic value. Indeed,

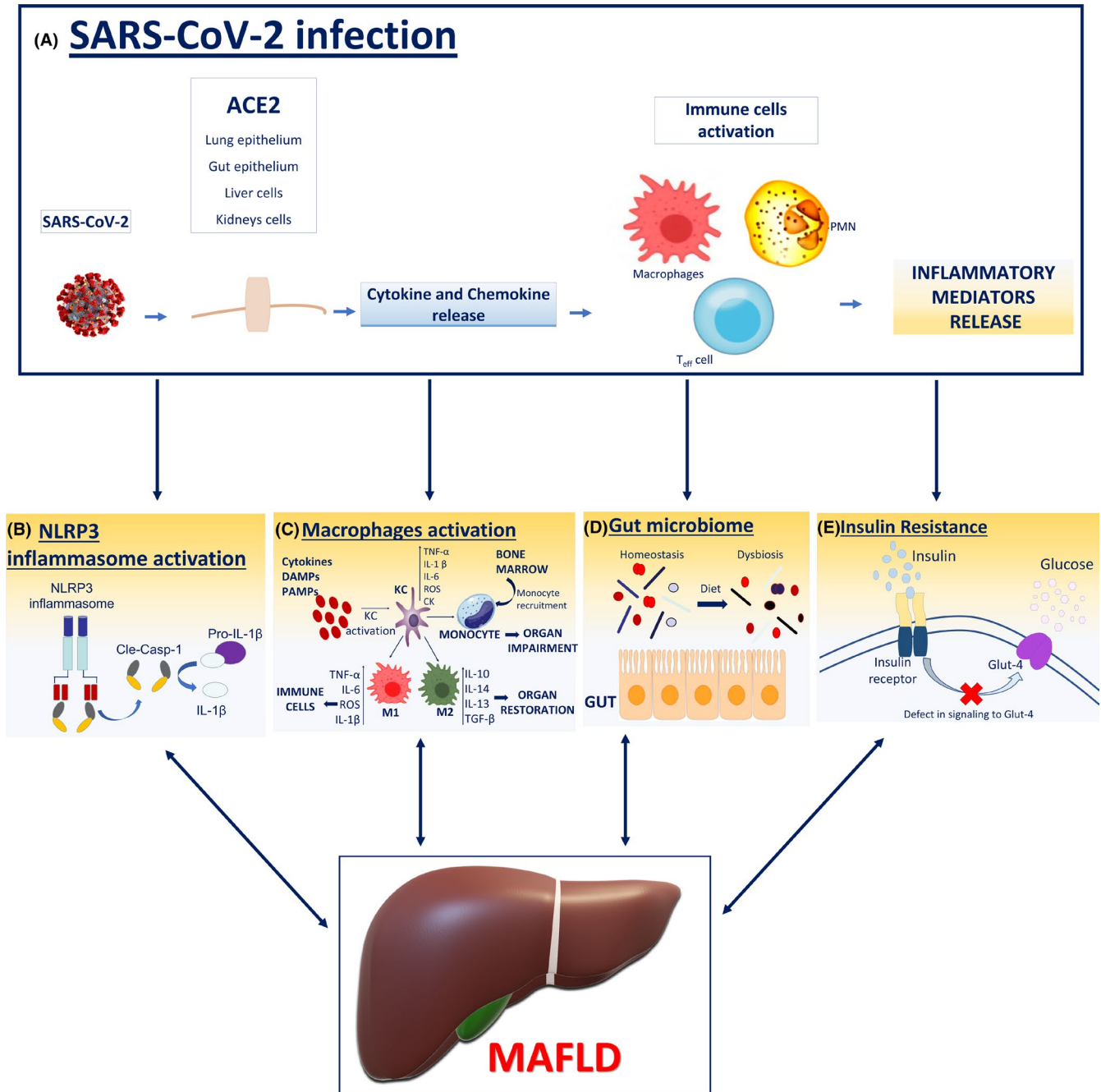
Key points

- Metabolic diseases are associated with a higher risk of severe COVID-19.
- The hepatic inflammatory status in MAFLD patients is amplified in case of SARS-CoV-2 infection.
- One of the determining mechanisms for COVID-19 progression is cytokine release syndrome or cytokine storm syndrome.
- In MAFLD, the polarization state of liver macrophages could be distorted by COVID-19 promoting inflammation.
- The gut microbiome plays a key role in MAFLD progression.

patients with cirrhosis, and to a lesser degree those with orthotopic liver transplantation, infected with SARS-CoV-2 have a high mortality risk^{12,16} suggesting that SARS-CoV-2 may worsen the outcome of end-stage liver disease. The possible pathogenic mechanisms linking cirrhosis with severe COVID-19 are the increased systemic inflammation, cirrhosis-associated immune dysfunction, coagulopathy and intestinal dysbiosis.¹⁴

The histological features in COVID-19 patients have been characterized by non-specific findings, including steatosis, mild lobular and/or portal inflammation and vascular pathology^{14,17-19} but confirm the presence of massive apoptosis and binuclear hepatocytes in the SARS-CoV-2 infected liver.¹⁰ Liver biopsy from deceased COVID-19 patients showed moderate microvascular steatosis and mild lobular and portal activity indicating that the injury may have been a consequence of SARS-CoV-2 infection, even if drug-induced liver disease may be a contributing factor for liver injury (Figure 1).¹⁷

FIGURE 1 Mechanisms leading from MAFLD to inflammation and disease progression. The development of liver inflammation in MAFLD patients leads to several complications. The factors participating in the amplification of inflammation are different (A, B, C, D) and could also include SARS-CoV-2 infection (E). A, SARS-CoV-2 infection. SARS-CoV-2 binds to target cells through receptor angiotensin-converting enzyme II (ACE2) determining the consequent activation of cells of the immune system and the release of mediators inflammatory. One of the determining mechanisms for COVID-19 progression is cytokine release syndrome or cytokine storm syndrome (CSS). B, NLRP3 inflammasome activation. The Nod-like receptor protein 3 (NLRP3) inflammasome activation is not only an intracellular machinery triggering inflammation but also produces uncanonical effects beyond inflammation. NLRP3 inflammasome activation may play a fundamental role in the development of NASH. C, Macrophages activation. Liver macrophages derive from resident Kupffer cells or recruited monocytes. M1 macrophages initiate inflammatory processes expressing high levels of pro-inflammatory cytokines and producing high amounts of reactive oxygen and nitrogen species. While M2 macrophages have anti-inflammatory function and promote tissue repair and remodelling, they have a clever phagocytic activity and express different chemokines profiles compared with M1 macrophage. D, Gut microbiome. Alteration in commensal microbiome composition, diversity and function may lead to increased gut permeability and production inflammatory factors. Gut dysbiosis is a modification of microbiome and promotes translocation of microorganisms and microbial products into the portal circulation (metabolic endotoxaemia). The gut microbiome plays a key role in MAFLD progression resulting in diversity and composition directly progression to NASH and liver fibrosis. E, Insulin Resistance. During insulin resistance, insulin receptor signalling to the GLUT 4 is inhibited, preventing GLUT 4 from transporting glucose. Thus, glucose is prevented from entering muscle and fat cells. Insulin resistance is one of the hallmarks of MAFLD is pivotal for disease pathogenesis and determines even disease progression. ACE2, angiotensin-converting enzyme 2; PMN, polymorphonuclear; DAMPs, Damage-associated molecular patterns; PAMPs, Pathogen-Associated Molecular Patterns; KC, Kupffer cells; TNF- α : Tumour Necrosis Factor; IL, Interleukine; ROS, Reactive oxygen species; M1, Macrophage 1; M2, Macrophage 2; NLRP3, Nod-like receptor protein 3; MAFLD, metabolic-associated fatty liver disease; NASH, non-alcoholic steatohepatitis; CSS, cytokine storm syndrome, GLUT4, Glucose transporter type 4



Therefore, patients with liver damage and SARS-CoV-2 infection require special attention and care. The clinical implication for the management of liver injury during COVID-19⁹ includes regular follow-up of liver biochemical parameters, cautious interpretation, and, in the context of a complex multi-organ disease,¹⁵ the serology evaluation for hepatitis B and C and investigation for other causes of liver disease.¹⁵

Another link between COVID-19 and MAFLD could be the evidence that the SARS-CoV-2 harbours the receptor angiotensin-converting enzyme 2 (ACE2). Thus, SARS-CoV-2 binds ACE2 and then, the cellular protease transmembrane protease serine 2 (TMPRSS2) cleaves the SARS-CoV-2 spike protein, allowing fusion of viral and cellular membranes.²⁰

High-fat diets seem to induce the expression of ACE2 in adipocytes. In the lungs, ACE2 is expressed by 2% of epithelial cells, increasing with cell differentiation, and being located on the apical pole, can serve as an accessible anchor point to airborne contaminants.^{21,22} Under normal conditions, ACE2 has anti-obesity and anti-inflammatory effects; therefore, metabolic syndromes are often treated with ACE inhibitors (ACE-Is), which could increase the expression of ACE2 receptors in the liver. Physiologically ACE2 is expressed in low quantities in cholangiocytes and hepatocytes, but an increase in ACE2 is observed in chronic liver damage and in MAFLD. Therefore, treating liver injuries and the metabolic syndrome itself with ACE-Is could probably promote SARS-CoV-2 susceptibility and disease severity of COVID-19.²³ Currently, has not been shown an

increased incidence of progressing to severe COVID-19 in hypertension patients treated with ACE-Is/angiotensin receptor blockers drugs compared to the patients taking other anti-hypertensive drugs.²⁴

The studies about the influence of MAFLD on the hepatic expression of ACE2 and TMPRSS2^{25,26} have shown that MAFLD is not associated with changes in liver expression of genes implicated in SARS-CoV-2 infection. But the SARS-CoV-2 entry factors are affected differently in T2DM and NAFLD. Obese women with T2DM have lower levels of ACE2 and TMPRSS2 compared with normoglycaemic obese women. It has been noted that obese patients with non-alcoholic steatohepatitis (NASH) show a higher expression of ACE2 and TMPRSS2, suggesting that the advanced stages of NAFLD could predispose individuals to SARS-CoV-2 entry factors.²⁶

In patients with metabolic disorders, and in consequence adipocyte dysregulation, the involvement of the angiotensin 1-7 system and its underlying inflammatory environment, SARS-CoV-2 infection leads to more severe outcome.²⁷

1.2 | Impact of MAFLD on outcomes of COVID-19 patients

Metabolic diseases have been reported to be risk factors for the severity of COVID-19. The mortality rate of patients with SARS-CoV-2 infection with metabolic comorbidities (ie obesity and diabetes) is significantly higher.²⁸

MAFLD is a more recent term with a definition for non-alcoholic fatty liver disease (NAFLD), which has been proposed by a panel of international experts to overcome limitations related to the NAFLD definition.²⁹ The MAFLD definition focuses on metabolic dysfunction as the driver of liver damage based on chronic low-grade inflammation.²⁹⁻³¹ The nature of inflammation in MAFLD could be an intermittent or chronic relapse, like in other chronic inflammatory liver disorders and could be missed by liver biopsy.³¹

In several reports, it had been observed that COVID-19 patients with fatty liver had a four-fold increased risk of severe COVID-19 compared with patients without fatty liver.³²⁻³⁴ MAFLD patients had a higher likelihood of abnormal liver biochemistries, higher risk of respiratory disease progression, more liver injury during hospitalization and a higher viral shedding time.^{34,35} A recent systematic literature review supports the hypothesis that the presence of metabolic dysfunction-associated fatty liver disease (MAFLD)³² may represent a risk factor for symptomatic, severe and progressive COVID-19.^{16,33,34,36-44} (Table 1).

A pooled analysis of Sachdeva et al showed the association between MAFLD and increased risk of severe COVID-19 even after adjusting for obesity.⁴⁰ The progression of COVID-19 seems to be correlated with age in MAFLD patients. Indeed, a multicentre preliminary analysis reported that COVID-19 patients with MAFLD aged younger than 60 years had a more than two-fold higher prevalence

of severe COVID-19 (55.9% of 327 COVID-19 patients) compared with those without MAFLD, moreover the presence of MAFLD in elderly patients was not associated with disease severity in the multivariable analysis.³⁹

The presence of fibrosis assessed by fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS), rather than the presence of MAFLD, was associated with increased risk for the worse outcome of COVID-19 (with mechanical ventilation, development of acute kidney injury and higher mortality).⁴⁵ MAFLD patients with increased FIB-4 or NFS are more likely to have severe COVID-19 disease, regardless of metabolic comorbidities.³⁸ Even if the non-invasive scores are used for fibrosis assessment, the correlation with clinical outcomes of COVID-19 could reflect the contributors of other clinical parameters (ie age or platelets) used in the non-invasive scores.^{41,42} Thus, MAFLD patients may be prone to SARS-CoV-2 infection and its complications. The link between MAFLD and COVID-19 is not yet fully clear, especially because in most cases a lack of information on the history of liver disease prior to the infection. These observations underscore the importance of identifying and monitoring patients with pre-existing liver disease, especially those with metabolic disorder, during and after the COVID-19.²³ Further studies, especially in cohorts of patients with biopsy-proven MAFLD prior to infection, are required to confirm MAFLD as a risk factor for COVID-19 severity, to separate MAFLD from its comorbidities and to identify factors causing the progression of COVID-19 in individuals with dysmetabolism.⁴⁶ Available studies contain severe methodological limitations, such as fatty liver disease evaluation after COVID-19 diagnosis often relies on scores based on liver enzymes, which are directly influenced by SARS-CoV-2 infection, confounder adjustment is lacking and multiple papers rely on the same relatively small cohorts.

Some studies report negative findings related to the impact of fatty liver disease predisposition on the risk of COVID-19. Valenti et al examined the impact of the MAFLD-GRS (genetic risk score) on the risk of COVID-19 in participants of the UK Biobank cohort (502 640 individuals).⁴⁷ The findings suggested that GRS was not associated with an increased risk of severe COVID-19 progression. Therefore, the genetic predisposition to liver fat accumulation could not increase predisposition to severe COVID-19 and the MAFLD does not play a causal role in this condition.⁴⁷ To date, larger studies with well-characterized cases are needed in order to understand the impact of genetic predisposition of MAFLD in relation to susceptibility and severity of COVID-19, and in particular, the risk of hospitalization and mortality, which also includes the relation to obesity, dyslipidaemia and T2DM.⁴⁰

Therefore, MAFLD subjects should be classified as high risk for COVID-19, intensifying preventive measurements, and prioritized for vaccination.⁴⁸ In fact, the COVID-19 vaccine appears to give a good immunogenicity in patients with NAFLD, with titres of neutralizing antibodies that persisted over time.⁴⁹

TABLE 1 List of MAFLD and COVID studies available in literature until February 2021

Authors and Title	Follow-up	Key words	Country	Setting-population	NTotal/N MAFLD	Age	M/F (%)
Retrospective study							
Huang R et al ⁶⁸ Clinical features of COVID-19 patients with non-alcoholic fatty liver disease.	January -February 2020.	Clinical features; COVID-19; liver injury; non-alcoholic fatty liver disease.	China	Single centre study- General population.	280/86	43.0 (32.0-56.0) ^a	52.1/47.9
Lopez-Mendez I et al ⁶⁹ Association of liver steatosis and fibrosis with clinical outcomes in patients with SARS-CoV-2 infection (COVID-19).	March - June 2020.	Liver; COVID-19; SARS-CoV-2; Fibrosis; Steatosis.	Mexico	Single centre study.	155/66	51 (42-62) ^a	71.6/28.4
Forlano R et al ⁷⁰ In-hospital mortality is associated with inflammatory response in NAFLD patients admitted for COVID-19.	February - April 2020.	NAFLD; COVID-19; Clinical features.	United Kingdom	Single centre study- General population	193/61	NAFLD: 60 (53-75); No NAFLD: 70.5 (53-79)	62.7/37.3
Gao F et al ⁷¹ Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in non-diabetic patients.	January- February 2020.	COVID-19; metabolic- associated fatty liver disease; non-diabetes.	China	Multicentre study- General population.	130/65	46 ± 13	63.1/36.9

Definition of MAFLD	Definition of Fibrosis	Comorbidities	Conclusion and perspective	Strengths and weaknesses
HSI	/	Hypertension, diabetes, chronic lung diseases, malignant tumour.	Patients with NAFLD are more likely to develop liver injury when infected by SARS-CoV-2. No patient with COVID-19 and NAFLD developed severe liver injury during hospitalization.	The use of HSI to define NAFLD may misclassify and under/overestimate the presence of NAFLD. The NAFLD patients could develop drug-induced hepatotoxicity, and this may have contributed to the greater AST/ALT values and influence the HSI scores. The fibrosis stages of patients were not assessed. FibroScan is not a routine test for patients with COVID-19.
HSI >36	AST to Platelet Ratio Index (APRI), NAFLD Fibrosis, Score and Fibrosis-4 index (FIB4); APRI >1.0, NAFLD FS >0.675 and/or FIB-4 > 3.25.	Obesity 28.4%, T2D 15.5%, hypertension 23.2%, cardiac disease 4.5%, dyslipidaemia 5.8%, oncologic disease 3.9%, rheumatologic disease 3.9%, chronic hepatic disease 1.3%, chronic kidney disease 3.8%, pneumopathy, obstructive sleep apnoea, neurologic disease, previous thromboembolism, smoking, alcoholism.	High prevalence of liver steatosis and advanced liver fibrosis in COVID-19 patients not associated with clinical outcomes; 96.8% of COVID-19 patients had at least one abnormal LFT. The metabolic comorbidities were associated with mortality and ICU admission.	This is a retrospective study conducted in a private hospital and the assessment of liver fibrosis has been made through non-invasive models. The management and timing of laboratory tests are based on each attending physician during hospital course.
NAFLD was diagnosed based on imaging or past medical history	Fibrosis-4 index (FIB-4).	T2D, hypertension, dyslipidaemia, ischaemic heart disease, lung disease, CKD.	NAFLD was not associated with outcomes in hospitalized COVID-19 patients and the presence of advanced liver disease was not associated with adverse outcomes in the NAFLD population. NAFLD patients were significantly younger at presentation, no difference in terms of age-stratified mortality. Mortality in the NAFLD patients was associated with male gender and with a pronounced host inflammatory response.	The study population is relatively small. The NAFLD patients were not followed up in a specialist setting, non-invasive markers of fibrosis and liver histology scores were not available, reducing the accuracy in stratifying for severity of liver disease. The number of patients with established NAFLD-associated cirrhosis was probably insufficient for definitive conclusions. The follow-up and outcomes were not included in the analysis
Recent set of consensus diagnostic criteria	/	T2D; hypertension, dyslipidaemia, obesity, overweight, metabolic dysregulation, both overweight and metabolic dysregulation, fatty liver.	Synergistic effect of MAFLD and metabolic risk factors for severe COVID-19 in non-diabetic patients. The pro-inflammatory mediators may contribute to the association between MAFLD and the severity of COVID-19. The risk of severe illness increased by 4 times in MAFLD patients.	Small cohort

(Continues)

TABLE 1 (Continued)

Authors and Title	Follow-up	Key words	Country	Setting-population	NTotal/N MAFLD	Age	M/F (%)
Zhou YJ et al ⁷² Metabolic-associated fatty liver disease is associated with severity of COVID-19.	/	MAFLD; Non-MAFLD; COVID-19.	China	Single centre study-General population.	110/55	42.1 ± 11.4	74.5/25.5
Bramante CT et al ⁷³ Non-alcoholic fatty liver disease (NAFLD) and risk of hospitalization for COVID-19.	March-August 2020.	NAFLD; COVID-19; Hospitalized patients.	USA	Multicentre study-General population.	6700/373	46 (28-66) ^a	66.0/44.0
Mahamid M et al ⁷⁴ Non-alcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study.	March-April 2020.	COVID-19; metabolic syndrome; non-alcoholic fatty liver disease; severity.	Israel	Single centre study-General population.	71/22	51.0 ± 21.7 ^b	28.2/71.8
Targher G et al ⁷⁵ Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores.	January-February 2020.	NAFLD; COVID-19; Severe illness.	Italy, China, Australia.	Multicentre study-General population.	310/94	No MAFLD: 45.9 ± 15.4; MAFLD with FIB-4 (≤1.3): 41.2 ± 14.2; MAFLD with FIB-4 (1.3-2.67): 54.2 ± 10.8; MAFLD with FIB-4 (>2.67): 59.9 ± 9.1 ^b	/

Definition of MAFLD	Definition of Fibrosis	Comorbidities	Conclusion and perspective	Strengths and weaknesses
CT and Recent set of consensus diagnostic criteria	/	Obesity, T2D, hypertension, dyslipidaemia.	MAFLD is independently associated with severe and/or critical COVID-19 in patients less than 60 years of age. The spike glycoprotein of SARS-CoV-2 binds to human ACE2 with high affinity, resulting in coronavirus recognition and infection. This mechanism might explain the association between MAFLD and COVID-19 disease severity. Transaminase values elevated in patients with COVID-19 during hospitalization, suggesting that the infection and hospitalization can impact on liver function.	Fatty liver was detected by CT rather than the 'gold standard', liver biopsy or magnetic resonance proton density fat fraction (MR-PDFF). Asian ethnicity of the cohort and small sample size.
ICD codes for NAFLD or NASH or a BMI ≥ 30 kg/m ² and an elevated ALT on 3 separate dates.	/	Obesity.	The visceral adiposity determines a state of chronic inflammation in NAFLD/NASH patients that is a significant risk factor for COVID-19 hospitalization	Findings in a sample in the upper Midwest may not be generalizable. Hepatitis B and C were not excluded.
CT and subsequently diagnosed as NAFLD according to the new definition for MAFLD	/	Obesity; metabolic syndrome; diabetes; smoking.	NAFLD, obesity, hypertension and metabolic syndrome significantly associated with severe COVID-19. NAFLD patients have an increased risk of severe COVID-19, in men specifically	Retrospective and case-control design. The follow-up and natural history learning were unfeasible. Self-reported viral hepatitis and/or other liver diseases may have introduced recall bias. The small number of COVID-19 patients underwent CT to diagnose NAFLD coexistence.
Recent set of consensus diagnostic criteria	Fibrosis-4 (FIB-4) index and NAFLD fibrosis score (NFS)	Obesity, prior diabetes	MAFLD patients with increased FIB-4 or NFS are at higher likelihood of having severe COVID-19 illness, irrespective of metabolic comorbidities. The presence of MAFLD with significant/ advanced fibrosis might exacerbate the virus-induced CSS	/

(Continues)

TABLE 1 (Continued)

Authors and Title	Follow-up	Key words	Country	Setting- population	NTotal/N MAFLD	Age	M/F (%)
Hashemi et al ¹⁶ Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: A multicentre United States experience.	March - April 2020.	Chronic liver disease; COVID-19.	USA	Multicentre study- General population.	363/55	63.4 ± 16.5 ^b	/
Letter to the editor							
Ji D et al ³⁵ Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study.	January- February 2020.	COVID-19; Fatty liver; NAFLD.	China	Multicentre study- General population.	202/76	44.5 (34.8-54.1) ^a	55.9/44.1
Zhou YJ et al ³⁹ Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicentre preliminary analysis.	January - February 2020.	COVID-19; MAFLD; Younger patients.	China	Multicentre study- General population.	327/93	<60 years: 28.5%; >60 years: 28.4%.	/
Zheng KI et al ³⁷ Obesity as a risk factor for greater severity of COVID-19 in patients with metabolic associated fatty liver disease	January- February 2020.	COVID-19; MAFLD.	China	Multicentre study- General population.	214/66	MAFLD patients 18-44yrs: 39 (59.1%); MAFLD patients 45-64yrs: 22 (33.3%); MAFLD patients ≥65yrs: 5(7.6%)	/

Definition of MAFLD	Definition of Fibrosis	Comorbidities	Conclusion and perspective	Strengths and weaknesses
Diffuse hepatic steatosis on any prior imaging studies or liver histology in the absence of secondary causes of hepatic fat accumulation	/	Hypertension; diabetes mellitus; hyperlipidaemia; coronary artery disease; congestive heart disease; pulmonary disease.	Nearly one-fifth of hospitalized COVID-19 patients had CLD associated with more critical illness. NAFLD patients had a higher rates of ICU admission and require mechanical ventilation, only those with cirrhosis, had an increased risk of mortality	Retrospective design. The diagnosis of CLD was based on prior evaluations such as imaging studies or histopathology. Only hospitalized patients.
MAFLD	Fibrosis	Comorbidities	Conclusion and perspective	Strengths and weaknesses
HSI	/	Older, high BMI.	The postmortem liver biopsy in COVID-19 patient showed only microvesicular steatosis and overactivation of T cells, suggesting that liver injury in is likely immune mediated rather than being the result of direct cytopathic damage. NAFLD patients had a higher risk of progression to severe COVID-19 and longer viral shedding time. In patients with NAFLD, the polarization status of hepatic macrophages might be skewed from inflammation-promoting M1 macrophages to inflammation-suppressing M2 macrophages, leading to progression of COVID-19.	Absence of data on medical history of the patients.
Recent set of consensus diagnostic criteria	/	Overweight (BMI) >23 kg/m ² , obesity BMI >25 kg/m ² , diabetes mellitus, hypertension	Synergistic effect of MAFLD for severe COVID-19 in patient aged less than 60 years. The hepatic and systemic immune responses caused by MAFLD contribute to the CSS in younger patients with COVID-19. In the elderly patients, other comorbidities are more prevalent and any association with MAFLD might be masked by their impact.	Smaller sample size of the older cohort of patients. Further validation in a larger cohort including other ethnicities is warranted.
CT and MAFLD diagnostic criteria.	/	Obesity	The risk of obesity to COVID-19 severity is greater in MAFLD patients than in patients without MAFLD, with a six-fold increased risk of severe COVID-19 illness independent to hypertension, diabetes and dyslipidaemia. Obese patients with MAFLD had significantly higher AST and ALT respect to non-obese MAFLD patient.	Absence of liver biopsy. Asian ethnicity only.

(Continues)

TABLE 1 (Continued)

Authors and Title	Follow-up	Key words	Country	Setting-population	NTotal/N MAFLD	Age	M/F (%)
Mushtaq K et al ⁷⁶ NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression.	May-June 2020.	COVID-19; fatty liver; NAFLD; MAFLD; mortality; liver injury.	Qatar	Multicentre study-General population.	589/320	No NAFLD: 44.5 ± 13.85; NAFLD: 47.78 ± 13.4 ^b	84.7/15.3
Biquard L et al ²⁵ No evidence for an increased liver uptake of SARS-CoV-2 in metabolic-associated fatty liver disease.	September 2020.	MAFLD; SARS-CoV-2; ACE2; TMPRSS2; gene expression.	/	General human population and murine population.	12 lean patients without MAFLD, 16 obese patients without MAFLD, 9 patients with simple steatosis and 17 patients with NASH. 4 mouse chow and 9 mice with NASH.	/	/
Fondevila MF et al ²⁶ Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points.	February 2020.	MAFLD; COVID-19; TMPRSS2; ACE2; Gene expression.		Patients with obesity.	No NAFLD:17; Steatosis: 57; NASH: 20	No NAFLD: 43.1 ± 8.7; Steatosis: 46 ± 10.9; NASH: 49.2 ± 10.4 ^b	39.5/48.9
Review article							
Sy-Janairo ML et al ⁷⁷ Association of metabolic-associated fatty liver disease and risk of severe coronavirus disease 2019 illness.	January - April 2020.	COVID-19, fatty liver, non-alcoholic fatty liver disease, SARS-CoV2.		China, USA, Israel	Multicentre study-General population.	1469/471	/ /
Sharma P et al ⁷⁸ Metabolic dysfunction-associated fatty liver disease increases risk of severe Covid-19.	May 2020.	Fatty liver; MAFLD; COVID-19; PubMed database.			PubMed database. /	/	/ /

MAFLD	Fibrosis	Comorbidities	Conclusion and perspective	Strengths and weaknesses
HSI index of 36	/	Diabetes mellitus, hypertension, smoking, obesity, coronary artery disease, chronic kidney disease, cirrhosis, malignancy, lung disease, use of immunosuppressive drugs.	NAFLD is an independent predictor of liver injury in hospitalized COVID-19 patients. NAFLD is not an independent predictor of mortality or COVID-19 severity (on presentation or progression of the disease).	A large sample size of NAFLD patients from heterogeneous ethnic populations is needed. The HSI it is affected by inflammation and potentially could overestimate the prevalence of NAFLD.
/	/	Obesity	None of the genes necessary for SARS-CoV-2 infection was differentially expressed between lean or obese and patients with simple steatosis or with NASH. In mouse dataset no increase in liver gene expression of the 4 proteins implicated in SARS-CoV-2 infection was observed between MAFLD mice and control mice. MAFLD is not associated with changes in liver expression of genes implicated in SARS-CoV-2 infection.	Results obtained with microarray or RNA sequencing that are less quantitative techniques than real-time PCR. Small cohort.
/	/	T2D; Obesity.	In the livers of obese patients, SARS-CoV-2 entry factors are differently affected by T2D and NAFLD. Obese women with T2D have lower levels of ACE2 and TMPRSS2 than obese normoglycaemic women, obese patients with NASH show higher expression of ACE2 and TMPRSS2.	Small cohort
Fatty liver by CT scan, MAFLD diagnostic criteria, Hepatic steatosis index (HSI) >36 and/or abdominal ultrasound examination.	/	DM, overweight/obesity, hypertension, and dyslipidaemia	Significant association between MAFLD and COVID-19 severity, regardless of coexisting DM, overweight/obesity, hypertension, and dyslipidaemia. Obesity increased the risk of severe COVID-19 illness. Increasing non-invasive fibrosis scores are correlate with a higher risk for severe COVID-19 illness	The studies included are retrospective and mostly involved Asian populations. Only two studies were conducted in other countries aside from China, making the applicability of the results to other ethnic groups uncertain. The studies do not have information regarding liver biopsy, not assess the relationship to liver histology of MAFLD with COVID-19 severity
/	/	/	MAFLD is associated with four- to six- fold increased risk of severe COVID-19, more deranged liver function, increased viral shedding duration compared to patients with no MAFLD. Younger patients (<60 years) were associated with increased severity of COVID-19. The dysregulated hepatic innate response, polarization status of hepatic macrophages from inflammation-promoting (M1) to inflammation suppressing (M2) could explain the increased liver injury causing severe disease in these patients.	/

(Continues)

TABLE 1 (Continued)

Dongiovanni P et al ⁷⁹ MAFLD in COVID-19 patients: an insidious enemy.	August 2020.	SARS-CoV-2; infection; COVID-19; MAFLD; progressive liver disease.	Italy	General population.	/	/	/
Portincasa P et al ⁴² COVID-19 and non-alcoholic fatty liver disease: Two intersecting pandemics.	October 2020.	Fatty liver; mitochondria; nitrosative stress; oxidative stress; SARS-CoV-2.	Italy, Germany, Poland.	Multicentre study- General population.	/	/	/
Sachdeva S et al ⁸⁰ NAFLD and COVID-19: a Pooled Analysis.	November 2020.	SARS-CoV-2; COVID-19; Coronavirus; NAFLD; MAFLD; Fatty liver.	China, USA, Israel.	Multicentre study- General population.	8142/833		

Abbreviations: ACE2, angiotensin-converting enzyme 2; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, Chronic kidney disease; COVID-19, Coronavirus disease 2019; CSS, Cytokine Storm Syndrome; CT, Computed tomography; HIS, hepatic steatosis index; ICD, International Classification of Disease; ICU, Intensive care unit; LFT, Liver Function Tests; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; T2DM, Type 2 diabetes mellitus.

^aAge/Years, (median-IRQ).

^bAge/Years, (mean \pm SD).

has demonstrated that patients with MAFLD and elevated serum IL-6 levels at admission are at higher risk for severe COVID-19.⁵⁵

It has been observed that patients with severe COVID-19 present an increase in the mononuclear phagocyte (MNP) population, present in the bronchoalveolar fluid, and above all increased positive monocytes for the CC-chemokine receptor 2 (CCR2+) compared with patients with mild disease or healthy controls. Another relevant feature of the MNP population in serious COVID-19 cases is the depletion of tissue alveolar macrophages despite of an abundance of inflammatory monocyte-derived macrophages. In addition, in COVID-19 patients, it has been reported a subgroup of macrophages enriched with genes dedicated to tissue repair, which promote the generation of fibrosis, as well as in cirrhosis of the liver. This suggests that the pathogenicity of infiltrating macrophages may extend beyond the promotion of acute inflammation, which is also in line with the fibrotic complications observed in patients undergoing mechanical ventilation.⁵⁰

The liver is enriched by innate immune cells and the functional status of the adaptive response might influence the clinical severity of SARS-CoV-2 infection. The presence of fatty liver may influence the adaptive response since it can be associated with a reduced functional status.⁵⁶ Moreover, the presence of NASH is associated with a low-grade inflammatory status involving cytokines, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress and Nod-like receptor protein 3 (NLRP3) inflammasome activation.⁴⁷ Thus, NASH in COVID-19 patients could boost the virus-induced cytokine storm syndrome (CSS),⁴⁸ through the hepatic release of multiple inflammatory mediators, contributing to severe COVID-19. The liver contains the largest number of macrophages, which are a powerful cytokine producer. In order to better understanding the link between the possible MAFLD progression and SARS-CoV-2 infection, all aspects, which can lead to an amplification of inflammation, and therefore, a major activation of inflammatory mediators such as macrophages must be assessed. Hepatic macrophages

/	/	Hypertension, obesity, DM and cardiovascular diseases.	Abnormal liver tests increase the risk of more severe COVID-19. Patients with MAFLD have almost double the risk of the general population to progress severe COVID-19, they are more likely to have abnormal transaminases, higher viral shedding time, and more liver injury during hospitalization compared to non-MAFLD patients. To identify and monitor patients with pre-existing liver disease, especially those with metabolic disorder, during and after COVID-19 crisis.	/
/	/	/	<p>COVID-19 often develops in patients with metabolic abnormalities, including fatty liver disease. The chronic presence of the complex inflammatory pathways in NAFLD can be acutely boosted in the setting of COVID-19, like liver injury and worse outcome in metabolically compromised populations.</p> <p>NAFLD should be considered as prognostic indicator during COVID-19. The presence of liver fibrosis might represent an additional and independent risk factor for COVID-19 outcome in NAFLD patients. A close long-term monitoring of patients with NAFLD who experienced COVID-19 might be needed.</p>	/
CT or abdominal ultrasound coupled with an internal expert consensus statement to diagnose NAFLD.	NFS/FIB-4 score.	/	Non-alcoholic fatty liver disease is associated with a higher risk of symptomatic, severe, and progressive COVID-19. The association is significant even after adjusting for an important confounding factor, obesity. Hence, it can be concluded that the hepatic manifestation of COVID-19 is independently linked to the severity of coronavirus disease.	The exact relationship between liver fat and COVID-19 remains to be elucidated.

1.3 | MAFLD may facilitates cytokine storm syndrome

COVID-19 is associated with an excessive inflammatory response related to the altered and uncontrolled activation of cytokines, deep and substantial lymphopenia and infiltration of mononuclear cells in the lungs. Other organs are important for disease prognosis. In fact, observational studies demonstrated that higher levels of inflammatory markers in blood (C-reactive protein, ferritin and D-dimers), an increased neutrophil-to-lymphocyte ratio and increased inflammatory cytokines and chemokines were associated with disease severity and poor prognosis.⁵⁰

Dysregulation of the innate immune response can be one aspect of liver injury in COVID-19. Patients with COVID-19 exhibit activation of inflammatory markers, including abnormal levels of CRP, lymphocytes, neutrophils and cytokines.⁵¹ These mechanisms may

contribute to pulmonary and extrapulmonary injuries because of loss of control of cytokine regulation, which, at an early stage, could be beneficial to curb disease progression.⁵² Fulminant and fatal hypercytokinaemia could initiate a chain of events, which lead to tissue and multiorgan injuries or failure, including the liver. The inflammatory response could cause hepatomegaly and elevated serum transaminase levels, as well as jaundice and hepatic encephalopathy.⁵³

In the liver, the innate immune mechanisms play a central role in COVID-19 outcome and in the transition to hepatic inflammation, macrophages have a critical role.⁵⁴ After the SARS-CoV-2 infection, pathogenic T cells activation and produce several inflammatory mediators, aka granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-6 and other pro-inflammatory factors. GM-CSF will further activate CD14+CD16+ inflammatory monocytes, producing a larger amount of IL-6 and other pro-inflammatory factors inducing an inflammatory 'storm' that leads to immune damage of other organs, such as the lungs and the liver. A recent research

consist of different cell populations including resident macrophages (Kupffer cells-KCs), which are the dominant liver phagocyte, and bone marrow-derived monocytes.⁴⁵ Macrophages are highly versatile and play a central role in the development of liver disease. Pro-inflammatory macrophages promote MAFLD progression and determine disease severity. The polarization process differentiates hepatic macrophages into sub-phenotypes, which have specific biological functions in response to signals from the microenvironment and consist of cytokines, growth factors, fatty acids, prostaglandins and molecules derived from pathogens.⁵⁴ In response to distinct inflammatory signals, macrophages can be classified into two classes, M1 and M2.⁴⁵ M1 macrophages are activated and stimulated by Toll-like receptor (TLR) ligands and Th1 immune factors and mediate the host defence against pathogens including bacteria, viruses or protozoa. Therefore, M1 macrophages initiate the inflammatory processes by the expression of high pro-inflammatory cytokines levels and produce high amounts of reactive oxygen and nitrogen species.⁵⁷ While M2 macrophages have anti-inflammatory function and promote tissue repair and remodelling, they have a phagocytic activity and express different chemokines profiles compared with M1 macrophage.^{54,57,58}

In the same way, at different stages of hepatic injury, both resident KCs and recruited monocyte-derived macrophages have important roles in the regulation of inflammation, fibrosis and fibrolysis.⁵⁴ It is assumed that in patients with MAFLD, the polarization state of liver macrophages could be distorted by M1 macrophages, which promote inflammation suppressing M2 macrophages, leading to progression of COVID-19.³² Moreover, cases with severe COVID-19 are associated with a clinical picture similar to macrophage activating syndrome (MAS) which is associated with high levels of ferritin.⁵⁹

Interestingly, in a study exploring the pulmonary pathology of early phase COVID-19 pneumonia, immunohistochemical staining results showed an abnormal accumulation of CD163+ M2 macrophages in lung tissue.⁶⁰ CD163 is a surface scavenger receptor for haptoglobin-haemoglobin complexes expressed almost exclusively on macrophages and monocytes. Increased levels of sCD163 are observed in paediatric and adult obese subjects and are associated with liver fibrosis and cirrhosis in patients with MAFLD, insulin resistance and type II diabetes. Furthermore, the involvement of sCD163 in the development of an acute inflammation state in parallel with ferritin has been observed, which in turn is able to activate macrophages, and this could explain the hyperferritinaemic syndrome found in COVID-19 patients.⁵⁹ Recently, the role of the ferritin H-chain in activating macrophages to increase the secretion of inflammatory cytokines was explained.⁵⁹

Finally, we should consider gut dysbiosis as a powerful activator of the pro-inflammatory cytokine production in the liver macrophages.⁵⁶ Gut dysbiosis is a perturbation of microbiome and promotes translocation of micro-organisms and microbial products into the portal circulation (metabolic endotoxaemia). The gut microbiome plays a key role in MAFLD progression resulting in NASH and liver fibrosis.⁶¹ The pathogenesis of fatty liver postulates the involvement of 'multiple parallel hits' suggesting that molecular mediators from various

organs, particularly the adipose tissue and the gut, participate in triggering inflammation pathways, which may later progress to fibrosis and, finally cirrhosis and carcinogenesis.⁶² The small intestine has a high expression of ACE2, and a high viral load has been found in faeces of COVID-19 patients, suggesting a central role in viral infection and inflammation. Gastrointestinal symptoms, which are common in COVID-19 patients, are related to liver injury markers indicating an increase in pathogen-associated molecular patterns to the liver, which are a possible cause for CSS amplification.⁴⁶ The role of the intestinal microbiota influencing lung diseases has been well discussed, and it is known that respiratory virus infection causes perturbations.⁶³ Furthermore, the intestinal microbiota has a possible protective role against coronavirus disease infections, which might explain why some COVID-19 patients are asymptomatic.⁶⁴ The severity of digestive symptoms in COVID-19 patients increases along with respiratory symptoms and liver damage^{9,65,66} and it is currently unclear whether this induces high levels of cell death or increases the permeability of the intestinal barrier. However, intestinal symptoms correlate with markers of liver damage⁶⁵ supporting the theory of increased transmission of pathogen-associated molecular patterns (PAMP) to the liver. This process could increase the severity of COVID-19 by sequestering immune resources from the lungs for the gut and liver or by 'triggering' the over activity of the immune system, known as CSS. The latter explanation may be supported by the similarities between circulating pro-inflammatory cytokines induced by non-alcoholic steatohepatitis during severe COVID-19.⁴⁶ There might be the possibility that the increased risk seen in MAFLD patients is because of gut infection with SARS CoV-2, which contributes to the systemic immune dysfunction characteristic of severe COVID-19. This process may also explain the increased risk of COVID-19 progression in obesity, T2DM and even IBD which are associated with similar gut microbiota, gut inflammation and barrier integrity disorders.⁴⁶ The gut-liver axis alterations, because of metabolic diseases, can contribute to severe COVID-19 progression. Therefore, the study of the gut microbiota can be of considerable help both to understand the pathogenesis and evolution of COVID-19, but also and above all to apply therapies and personalized nutrition.^{38,46} Moreover, the researches on the gut microbiota could be helpful in order to prevent the amplification of the inflammatory signal and the onset of NASH, especially in COVID-19 subjects.

1.4 | COVID-19 may influence the natural history of MAFLD

COVID-19 seems to have a bidirectional relationship with diabetes.⁶⁷ Severe COVID-19 patients may have an imbalance in the activation of angiotensin II-linked pathways with an increase in the activation of the angiotensin 1 (AT1R) and AT2R receptors, as in the case of T2DM, hypertension and states of insulin resistance. T2DM patients may be particularly vulnerable to SARS-CoV-2 infection and induce the expression of ACE2 in other organs, including the liver, which explains why T2DM can contribute to multiorgan failure

in COVID-19. Thus, the combination of COVID-19 and T2DM triggers a dysregulated immune response, resulting in a more severe outcome. Considering these data, factors contributing to the development of a worse COVID-19 outcome in patients with MAFLD are manifold and overlap often. We hypothesize these could include the infection of the liver itself or an indirect association because of comorbidities such as obesity and insulin resistance, an additional impact on the immune system and a dysregulated hepatic innate response with the skewed polarization status of hepatic macrophages.

Understanding mechanisms, which lead from MAFLD to inflammation, are important to design novel therapies to reduce morbidity and mortality in MAFLD patients with COVID-19. The presence of fibrosis in MAFLD patients is another risk factor for COVID-19 severity because fibrotic pathological findings could be a trigger for the cytokine storm cascade. The biggest gap in literature is the lack of biomarkers and information about the natural history of the infection and the involvement of the liver. A stringent and long-term follow-up of post-COVID-19 MAFLD patients is advisable to report further worsening of liver damage.

The SARS-CoV-2 infection could be identified as one of the factors contributing to the amplification of liver inflammation. However, it was not possible to evaluate the longtime impact of COVID-19 on liver disease progression.

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CONFLICT OF INTEREST

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

All authors contributed to editing and discussion of content.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Luca Miele  <https://orcid.org/0000-0003-3464-0068>

Cecilia Napodano  <https://orcid.org/0000-0002-8720-6284>

Umberto Basile  <https://orcid.org/0000-0002-8328-2570>

Antonio Gasbarrini  <https://orcid.org/0000-0003-4863-6924>

Antonio Grieco  <https://orcid.org/0000-0002-0544-8993>

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