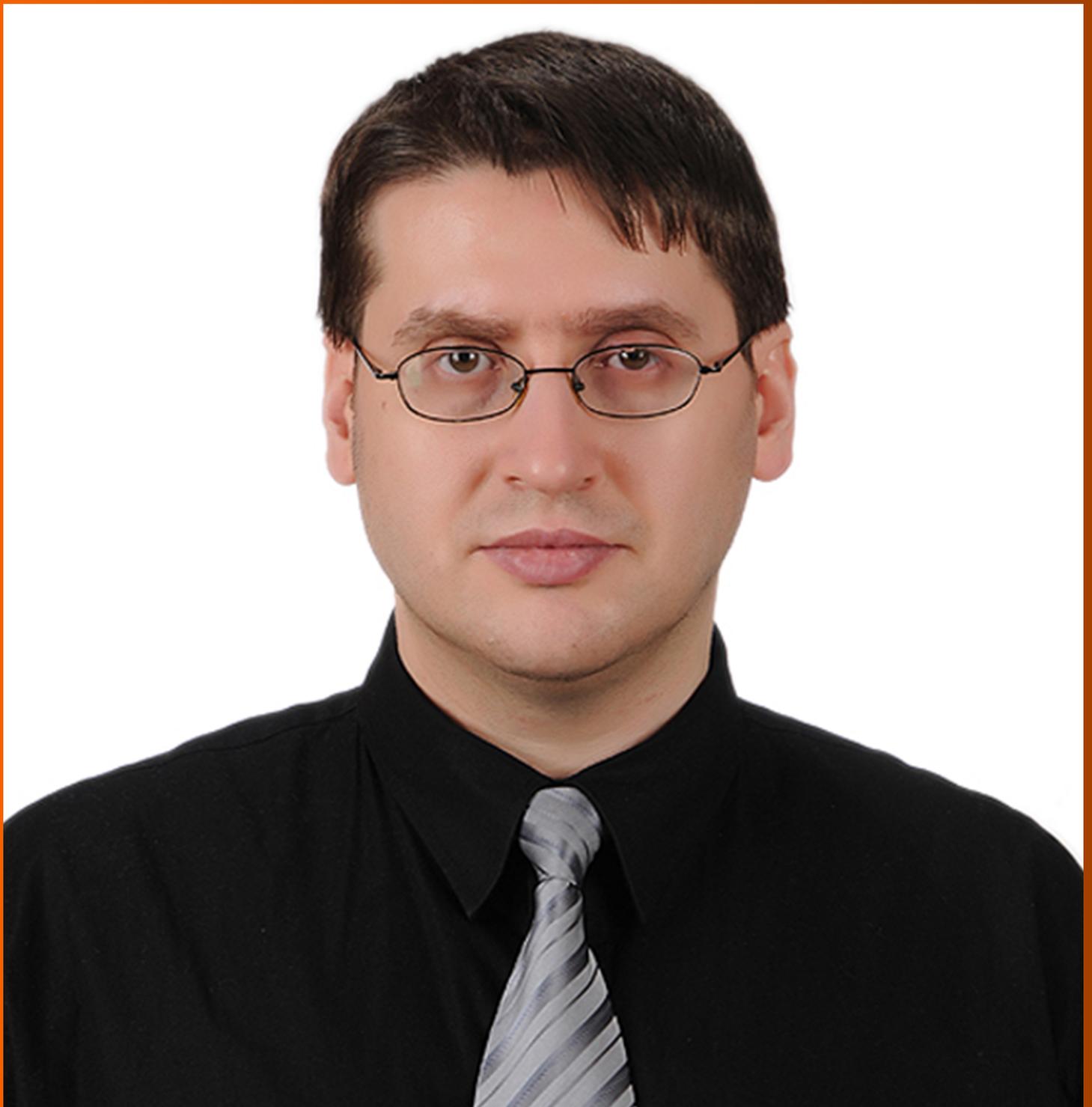


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Clinical perspectives, assessment, and mechanisms of metabolic-associated fatty liver disease in patients with COVID-19

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Abstract

Metabolic diseases are highly prevalent worldwide and have been associated with adverse clinical outcomes, including mortality, in patients developing coronavirus disease (COVID-19). Because of the close relationship between metabolic diseases such as type 2 diabetes mellitus and obesity and the presence of metabolic-associated fatty liver disease (MAFLD), a high number of cases of patients affected by both MAFLD and COVID-19 would be expected, especially in high-risk populations. Some studies have shown an increased risk of adverse clinical outcomes, viral shedding, and deep vein thrombosis, especially in patients with MAFLD-related liver fibrosis. The predisposition to poor outcomes and severe acute respiratory syndrome coronavirus 2 infection in patients with MAFLD could be secondary to mechanisms common to both, including preexisting systemic chronic inflammation, endothelial dysfunction, and involvement of the renin-angiotensin system. Because of the increased risk of adverse outcomes, MAFLD should be screened in all patients admitted for COVID-19. Available computed tomography scans could be of help, assessment of liver fibrosis is also recommended, favoring noninvasive methods to limit the exposure of healthcare workers. Liver involvement in this population ranges from abnormalities in liver chemistry to hepatic steatosis in postmortem biopsies. Finally, preventive measures should be strongly advocated in patients already known to have MAFLD, including the use of telemedicine and vaccination in addition to general

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic arrived amid a population increasingly affected by metabolic diseases such as type 2 diabetes mellitus and metabolic-associated fatty liver disease (MAFLD). Patients with MAFLD can have chronic inflammation, endothelial dysfunction, and increased expression of angiotensin-converting enzyme 2 receptor, which could synergize with severe acute respiratory syndrome coronavirus 2 pathophysiology, predisposing to a greater risk of adverse outcomes. Interestingly a high prevalence of liver steatosis in postmortem samples of patients who had COVID-19 has been found. Moreover, the presence of liver fibrosis has been shown to worsen prognosis in those patients. As a result, all patients with COVID-19 should be assessed for the presence of these comorbidities and closely follow-up.

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INTRODUCTION

In late 2019, a new coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first described in Wuhan, China[1], and has since spread to the rest of the world[2]. The dimension of this pandemic can be partly explained by the higher level of transmissibility of SARS-CoV-2 and a higher number of asymptomatic carriers, compared with other viruses such as Middle East Respiratory Syndrome (MERS) and SARS-CoV[3]. SARS-CoV-2 belongs to the beta-coronavirus family, and together with MERS and SARS-CoV virus, has been responsible for a high fatality rate during outbreaks[4].

The clinical manifestations of SARS-CoV-2 infection are extensive, ranging from asymptomatic disease, mild respiratory symptoms, to severe disease that may require mechanical ventilation because of severe acute respiratory syndrome, with a high risk of death. Most patients dying from COVID-19 are clustered by the presence of risk factors including older age, obesity, and chronic and metabolic diseases[5-8]. Among the risk factors, highly prevalent metabolic diseases such as type 2 diabetes mellitus (T2DM), hypertension, and obesity, are of utmost importance, being associated with a more severe clinical course that includes the need for intubation, and death[9]. Nonalcoholic fatty liver disease (NAFLD), recently renamed as metabolic-associated fatty liver disease (MAFLD), is strongly related to metabolic comorbidities and insulin resistance. It is regarded as the hepatic manifestation of metabolic syndrome[10,11]. The most important predictor of liver and non-liver-related outcomes in patients with MAFLD is the presence of liver fibrosis[12]. The association between metabolic risk factors such as obesity and diabetes, and MAFLD, means that the probability of facing patients with MAFLD and COVID-19 is high. Therefore, understanding the possible mechanisms of synergism between these entities, epidemiology, risk factors, clinical assessment, and prevention is of great clinical relevance. This review addresses these topics, focusing on proposing ways to identify and manage MAFLD in patients with COVID-19.

EPIDEMIOLOGY OF MAFLD

MAFLD is the most prevalent chronic liver disease worldwide, found in 10%-30% of the general population. The prevalence varies across countries and at the same time it varies among different regions from the same country[13]. Several factors can explain the variability in the prevalence of MAFLD, including age, sex, genetic factors such as the PNPL3 allele, environmental factors such as the typical western diet and sedentary lifestyle, access to health care, and the diagnostic methods used in epidemiological studies, especially with its recent re-classification[13-15].

EPIDEMIOLOGY OF SARS-COV-2 INFECTION

As of July 29, 2021 the World Health Organization reported more than 195 million confirmed cases of COVID-19 infection worldwide, with a death toll of more than 4 million[16]. United States is the country with the most confirmed cases, followed by India, Brazil, Russia, and France, and the United Kingdom. The countries with the highest mortality are the United States, Brazil, India, Mexico, and Italy. Interestingly the fatality rate is considerably higher in countries like Mexico, Iran, and Peru. The disparity in mortality could have several explanations including population characteristics (*e.g.*, sex, age, presence of comorbidities, and genetic factors), time since the initial outbreak, outbreak management, quality of the healthcare system, and the number of testing and treatment options, including the availability of mechanical ventilation[17].

Figure 1 shows the ten countries with the most COVID-19 cases and the prevalence of NAFLD reported by each country[13,18-21]. It is noteworthy that of the ten countries five have a prevalence of NAFLD > 30%, four between 20% and 29.9%, and only one country has a prevalence < 10%. Figure 2 shows the countries with the highest case fatality rate, which refers to the proportion of deaths in the population diagnosed with the disease. The rate is disproportionately higher in Mexico, and once more, five of the countries have a prevalence of NAFLD > 30% and three have a prevalence between 20% and 29.9%. Although this is not a causal explanation, it is certainly an interesting association. Finally, Figure 3 shows the number of deaths adjusted for every 100,000 inhabitants in order to standardize the comparison. Two countries have rates > 30% and four have rates between 20% and 29.9% while the rest have rates between 10% and 19.9%.

PROPOSED MECHANISMS OF LIVER INJURY IN PATIENTS WITH MAFLD AND SARS-COV-2 INFECTION

Multiple factors in MAFLD contribute to liver damage and progression of the disease, beyond insulin resistance and oxidative stress alone, as was previously thought[22]. In general, three mechanisms are associated with a higher risk of adverse outcomes in patients with MAFLD who develop COVID-19. The relationship stems from the fact that MAFLD is a part of the metabolic syndrome, and shares the following characteristics: (1) A preexisting systemic inflammatory milieu (*i.e.* systemic chronic inflammation and insulin resistance); (2) Endothelial dysfunction; and (3) Differential regulation of the renin-angiotensin-aldosterone system (RAAS)[23-29].

Long-term inflammation is a common denominator in chronic metabolic diseases, including MAFLD[30]. Obese patients express 2.5-fold more tumor necrosis factor (TNF)- α in fat tissue compared with lean controls, and weight loss is accompanied by a decrease in TNF- α mRNA expression[31]. Contrary to the belief that patients with simple steatosis do not have inflammation, some studies have shown otherwise. In murine models, it has been shown that liver steatosis leads to inflammation through NF- κ B activation and downstream cytokine production[32]. Patients with both NAFLD and nonalcoholic steatohepatitis (NASH) have significantly higher serum levels of IL-6 and CRP compared with healthy controls, where inflammation levels are similar in both stages[33,34]. Also CCL2/MCP-1, which regulates migration and infiltration of monocytes/macrophages was found to be increased in both NAFLD and NASH patients[33]. The studies reported that patients with NAFLD were characterized by low-grade systemic inflammation; furthermore, compared with healthy individuals, the presence of advanced liver fibrosis was accompanied by significantly higher markers of systemic circulatory dysfunction and higher levels of proinflam-

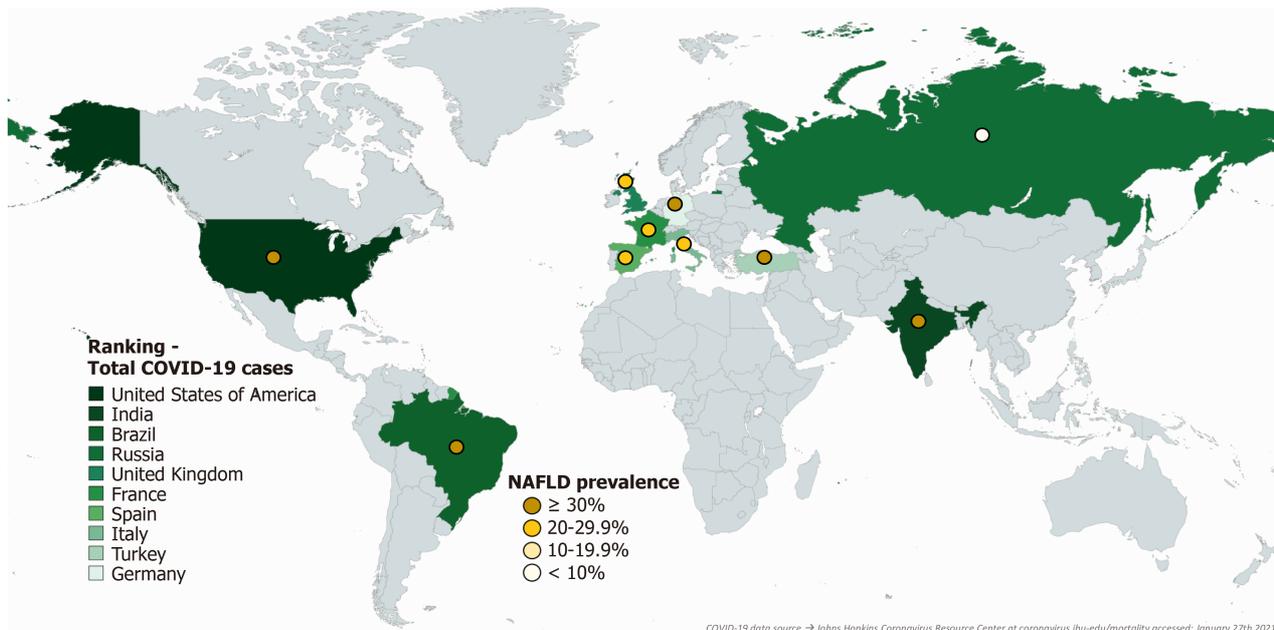


Figure 1 Total coronavirus disease 2019 cases and nonalcoholic fatty liver disease prevalence. United States of America 25439570, India 10689527, Brazil 8933356, Russia 3716228, United Kingdom 3700268, France 3138498, Spain 2629817, Italy 2485956, Turkey 2442350, Germany 2164043.

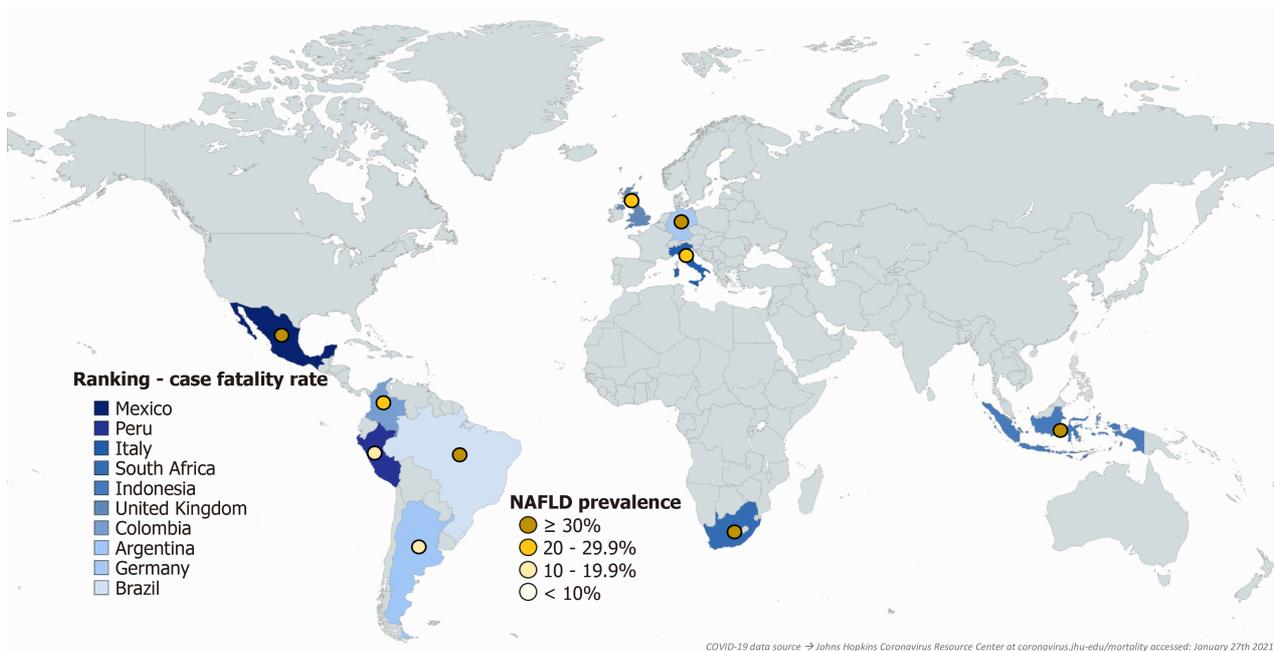


Figure 2 Coronavirus disease 2019 case fatality rate and nonalcoholic fatty liver disease prevalence. Mexico 8.5%, Peru 3.6%, Italy 3.5%, South Africa 2.9%, Indonesia 2.8%, United Kingdom 2.7%, Colombia 2.6%, Argentina 2.5%, Germany 2.5% and Brazil 2.5%. The prevalence of nonalcoholic fatty liver disease in those countries is indicated by the colored circles.

matory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-8, monocyte chemoattractant protein (MCP)-1, interferon- γ -inducible protein (IP)-10, and macrophage inflammatory protein (MIP)-1b[35]. On the other hand, in patients with COVID-19, the presence of hyperinflammation, described as hypercytokinemia or “cytokine storm”, immune hyperactivation, and even in some cases secondary hemophagocytic lymphohistiocytosis have been reported[1,36-38]. One of the cytokines reported to be elevated in patients with COVID-19 is IL-1B, which is the final effector of pyroptosis, a known mechanism of liver cell death[39,40]. Apart from IL-1B, other cytokines have been found to increase in COVID-19, including IL-6, IP-10, TNF, interferon- γ , vascular endothelial growth factor, and MIP 1 α and 1 β [36]. Obese patients with COVID-19 present a more prominent inflammatory profile than

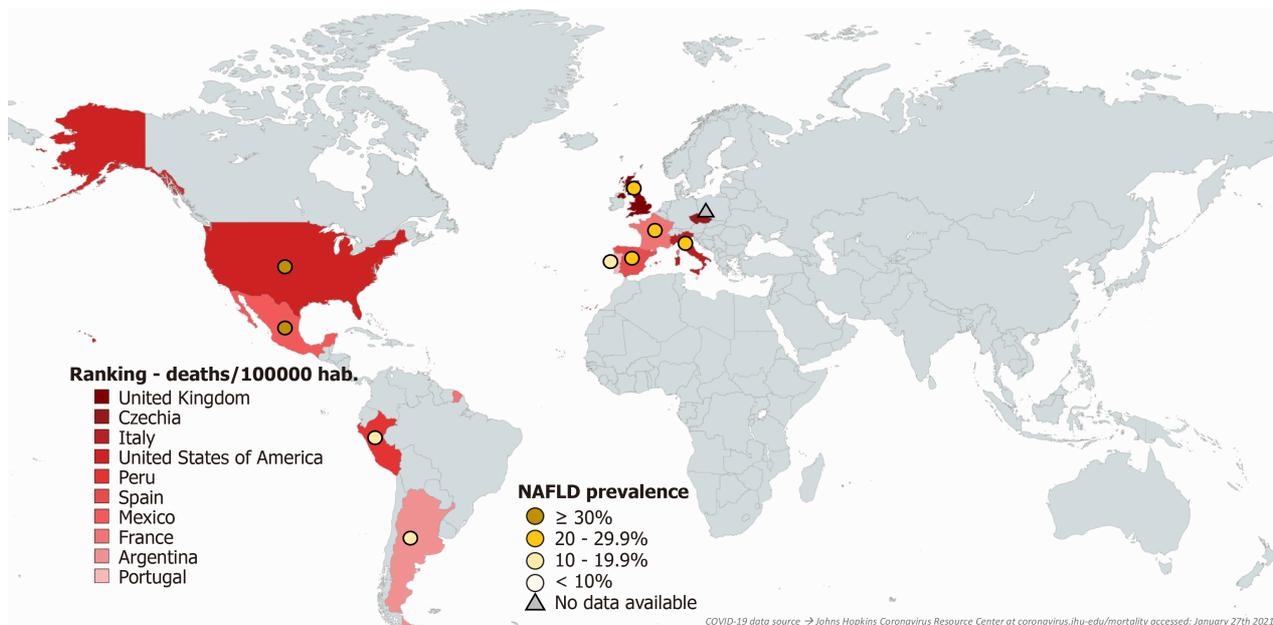


Figure 3 Number of deaths from coronavirus disease 2019 per 100000 habitants and nonalcoholic fatty liver disease prevalence. United Kingdom 150.94, Czechia 146.98, Italy 143.01, United States of America 129.94, Peru 125.38, Spain 121.55, Mexico 120.47, France 110.84, Portugal 107.10, Argentina 106.20.

nonobese COVID patients[41]. Dexamethasone has shown a mortality benefit in patients with severe COVID-19 because of its ability to inhibit the generation of cytokines and their deleterious effects[42]. The possible effect of an “acute-on-chronic inflammation” process in patients with MAFLD, including those with or without liver fibrosis, and COVID-19, deserves further research, including the possibility of different anti-inflammatory responses to corticosteroids such as dexamethasone.

Another point of convergence between COVID-19 and metabolic diseases such as MAFLD is endothelial dysfunction. Endothelial dysfunction has been described in patients with liver steatosis. Healthy individuals have better endothelial function than biopsy-proven NAFLD patients[27], which partially explains the increased risk of cardiovascular disease in that population[43]. Endothelial dysfunction results in a prothrombotic state leading to occlusion and micro thrombi formation in patients with COVID-19[44]. Moreover, endothelial dysfunction can result in insufficient nitric oxide and consequent vessel constriction[45]. Taken together, the studies show that preexisting endothelial dysfunction could explain the high prevalence of thrombosis in patients with COVID-19 and MAFLD[46].

Finally, some of the pathways involved in liver fibrosis, which is the key event determining the outcome in patients with NAFLD[12], are specially relevant and could have an important role in patients with COVID-19. One of them, the RAAS, is involved in liver fibrosis development, where angiotensin II induces a profibrogenic phenotype in stellate cells and has an important role in the pathophysiology of cirrhosis[47,48]. Similarly, RAAS has a role in the pathogenesis of NAFLD, where the hepatic local RAAS is overactivated, and more importantly, patients with NASH have significantly higher expression of angiotensin-converting enzyme 2 (*ACE2*) gene, suggesting that those patients have a greater risk of liver affection by SARS-CoV-2[49] given the fact that SARS-CoV-2 entry into the cell is accomplished through the binding and interaction of the spike glycoprotein (S-glycoprotein) and *ACE2*[50]. This could partially explain the relationship between adverse outcomes and liver fibrosis in patients with MAFLD and COVID-19.

In conclusion, various mechanisms explain the association observed in different studies between MAFLD and/or fibrosis and adverse outcomes in patients with COVID-19, where its directionality is important to explain what happens in the liver. One is that a previous chronic state (*e.g.*, inflammation, endothelial dysfunction, differential regulation of the RAAS, *etc.*) “primes” the body to develop a stronger response upon SARS-CoV-2 infection, thereby increasing its lethality. Another possible scenario is that acute systemic inflammation induces a prosteatotic and profibrogenic response in patients with COVID-19. These mechanisms need further study in order to shed light on the main pathways explaining the relevance of MAFLD in patients with

COVID-19.

METABOLIC RISK FACTORS ASSOCIATED WITH SEVERE COVID-19

The risk of severe COVID-19 is higher in older individuals and in those with underlying medical comorbidities. The established risk factors for severe COVID-19, according to the Centers for Disease Control and Prevention (CDC), are T2DM, serious cardiovascular disease, obesity, chronic kidney disease, cancer, chronic obstructive pulmonary disease, immunocompromised state from solid organ transplant, smoking and sickle cell disease[51]. Given the association between MAFLD, obesity, and diabetes mellitus, it could be proposed as a high-risk metabolic condition[52,53].

Obesity

Obesity is a fast-growing public health problem. In 2016, 39% of the adult population worldwide were overweight and 13% were obese. There is a direct relationship between obesity and adverse clinical outcomes[54]. The association has also been observed in patients with SARS CoV2 infection, where observational data links obesity with an increased risk of severe disease and death[55-61]. In addition to the body mass index (BMI), visceral adiposity probably favors the development of severe COVID-19. This was addressed in a single-center cohort study in Italy, where the investigators found that abdominal adipose tissue distribution positively correlated with the risk of intensive care unit (ICU) admission in patients with COVID-19[62].

Diabetes mellitus

Diabetes is among the ten leading causes of death worldwide[63]. There is a relation between diabetes mellitus and the development of severe COVID-19[64-69]. In an observational cohort study, COVID-19-related mortality in people with diabetes mellitus was associated with the preceding level of hyperglycemia (HbA1c). In T2DM patients, the risk was significantly higher in those with an HbA1c > 7.5% and the risk increased as HbA1c levels did[70]. Another study found lower mortality in hospitalized patients with COVID-19 and T2DM with better glycemic control[65]. Conversely, Agarwal *et al*[71] did not find a clear association between HbA1c level and mortality in patients with diabetes and COVID-19, but the risk of mortality was greater in patients on previous insulin therapy.

The pathophysiological mechanisms that increase the risk of mortality in people with COVID 19 and obesity/diabetes mellitus are complex and not completely clear. The two factors have immune dysfunction characterized by a state of chronic low-grade inflammation in common[72,73]. There is evidence that patients with obesity and SARS CoV2 infection have a higher expression of inflammatory markers including IL6, IL-4, erythrocyte sedimentation rate, and high-sensitivity C-reactive protein (hsCRP) than nonobese patients[74].

SPECTRUM OF LIVER DAMAGE IN PATIENTS WITH MAFLD AND COVID-19

Several studies have been conducted to elucidate whether MAFLD is a risk factor for adverse clinical outcomes in patients with COVID-19. A summary of all of the studies, published until December 7, 2020 evaluating the association between MAFLD and clinical outcomes in patients with COVID-19 is presented in Table 1. It is important to acknowledge that comparison of the studies is limited by differences such as the number of available cases, the clinical outcomes evaluated, definitions of severity, demographic characteristics and comorbidities, and the methods of assessing both MAFLD and liver fibrosis. Despite this limitation, there are consistent results among the published data. All studies compared patients with or without MAFLD and all found different risk factors for the development of various poor clinical outcomes. Most studies concluded that MAFLD patients have an increased risk of developing abnormal liver function tests, liver injury, and severe disease in the acute setting of COVID-19. In addition, some studies found no differences in disease severity, disease progression, complications, or mortality among patients with or without MAFLD. Others emphasized that MAFLD only conferred an increased risk of severe disease in younger patients < 60 years of age, in those with advanced fibrosis detected by noninvasive methods such as the FIB-4 score or NAFLD fibrosis score (NFS) or with an

Table 1 Studies evaluating metabolic-associated fatty liver disease in coronavirus disease 2019 patients

Ref.	Type of study and population	MAFLD/non-MAFLD patients (n)	MAFLD diagnosis	Liver fibrosis criteria	Clinical outcomes	Results
Gao <i>et al</i> [61]	Cohort, n = 130 pts, China	65/65	Hepatic steatosis by CT and MAFLD consensus criteria	N/A	COVID-19 severity	MAFLD: Increased risk of severe COVID-19 (OR 4.07, 95%CI: 1.1-15.09, P = 0.003)
Ji <i>et al</i> [52]	Cohort, n = 202 pts, China	76/126	HSI > 36 points and/or abdominal US	N/A	Liver injury and COVID-19 severity	MAFLD: Increased risk of severe COVID-19 (44.7% vs 6.6%, P < 0.0001), abnormal liver function tests from admission to discharge (70% vs 11.1%, P < 0.0001) and longer viral shedding time (17.5 vs 12.1 d, P < 0.0001)
Targher <i>et al</i> [53]	Cohort, n = 310 pts, China	94/216	Hepatic steatosis by CT and MAFLD consensus criteria	FIB-4, NFS	COVID-19 severity	MAFLD: Intermediate/high FIB-4 increased risk of severe COVID-19 (OR 2.95, 95%CI: 1.37-6.34, P < 0.005), intermediate/high NFS increased risk of severe COVID-19 (OR 2.91, 95%CI: 1.20-7.06)
Huang <i>et al</i> [83]	Cohort, n = 280 pts, China	86/194	HSI >36 points	N/A	Laboratory abnormalities, liver injury, COVID-19 severity, clinical outcomes	MAFLD: Increased levels of white blood cells (5.5 vs 4.7, P < 0.001), lymphocytes (1.4 vs 1.2, p 0.041), ALT (34.5 vs 23, P < 0.0001) and GGT (34 vs 21, P < 0.001). No difference in severity, complications and clinical outcomes
Mahamid <i>et al</i> [84]	Case control, n = 71 pts, Israel	22/49	Hepatic steatosis by CT and MAFLD consensus criteria	N/A	COVID-19 severity	MAFLD: Increased risk of severe COVID-19 (men: OR 3.29, 95%CI 3.28-3.58, P = 0.001; women: 3.25, 95%CI: 3.09-3.47, P = 0.002)
Zhou <i>et al</i> [85]	Cohort, n = 327 pts, China	59/268	Hepatic steatosis by CT and MAFLD consensus criteria	N/A	COVID-19 severity in younger (< 60 yr of age) and elderly (> 60 yr of age) patients	MAFLD: Younger patients increased risk of severe COVID-19 (OR 2.67, 95%CI: 1.13-6.34, P = 0.03). Elderly patients no difference in COVID-19 severity
Chen <i>et al</i> [86]	Cohort, n = 342 pts, United States	178/164	HSI > 36 points for Asians and HSI > 39 points for non-Asians or imaging evidence of hepatic steatosis	N/A	Liver injury and COVID-19 severity	MAFLD: Increased risk of transaminitis (ALT > 5 × ULN) (OR 2.12, 95%CI: 1.03-4.37, P = 0.04), ICU admission (OR 1.60, 95%CI: 1.00-2.57, P = 0.05), intubation (OR 2.51, 95%CI: 1.52-4.16, P ≤ 0.001), and vasopressor use (OR 1.22, 95%CI: 1.11-1.34, P ≤ 0.001)
Zhou <i>et al</i> [87]	Cohort, n = 110 pts (all patients < 60 yr of age), China	55/55	Hepatic steatosis by CT and MAFLD consensus criteria	N/A	COVID-19 severity	MAFLD: Increased risk of severe COVID-19 (OR 4.07, 95%CI: 1.20-13.79, P = 0.02)
Pan <i>et al</i> [88]	Meta-analysis, n = 110 pts (all patients < 60 yr of age), China	401/892	Hepatic steatosis plus one of the following: overweight, type 2 diabetes mellitus or metabolic dysregulation	N/A	Pooled prevalence of MAFLD and COVID-19 severity	MAFLD: Prevalence of MAFLD in COVID-19 patients (OR 0.31, 95%CI: 0.28-0.35, I ² = 38.8%, P = 0.1799). Increased risk of severe COVID-19 (OR 2.93, 95%CI: 1.87-4.60, I ² = 34.3%, P = 0.166)
Bramante <i>et al</i> [75]	Cohort, n = 6700 pts, United States	373	ICD codes for NAFLD or NASH or BMI 30 kg/m ² and elevated ALT	N/A	Admission or hospitalization for COVID-19	MAFLD: Increased risk of hospitalization (OR 1.43, 95%CI: 1.09-1.88, P < 0.01). Patients who had undergone bariatric surgery decreased risk of hospitalization (OR 0.22, 95%CI: 0.05-0.98, P < 0.05)
Lopez-Mendez <i>et al</i> [76]	Cross sectional, n = 155 pts, Mexico	66/89	HSI > 36 points	APRI, NFS and/or FIB-4	Prevalence of liver steatosis and fibrosis in COVID-19 patients, COVID-19 severity	MAFLD: Prevalence of steatosis 42.6% (66/155) and of advanced fibrosis 44.5% (69/155). Advanced liver fibrosis by FIB-4 increased risk of ICU admission (OR 1.74, 95%CI: 1.74-2.68, P = 0.023) and mortality (OR 6.45, 95%CI: 2.01-20.83, P = 0.002). No difference in disease severity
Forlano <i>et al</i> [77]	Cohort, n = 193 pts, United Kingdom	61/132	Imaging evidence of hepatic steatosis or previous diagnosis of MAFLD	FIB-4	ICU admission and in-hospital mortality	MAFLD: No difference in rates of ICU admission (OR 1.14, 95%CI: 0.53-2.5, P = 0.69) and in-hospital mortality (OR 0.86, 95%CI: 0.44-1.69, P = 0.67), regardless of the FIB-4 values (low <1.45, intermediate 1.45-3.25 or high > 3.25 risk of advanced

Mushtaq <i>et al</i> [78]	Cross sectional	320/269	HSI > 36 points	N/A	Mortality, COVID-19 severity, COVID-19 progression and liver injury	fibrosis) MAFLD: Increased risk of mild (OR 2.99, 95%CI: 1.62-4.37, <i>P</i> = 0.000) and moderate (OR 5.104, 95%CI: 3.21-6.99, <i>P</i> = 0.000) liver injury. No difference in disease severity, progression or mortality
Targher <i>et al</i> [79]	Cohort, <i>n</i> = 589 pts, Qatar	94/216	Hepatic steatosis by CT and MAFLD consensus criteria	N/A	COVID-19 severity according to NLR	MAFLD: MAFLD+NLR 2.8 (OR 5.32, 95%CI: 0.98-29.9, <i>P</i> = 0.053), non-MAFLD+NLR > 2.8 (OR 17.7, 95%CI: 3.89-80.6, <i>P</i> < 0.001), MAFLD+NLR>2.8 (OR 25.9, 95%CI: 5.32-127, <i>P</i> < 0.001) compared to those with non-MAFLD+NLR2.8. Patients with MAFLD and high NLR values have increased risk of severe COVID-19
Ji <i>et al</i> [46]	Cohort, <i>n</i> = 200 pts, China	125/75	HSI > 36 points and/or abdominal US	N/A	D-dimer levels	MAFLD: Increased D-dimer values at admission (0.72 vs 0.38 g/mL, <i>P</i> = 0.003) and peak levels (1.81 vs 0.63 g/mL, <i>P</i> = 0.003)
Ji <i>et al</i> [46]	Cohort, <i>n</i> = 81 pts (DVT 21 pts and non-DVT 60 pts), China	43/38	HSI > 36 points and/or abdominal US + Doppler US	N/A	Prevalence of MAFLD in DVT and non-DVT patients	MAFLD: Increased prevalence in patients with DVT compared to those without DVT (76% vs 45%, <i>P</i> = 0.01)
Sachdeva <i>et al</i> [80]	Systematic review and meta-analysis, <i>n</i> = 8142 pts, 8 studies (7 studies from China and 1 study from Israel)	833/7309	Imaging evidence of hepatic steatosis and MAFLD consensus criteria	N/A	COVID-19 severity	MAFLD: Increased risk of severe COVID-19 (OR 2.358, 95%CI: 1.902-2.923, <i>P</i> < 0.001)
Hashemi <i>et al</i> [81]	Cohort, <i>n</i> = 363 pts, United States	55/308 (69 w/CLD)	Imaging evidence or biopsy evidence of hepatic steatosis	N/A	Clinical outcomes	MAFLD: Increased risk of ICU admission (OR 2.30, 95%CI: 1.27-4.17, <i>P</i> = 0.03) and need of mechanical ventilation (OR 2.15, 95%CI: 1.18-3.91, <i>P</i> = 0.02). No difference in mortality rates

ALT: Alanine aminotransferase; BMI: Body mass index; CLD: Chronic liver disease; COVID-19: Coronavirus disease; 2019; CT: Computed tomography; DVT: Deep vein thrombosis; HSI: Hepatic steatosis index; MAFLD: Metabolic-associated fatty liver disease; N/A: Not available; NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; NLR: Neutrophil/lymphocyte ratio; US: Ultrasound.

elevated neutrophil/lymphocyte ratio (NLR) of > 2.8. One study found that MAFLD patients had increased viral shedding time and another identified an increased risk of deep vein thrombosis[46,52,53,75-88].

HISTOLOGICAL FINDINGS

Information regarding liver histopathological findings in COVID-19 is scarce. Some case series have reported a high prevalence of liver steatosis in postmortem biopsies and autopsies, ranging between 48% and 75%. Sonzogni *et al*[89] reported liver biopsies from 48 patients who died from COVID-19 in northern Italy, none of whom had signs or symptoms of liver disease before and during hospitalization. Obesity was present in 16% of the patients, hypertension in 53%, and diabetes in 29%. Macrovesicular steatosis was observed in 48% of the samples; all patients with obesity had liver steatosis. The use of steroids was not reported in this paper. Lagana *et al*[90] reported the liver histology of 40 patients who died of COVID-19 in New York, 50% had diabetes and 75% had hypertension. The most common finding was macrovesicular steatosis, present in 75% of the patients. Interestingly, the distribution of liver steatosis was not typical of MAFLD and did not correlate with BMI or T2DM. Twenty-two patients (55%) received steroids during their hospital stay. Bradley *et al*[91] reported postmortem examinations performed on 14 patients who died of COVID-19 in Washington state. Liver steatosis was reported in 64% of the patients. Ten of the 14 patients had at least one metabolic disease (*i.e.* hypertension T2DM, dyslipidemia, or obesity), steroid use was not reported. A report of autopsy findings of 22 COVID-19 patients in Italy revealed microvacuolar and microvacuolar steatosis in 54% of the patients[92]. Table 2 further describes the studies.

Table 2 Histological findings from liver biopsies of coronavirus disease 2019 patients

Ref.	Inclusion criteria	Population characteristics n (%)	Histopathological results	
Sonzogni <i>et al</i> [89]	Postmortem SARS-CoV-2-positive patients. (n = 48) ¹ ; Male/Female (n): 35/13 ¹ ; Age (yr): 71 (32-86)	No comorbidities: 6 (13.3); Hypertension 24 (53.3); Cardiovascular Disease (different than hypertension) 17 (37.8); Diabetes 13 (28.9); Obesity 7 (15.6); Kidney disease 10 (22.2); Pulmonary disease 5 (11.1)	Portal vein parietal fibrosis	Absent 39%; Focal 29%; Multifocal 22%; Diffuse 8%
			Herniated portal vein in periportal parenchyma	Absent 25%; Focal 37%; Multifocal 27%; Diffuse 10%
			Periportal abnormal vessels	Focal 56%; Multifocal 37%; Diffuse 6%
			Fibrosis	Absent 24%; Portal fibrosis 60%; Incomplete fibrous septa 16%
			Lobular inflammation	Absent 50%; Mild 48%; Moderate 2%; Severe 0%
			Portal inflammation	Absent 33%; Mild 66%; Moderate 0%; Severe 0%
			Vascular thrombosis	Partial portal 50%; Complete portal 23%; Incomplete sinusoidal 14%; Complete sinusoidal 12%
			Parenchymal confluent necrosis	Absent 65%; Mild 11%; Moderate 15%; Severe 12%
			Steatosis	Absent 46%; Small droplets 6%; Large droplets 2%; Mixed small and large 46%
Lagana <i>et al</i> [90]	Patients who died from illness related to COVID-19. (n = 40) ¹ ; Male/Female (n): 28/12 ¹ ; Age (yr): 70 (66-80)	BMI, N = 32 mean (range) 26.5 (23.9-32.0); Chronic liver disease: 2 (13); Diabetes: 18 (50); Hypertension: 29 (76); Chronic kidney disease: 7 (22); Cardiac disease: 10 (36)	Lobular necroinflammation	20 (50%)
			Portal inflammation	20 (50%)
			Lobular apoptosis (individual hepatocytes)	10 (25%)
			Fat 0%–5%; 6%–33%; 34%–66%; 67%–100%	10 (25%); 19 (48%); 6 (15%); 5 (12%)
			Cholestasis	15 (38%)
Bradley <i>et al</i> [91]	Patients with a positive antemortem or post-mortem SARS-CoV-2. (n = 14) ¹ ; Male/Female: 6/8 ¹ ; Age (yr): 73.5 (42-84)	-	Periportal lymphocytic inflammation	2 (14%)
			Centrilobular necrosis	4 (28%)
			Steatosis	9 (64%)
			Congestion	11 (78%)
Falasca <i>et al</i> [92]	Postmortem SARS-CoV-2-positive patients. (n = 22) ¹ ; Male/Female: 15/7 ¹ ; Age (yr): 67.9 (27-92)	Chronic obstructive pulmonary disease: 6 (27.2); Cardiac disease: 8 (36.3); Malignancy: 5 (22.7); Hypertension: 4 (18.2); Diabetes: 4 (18.2); Kidney disease: 2 (9.1)	Inflammatory infiltrate	11 (50%)
			Congestion	10 (45.5%)
			Steatosis	12 (54.5%)

¹Age was reported as median (interquartile range). SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BMI: Body mass index.

Two explanations can be made of the high-frequency of macrovesicular steatosis in patients who died with severe COVID-19. The first is that the patients had liver steatosis before they acquired COVID-19, which represents a risk factor for mortality as the prevalence was higher than that reported in the general population[93]. MAFLD might contribute to the COVID-19-induced inflammatory “storm” through the hepatic release of proinflammatory cytokines, thereby contributing to the severity of the disease[79]. The second explanation is that liver steatosis developed in some patients during the course of the infection, with the etiology being multifactorial[90]. Hypoxia is associated with lipid homeostasis maintained by hypoxia-inducible factors (HIFs). HIFs regulate hepatic lipid metabolism to increase the liver lipid storage capacity[94,

95]. The corticosteroid therapy that is frequently given to patients with severe COVID-19 can cause hepatic steatosis. The effect can occur rapidly and is not usually clinically relevant[96]. Liver steatosis has been associated with viral infections, specifically hepatitis C virus infection, through impaired secretion, increased neosynthesis, and impaired degradation[97]. In summary, there is no pathophysiological evidence supporting SARS-CoV-2 as a direct cause of liver steatosis. However, as seen above, liver steatosis is a common histopathological finding in patients who died from severe COVID-19. The explanation of the findings is undoubtedly multifactorial, including a history of metabolic risk factors, use of corticosteroid therapy, and the universal presence of hypoxia in these patients.

FUTURE PERSPECTIVES IN PATIENTS WITH MAFLD AND COVID-19

MAFLD patients can be vulnerable to SARS-CoV-2 infection and COVID-19 complications because of the deleterious interaction of complex inflammatory pathways[98]. As we show in this review, based on currently available clinical evidence, patients with MAFLD have an increased risk of developing abnormal liver function tests and are more likely to progress to severe COVID-19[52,53,80-82,84,86-88]. Therefore, MAFLD should be considered a prognostic indicator for COVID-19.

We recommend taking these observations into account when assessing such patients. It is important to identify and closely monitor patients with preexisting liver diseases, including those with MAFLD. An Asia-Pacific position statement also recommends proper monitoring and management of blood pressure and glycemic control in MAFLD patients who have COVID-19, as it is associated with poor clinical outcomes[99]. As we do not yet know the long-term effects that COVID-19 can have on patients with MAFLD with respect to fibrosis, we also encourage long-term monitoring. Below, we discuss the available options for clinical assessment and prevention.

Clinical assessment

Given the high prevalence of MAFLD and the implications of liver fibrosis for the risk of adverse outcomes in patients with COVID-19[100], all patients admitted to hospital should be evaluated for the presence of MAFLD and assessed for the risk of liver fibrosis. Most patients with MAFLD are asymptomatic, and therefore, are not aware of their disease. Establishing the diagnosis of MAFLD requires the presence of metabolic risk factors such as overweight/obesity, T2DM, or evidence of metabolic dysregulation in addition to evidence of fat accumulation in the liver[101]. The first step in the evaluation of MAFLD and fibrosis in patients with COVID-19 should be to determine the presence of metabolic risk factors such as insulin resistance, T2DM, hypertension, obesity, and dyslipidemia. In those patients, the presence of liver steatosis should be determined either by imaging or by risk scores. The ideal imaging methods to assess liver fat content are ultrasound, transient elastography, or magnetic resonance imaging, however in the context of COVID-19 patients, the use of available images such as those derived from chest computed tomography (CT) scans can be useful, shorten the evaluation time, and limit the exposure of healthcare workers. Chest CT has high sensitivity and specificity for detecting lung lesions in patients with COVID-19 and is performed frequently in patients with severe disease[102]. Images of the liver and the upper pole of the spleen can be seen in chest CT scans. In those cases, the CT scan can be used to diagnose moderate and severe steatosis[101]. CT diagnostic criteria for steatosis are liver attenuation of at least ten Hounsfield Units (HU) less than that of the spleen or an absolute liver attenuation of less than 40 HU. These criteria have variable specificity (43%-95%) and high sensitivity (90%-100%)[103]. When a chest CT is not available or the image is not ideal, risk scores are a useful alternative. Several scores have been developed for that purpose, including the NAFLD liver fat score, the Framingham steatosis index (FSI), and the Dallas Steatosis Index. The NAFLD liver fat score is calculated using the presence of metabolic syndrome, T2DM, fasting serum insulin, fasting serum aspartate transaminase (AST)/alanine transaminase (ALT) ratio. A cutoff of 0.640 predicts increased liver fat content with a sensitivity of 86% and specificity of 71%[104]. The need of a serum insulin assay makes this score impractical in some hospitals. The FSI includes the patient age, sex, BMI, triglyceride level, hypertension, T2DM, and the ALT/AST ratio. At a cutoff point of 23, the FSI has a sensitivity of 79%, a specificity of 71%, a positive predictive value (PPV) of 50%, and a negative predictive value (NPV) of 90% for hepatic steatosis[105]. The disease severity index is a novel, recently developed score based on ALT level, DMI, age, sex, trigly-

ceride and glucose levels, T2DM, hypertension, and ethnicity. At a threshold of < 20% risk, MAFLD can be excluded with 86% sensitivity and 90% NPV[106]. A major drawback of these scores is that all of them require transaminase values, which may be elevated in patients with COVID-19[107], increasing the risk of overestimating the risk of liver steatosis.

For patients who meet the criteria for MAFLD, evaluation of fibrosis is essential. The gold standard for the evaluation of liver fibrosis is liver biopsy, however, as it is an invasive procedure, is not suitable for this clinical scenario. Elastography is another useful method, and it has become the noninvasive method of choice to quantify liver stiffness. However, liver inflammation caused by SARS-CoV-2 can by itself increase liver stiffness[108]. Furthermore, elastography is not widely available in all hospitals, and biosecurity measures could make it difficult to perform this evaluation of patients with COVID-19 and MAFLD. Noninvasive tools for the assessment of liver fibrosis include serologic tests, risk scores, and imaging studies[12]. None of the currently available biomarkers by itself has sufficient accuracy for diagnosing fibrosis, therefore, predictive scores have an important role in evaluating the risk of advanced fibrosis in patients with MAFLD. Among the prediction scores, FIB-4 index, NFS, the BARD score, FibroTest, HepatoScore, Hepamet fibrosis score (HFS), and AST/platelet ratio index (APRI) score, are the most widely used. Overall, predictive scores for fibrosis have high NPVs for excluding advanced fibrosis with low PPVs. Therefore, these scores may be confidently used for baseline risk stratification to exclude advanced fibrosis. A Fagan's nomogram analysis of post-test probability for detecting advanced fibrosis found that the HFS, HepatoScore and FibroMeter test to be the best noninvasive measures[12]. As mentioned before, a major disadvantage of these scores is the use of liver transaminases as a variable, and as previously known, patients with COVID-19 frequently have hypertransaminasemia, which would increase the risk of overestimating the presence of liver fibrosis. A confirmatory test should be made after the patient has been discharged and close follow-up should be continued.

Preventive measures

The general preventive recommendations for patients with MAFLD and liver fibrosis are those given for the general population, and include, wearing a mask when out in public or in areas without ventilation, practicing social distancing, and performing frequent hand hygiene. If possible, healthcare visits should be avoided in favor of telemedicine consultations[109]. It is important to mention that vaccination against SARS-CoV-2 has started worldwide and there are many doubts to be clarified regarding patients with liver diseases. We must keep in mind that several thousand people have participated in clinical trials of the different vaccines against SARS-CoV-2. However, there are few data on patients with liver diseases, and some trials have excluded such patients[110].

Three SARS-CoV-2 vaccines have been approved recently. The BNT162b2 vaccine (Pfizer-BioNTech) was evaluated in 43,448 participants of whom 0.6% ($n = 214$) had mild liver disease, only three had moderate or severe liver disease, 31% ($n = 13218$) of the participants had obesity, and 8.4% ($n = 3163$) had diabetes. In both conditions associated with MAFLD the vaccine safety and efficacy were high[111]. The ChAdOx1 nCoV-19 vaccine (AstraZeneca/University of Oxford), excluded individuals with chronic liver diseases, and only 135 (0.5%) patients with diabetes were included[112]. The mRNA-1273 vaccine (ModernaTX) was evaluated in 30,420 volunteers of whom 0.6% ($n = 96$) had unspecified liver disease, 9.5% ($n = 2874$) had diabetes, and 6.7% ($n = 2046$) had severe obesity[113]. Considering the high risk of severe COVID-19 in patients with chronic liver and metabolic diseases, the potential benefit of the newly developed vaccines outweigh the possible risks, therefore all patients should have the recommendation to get vaccinated and in those with with chronic liver diseases they should be counseled about the potential reduction in the immune response to the vaccine and the importance of continuing with the general preventive measures even after vaccination.

CONCLUSION

MAFLD is the most common liver disease worldwide and conveys an increased risk of adverse clinical outcomes in patients with COVID-19, especially in those patients with a high-risk of liver fibrosis. All patients with COVID-19, and principally those admitted to the hospital, should be screened for the presence of steatosis and fibrosis, and efforts should be made to promptly detect patients at risk for the provision of

early treatment. Close follow-up is encouraged after discharge. New studies of the pathophysiology, diagnostic approach, and the effectiveness of the available therapy and prevention are needed, aiming to improve the overall outcome in patients with MAFLD and COVID-19.

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