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

Campos-Murguía A *et al*. Metabolic-associated fatty liver disease and 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 measures.

**Key Words:** metabolic-associated fatty liver disease; COVID-19; Mortality; Fibrosis; Histology; Epidemiology

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**Core Tip:** The coronavirus disease 2019 (COVID-19) pandemic arrives 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.

**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 mechanical ventilation availability[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 its 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 disproportionally 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 habitants 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-kB 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 proinflammatory 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 1α and 1β[36]. Obese patients with COVID-19 present a more prominent inflammatory profile than 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) andACE2[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 are 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 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 TD2M, 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.

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-CoV2 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, triglyceride 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 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-CoV2 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-CoV2. 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 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.

**REFERENCES**

1 **Huang C**, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [PMID: 31986264 DOI: 10.1016/S0140-6736(20)30183-5]

2 **Johns Hopkins Coronavirus Resource Center**. COVID-19 Map. Johns Hopkins Coronavirus Resour. Cent. 2020 [cited 15 July 2020]. Available from: https://coronavirus.jhu.edu/map.html

3 **Romagnoli S**, Peris A, De Gaudio AR, Geppetti P. SARS-CoV-2 and COVID-19: From the Bench to the Bedside. *Physiol Rev* 2020; **100**: 1455-1466 [PMID: 32496872 DOI: 10.1152/physrev.00020.2020]

4 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]

5 **Fan VS**, Dominitz JA, Eastment MC, Locke E, Green P, Berry K, O'Hare AM, Shah JA, Crothers K, Ioannou GN. Risk Factors for testing positive for SARS-CoV-2 in a national US healthcare system. *Clin Infect Dis* 2020 [PMID: 33105485 DOI: 10.1093/cid/ciaa1624]

6 **Drefahl S**, Wallace M, Mussino E, Aradhya S, Kolk M, Brandén M, Malmberg B, Andersson G. A population-based cohort study of socio-demographic risk factors for COVID-19 deaths in Sweden. *Nat Commun* 2020; **11**: 5097 [PMID: 33037218 DOI: 10.1038/s41467-020-18926-3]

7 **Garibaldi BT**, Fiksel J, Muschelli J, Robinson ML, Rouhizadeh M, Perin J, Schumock G, Nagy P, Gray JH, Malapati H, Ghobadi-Krueger M, Niessen TM, Kim BS, Hill PM, Ahmed MS, Dobkin ED, Blanding R, Abele J, Woods B, Harkness K, Thiemann DR, Bowring MG, Shah AB, Wang MC, Bandeen-Roche K, Rosen A, Zeger SL, Gupta A. Patient Trajectories Among Persons Hospitalized for COVID-19 : A Cohort Study. *Ann Intern Med* 2021; **174**: 33-41 [PMID: 32960645 DOI: 10.7326/M20-3905]

8 **Munblit D**, Nekliudov NA, Bugaeva P, Blyuss O, Kislova M, Listovskaya E, Gamirova A, Shikhaleva A, Belyaev V, Timashev P, Warner JO, Comberiati P, Apfelbacher C, Bezrukov E, Politov ME, Yavorovskiy A, Bulanova E, Tsareva N, Avdeev S, Kapustina VA, Pigolkin YI, Dankwa EA, Kartsonaki C, Pritchard MG, Fomin V, Svistunov AA, Butnaru D, Glybochko P; Sechenov StopCOVID Research Team. Stop COVID Cohort: An Observational Study of 3480 Patients Admitted to the Sechenov University Hospital Network in Moscow City for Suspected Coronavirus Disease 2019 (COVID-19) Infection. *Clin Infect Dis* 2021; **73**: 1-11 [PMID: 33035307 DOI: 10.1093/cid/ciaa1535]

9 **Ayres JS**. A metabolic handbook for the COVID-19 pandemic. *Nat Metab* 2020; **2**: 572-585 [PMID: 32694793 DOI: 10.1038/s42255-020-0237-2]

10 **Sheka AC**, Adeyi O, Thompson J, Hameed B, Crawford PA, Ikramuddin S. Nonalcoholic Steatohepatitis: A Review. *JAMA* 2020; **323**: 1175-1183 [PMID: 32207804 DOI: 10.1001/jama.2020.2298]

11 **Watt MJ**, Miotto PM, De Nardo W, Montgomery MK. The Liver as an Endocrine Organ-Linking NAFLD and Insulin Resistance. *Endocr Rev* 2019; **40**: 1367-1393 [PMID: 31098621 DOI: 10.1210/er.2019-00034]

12 **Campos-Murguía A**, Ruiz-Margáin A, González-Regueiro JA, Macías-Rodríguez RU. Clinical assessment and management of liver fibrosis in non-alcoholic fatty liver disease. *World J Gastroenterol* 2020; **26**: 5919-5943 [PMID: 33132645 DOI: 10.3748/wjg.v26.i39.5919]

13 **Younossi Z**, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 11-20 [PMID: 28930295 DOI: 10.1038/nrgastro.2017.109]

14 **Sharma P**, Kumar A. Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19. *Diabetes Metab Syndr* 2020; **14**: 825-827 [PMID: 32540736 DOI: 10.1016/j.dsx.2020.06.013]

15 **Eslam M**, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* 2020; **158**: 1999-2014.e1 [PMID: 32044314 DOI: 10.1053/j.gastro.2019.11.312]

16 **World Health Organization.** WHO Coronavirus Disease (COVID-19) Dashboard. [cited 16 January 2021]. Available from: https://covid19.who.int/?gclid=EAIaIQobChMIq56a95Gi7gIVfTizAB3n3gdHEAAYASAAEgLx3fD\_BwE

17 **Roser M,** Ritchie H, Ortiz-Ospina E. Coronavirus Disease (COVID-19)-Statistics and Research. [cited 17 January 2021]. Available from: https://www.sipotra.it/wp-content/uploads/2020/03/Coronavirus-Disease-COVID-19-–-Statistics-and-Research.pdf

18 **Leitão J**, Carvalhana S, Cochicho J, Silva AP, Velasco F, Medeiros I, Alves AC, Bourbon M, Oliveiros B, Rodrigues V, Sousa R, Sampaio F, Carvalho A, Cortez-Pinto H. Prevalence and risk factors of fatty liver in Portuguese adults. *Eur J Clin Invest* 2020; **50**: e13235 [PMID: 32289180 DOI: 10.1111/eci.13235]

19 **López-Velázquez JA**, Silva-Vidal KV, Ponciano-Rodríguez G, Chávez-Tapia NC, Arrese M, Uribe M, Méndez-Sánchez N. The prevalence of nonalcoholic fatty liver disease in the Americas. *Ann Hepatol* 2014; **13**: 166-178 [PMID: 24552858 DOI: 10.1186/1471-230X-14-42]

20 **Ye Q**, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, Yang H, Liu C, Kam LY, Tan XXE, Chien N, Trinh S, Henry L, Stave CD, Hosaka T, Cheung RC, Nguyen MH. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2020; **5**: 739-752 [PMID: 32413340 DOI: 10.1016/S2468-1253(20)30077-7]

21 **Bernal-Reyes R**, Castro-Narro G, Malé-Velázquez R, Carmona-Sánchez R, González-Huezo MS, García-Juárez I, Chávez-Tapia N, Aguilar-Salinas C, Aiza-Haddad I, Ballesteros-Amozurrutia MA, Bosques-Padilla F, Castillo-Barradas M, Chávez-Barrera JA, Cisneros-Garza L, Flores-Calderón J, García-Compeán D, Gutiérrez-Grobe Y, Higuera de la Tijera MF, Kershenobich-Stalnikowitz D, Ladrón de Guevara-Cetina L, Lizardi-Cervera J, López-Cossio JA, Martínez-Vázquez S, Márquez-Guillén E, Méndez-Sánchez N, Moreno-Alcantar R, Poo-Ramírez JL, Ramos-Martínez P, Rodríguez-Hernández H, Sánchez-Ávila JF, Stoopen-Rometti M, Torre-Delgadillo A, Torres-Villalobos G, Trejo-Estrada R, Uribe-Esquivel M, Velarde-Ruiz Velasco JA. The Mexican consensus on nonalcoholic fatty liver disease. *Rev Gastroenterol Mex (Engl Ed)* 2019; **84**: 69-99 [PMID: 30711302 DOI: 10.1016/j.rgmx.2018.11.007]

22 **Friedman SL**, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nat Med* 2018; **24**: 908-922 [PMID: 29967350 DOI: 10.1038/s41591-018-0104-9]

23 **Gao B**, Tsukamoto H. Inflammation in Alcoholic and Nonalcoholic Fatty Liver Disease: Friend or Foe? *Gastroenterology* 2016; **150**: 1704-1709 [PMID: 26826669 DOI: 10.1053/j.gastro.2016.01.025]

24 **Furman D**, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, Slavich GM. Chronic inflammation in the etiology of disease across the life span. *Nat Med* 2019; **25**: 1822-1832 [PMID: 31806905 DOI: 10.1038/s41591-019-0675-0]

25 **Shoelson SE**, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; **116**: 1793-1801 [PMID: 16823477 DOI: 10.1172/JCI29069]

26 **Dandona P**, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 2004; **25**: 4-7 [PMID: 14698276 DOI: 10.1016/j.it.2003.10.013]

27 **Al-Hamoudi W**, Alsadoon A, Hassanian M, Alkhalidi H, Abdo A, Nour M, Halwani R, Sanai F, Alsharaabi A, Alswat K, Hersi A, Albenmousa A, Alsaif F. Endothelial dysfunction in nonalcoholic steatohepatitis with low cardiac disease risk. *Sci Rep* 2020; **10**: 8825 [PMID: 32483260 DOI: 10.1038/s41598-020-65835-y]

28 **Villanova N**, Moscatiello S, Ramilli S, Bugianesi E, Magalotti D, Vanni E, Zoli M, Marchesini G. Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. *Hepatology* 2005; **42**: 473-480 [PMID: 15981216 DOI: 10.1002/hep.20781]

29 **Francque SM**, van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. *J Hepatol* 2016; **65**: 425-443 [PMID: 27091791 DOI: 10.1016/j.jhep.2016.04.005]

30 **Monteiro R**, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm* 2010; **2010** [PMID: 20706689 DOI: 10.1155/2010/289645]

31 **Hotamisligil GS**, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. *J Clin Invest* 1995; **95**: 2409-2415 [PMID: 7738205 DOI: 10.1172/JCI117936]

32 **Cai D**, Yuan M, Frantz DF, Melendez PA, Hansen L, Lee J, Shoelson SE. Local and systemic insulin resistance resulting from hepatic activation of IKK-beta and NF-kappaB. *Nat Med* 2005; **11**: 183-190 [PMID: 15685173 DOI: 10.1038/nm1166]

33 **Haukeland JW**, Damås JK, Konopski Z, Løberg EM, Haaland T, Goverud I, Torjesen PA, Birkeland K, Bjøro K, Aukrust P. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J Hepatol* 2006; **44**: 1167-1174 [PMID: 16618517 DOI: 10.1016/j.jhep.2006.02.011]

34 **Tarantino G**, Colicchio P, Conca P, Finelli C, Di Minno MN, Tarantino M, Capone D, Pasanisi F. Young adult obese subjects with and without insulin resistance: what is the role of chronic inflammation and how to weigh it non-invasively? *J Inflamm (Lond)* 2009; **6**: 6 [PMID: 19291292 DOI: 10.1186/1476-9255-6-6]

35 **Clària J**, Stauber RE, Coenraad MJ, Moreau R, Jalan R, Pavesi M, Amorós À, Titos E, Alcaraz-Quiles J, Oettl K, Morales-Ruiz M, Angeli P, Domenicali M, Alessandria C, Gerbes A, Wendon J, Nevens F, Trebicka J, Laleman W, Saliba F, Welzel TM, Albillos A, Gustot T, Benten D, Durand F, Ginès P, Bernardi M, Arroyo V; CANONIC Study Investigators of the EASL-CLIF Consortium and the European Foundation for the Study of Chronic Liver Failure (EF-CLIF). Systemic inflammation in decompensated cirrhosis: Characterization and role in acute-on-chronic liver failure. *Hepatology* 2016; **64**: 1249-1264 [PMID: 27483394 DOI: 10.1002/hep.28740]

36 **Fajgenbaum DC**, June CH. Cytokine Storm. *N Engl J Med* 2020; **383**: 2255-2273 [PMID: 33264547 DOI: 10.1056/NEJMra2026131]

37 **Kalfaoglu B**, Almeida-Santos J, Tye CA, Satou Y, Ono M. T-cell dysregulation in COVID-19. *Biochem Biophys Res Commun* 2021; **538**: 204-210 [PMID: 33220925 DOI: 10.1016/j.bbrc.2020.10.079]

38 **Mehta P**, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**: 1033-1034 [PMID: 32192578 DOI: 10.1016/S0140-6736(20)30628-0]

39 **Tay MZ**, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; **20**: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]

40 **Macías-Rodríguez RU**, Inzaugarat ME, Ruiz-Margáin A, Nelson LJ, Trautwein C, Cubero FJ. Reclassifying Hepatic Cell Death during Liver Damage: Ferroptosis-A Novel Form of Non-Apoptotic Cell Death? *Int J Mol Sci* 2020; **21** [PMID: 32121273 DOI: 10.3390/ijms21051651]

41 **McNeill JN**, Lau ES, Paniagua SM, Liu EE, Wang JK, Bassett IV, Selvaggi CA, Lubitz SA, Foulkes AS, Ho JE. The role of obesity in inflammatory markers in COVID-19 patients. *Obes Res Clin Pract* 2021; **15**: 96-99 [PMID: 33390322 DOI: 10.1016/j.orcp.2020.12.004]

42 **Sharun K**, Tiwari R, Dhama J, Dhama K. Dexamethasone to combat cytokine storm in COVID-19: Clinical trials and preliminary evidence. *Int J Surg* 2020; **82**: 179-181 [PMID: 32896649 DOI: 10.1016/j.ijsu.2020.08.038]

43 **Forlano R,** Mullish BH, Nathwani R, Dhar A, Thursz MR, Manousou P. Non-Alcoholic Fatty Liver Disease and Vascular Disease. *Curr* *Vascul Pharmacol* 2021; **19**: 269 [PMID: 32188385 DOI: 10.2174/1570161118666200318103001]

44 **Pons S**, Fodil S, Azoulay E, Zafrani L. The vascular endothelium: the cornerstone of organ dysfunction in severe SARS-CoV-2 infection. *Crit Care* 2020; **24**: 353 [PMID: 32546188 DOI: 10.1186/s13054-020-03062-7]

45 **Jin Y**, Ji W, Yang H, Chen S, Zhang W, Duan G. Endothelial activation and dysfunction in COVID-19: from basic mechanisms to potential therapeutic approaches. *Signal Transduct Target Ther* 2020; **5**: 293 [PMID: 33361764 DOI: 10.1038/s41392-020-00454-7]

46 **Ji D**, Zhang M, Qin E, Zhang L, Xu J, Wang Y, Cheng G, Wang F, Lau G. Letter to the Editor: Obesity, diabetes, non-alcoholic fatty liver disease and metabolic dysfunction associated fatty liver disease are proinflammatory hypercoagulable states associated with severe disease and thrombosis in Covid-19. *Metabolism* 2021; **115**: 154437 [PMID: 33220249 DOI: 10.1016/j.metabol.2020.154437]

47 **Bataller R**, Sancho-Bru P, Ginès P, Lora JM, Al-Garawi A, Solé M, Colmenero J, Nicolás JM, Jiménez W, Weich N, Gutiérrez-Ramos JC, Arroyo V, Rodés J. Activated human hepatic stellate cells express the renin-angiotensin system and synthesize angiotensin II. *Gastroenterology* 2003; **125**: 117-125 [PMID: 12851877 DOI: 10.1016/S0016-5085(03)00695-4]

48 **Di Pascoli M**, La Mura V. Renin-angiotensin-aldosterone system in cirrhosis: There's room to try! *Dig Liver Dis* 2019; **51**: 297-298 [PMID: 30220630 DOI: 10.1016/j.dld.2018.07.038]

49 **Fondevila MF**, Mercado-Gómez M, Rodríguez A, Gonzalez-Rellan MJ, Iruzubieta P, Valentí V, Escalada J, Schwaninger M, Prevot V, Dieguez C, Crespo J, Frühbeck G, Martinez-Chantar ML, Nogueiras R. Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points. *J Hepatol* 2021; **74**: 469-471 [PMID: 33096086 DOI: 10.1016/j.jhep.2020.09.027]

50 **Yang J**, Petitjean SJL, Koehler M, Zhang Q, Dumitru AC, Chen W, Derclaye S, Vincent SP, Soumillion P, Alsteens D. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun* 2020; **11**: 4541 [PMID: 32917884 DOI: 10.1038/s41467-020-18319-6]

51 **Centers for Disease Control and Prevention**. Science Brief: Evidence used to update the list of underlying medical conditions that increase a person’s risk of severe illness from COVID-19. [cited 17 January 2021]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html

52 **Ji D**, Qin E, Xu J, Zhang D, Cheng G, Wang Y, Lau G. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. *J Hepatol* 2020; **73**: 451-453 [PMID: 32278005 DOI: 10.1016/j.jhep.2020.03.044]

53 **Targher G**, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, Pan KH, Zheng KI, Chen YP, Eslam M, George J, Zheng MH. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. *Gut* 2020; **69**: 1545-1547 [PMID: 32414813 DOI: 10.1136/gutjnl-2020-321611]

54 **Flegal KM**, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA* 2013; **309**: 71-82 [PMID: 23280227 DOI: 10.1001/jama.2012.113905]

55 **Lighter J**, Phillips M, Hochman S, Sterling S, Johnson D, Francois F, Stachel A. Obesity in Patients Younger Than 60 Years Is a Risk Factor for COVID-19 Hospital Admission. *Clin Infect Dis* 2020; **71**: 896-897 [PMID: 32271368 DOI: 10.1093/cid/ciaa415]

56 **Frank RC**, Mendez SR, Stevenson EK, Guseh JS, Chung M, Silverman MG. Obesity and the Risk of Intubation or Death in Patients With Coronavirus Disease 2019. *Crit Care Med* 2020; **48**: e1097-e1101 [PMID: 33045152 DOI: 10.1097/CCM.0000000000004553]

57 **Hur K**, Price CPE, Gray EL, Gulati RK, Maksimoski M, Racette SD, Schneider AL, Khanwalkar AR. Factors Associated With Intubation and Prolonged Intubation in Hospitalized Patients With COVID-19. *Otolaryngol Head Neck Surg* 2020; **163**: 170-178 [PMID: 32423368 DOI: 10.1177/0194599820929640]

58 **Simonnet A**, Chetboun M, Poissy J, Raverdy V, Noulette J, Duhamel A, Labreuche J, Mathieu D, Pattou F, Jourdain M; LICORN and the Lille COVID-19 and Obesity study group. High Prevalence of Obesity in Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) Requiring Invasive Mechanical Ventilation. *Obesity (Silver Spring)* 2020; **28**: 1195-1199 [PMID: 32271993 DOI: 10.1002/oby.22831]

59 **Kalligeros M**, Shehadeh F, Mylona EK, Benitez G, Beckwith CG, Chan PA, Mylonakis E. Association of Obesity with Disease Severity Among Patients with Coronavirus Disease 2019. *Obesity (Silver Spring)* 2020; **28**: 1200-1204 [PMID: 32352637 DOI: 10.1002/oby.22859]

60 **Palaiodimos L**, Kokkinidis DG, Li W, Karamanis D, Ognibene J, Arora S, Southern WN, Mantzoros CS. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metabolism* 2020; **108**: 154262 [PMID: 32422233 DOI: 10.1016/j.metabol.2020.154262]

61 **Gao F**, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Chen YP, Targher G, Byrne CD, George J, Zheng MH. Obesity Is a Risk Factor for Greater COVID-19 Severity. *Diabetes Care* 2020; **43**: e72-e74 [PMID: 32409499 DOI: 10.2337/dc20-0682]

62 **Battisti S**, Pedone C, Napoli N, Russo E, Agnoletti V, Nigra SG, Dengo C, Mughetti M, Conte C, Pozzilli P, Giampalma E, Strollo R. Computed Tomography Highlights Increased Visceral Adiposity Associated With Critical Illness in COVID-19. *Diabetes Care* 2020; **43**: e129-e130 [PMID: 32753457 DOI: 10.2337/dc20-1333]

63 **GBD 2017 Causes of Death Collaborators.**. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392**: 1736-1788 [PMID: 30496103 DOI: 10.1016/S0140-6736(18)32203-7]

64 **Richardson S**, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA* 2020; **323**: 2052-2059 [PMID: 32320003 DOI: 10.1001/jama.2020.6775]

65 **Zhu L**, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, Lei F, Wang H, Xie J, Wang W, Li H, Zhang P, Song X, Chen X, Xiang M, Zhang C, Bai L, Xiang D, Chen MM, Liu Y, Yan Y, Liu M, Mao W, Zou J, Liu L, Chen G, Luo P, Xiao B, Zhang C, Zhang Z, Lu Z, Wang J, Lu H, Xia X, Wang D, Liao X, Peng G, Ye P, Yang J, Yuan Y, Huang X, Guo J, Zhang BH, Li H. Association of Blood Glucose Control and Outcomes in Patients with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab* 2020; **31**: 1068-1077.e3 [PMID: 32369736 DOI: 10.1016/j.cmet.2020.04.021]

66 **Bode B**, Garrett V, Messler J, McFarland R, Crowe J, Booth R, Klonoff DC. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. *J Diabetes Sci Technol* 2020; **14**: 813-821 [PMID: 32389027 DOI: 10.1177/1932296820924469]

67 **Chen Y**, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y, Zheng L, Huang K. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care* 2020; **43**: 1399-1407 [PMID: 32409498 DOI: 10.2337/dc20-0660]

68 **Fadini GP**, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest* 2020; **43**: 867-869 [PMID: 32222956 DOI: 10.1007/s40618-020-01236-2]

69 **Barron E**, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N, Wareham NJ, Young B, Valabhji J. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; **8**: 813-822 [PMID: 32798472 DOI: 10.1016/S2213-8587(20)30272-2]

70 **Holman N**, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diabetes Endocrinol* 2020; **8**: 823-833 [PMID: 32798471 DOI: 10.1016/S2213-8587(20)30271-0]

71 **Agarwal S**, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission Diabetes-Specific Risk Factors for Mortality in Hospitalized Patients With Diabetes and Coronavirus Disease 2019. *Diabetes Care* 2020; **43**: 2339-2344 [PMID: 32769128 DOI: 10.2337/dc20-1543]

72 **Andersen CJ**, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity. *Adv Nutr* 2016; **7**: 66-75 [PMID: 26773015 DOI: 10.3945/an.115.010207]

73 **Dhurandhar NV**, Bailey D, Thomas D. Interaction of obesity and infections. *Obes Rev* 2015; **16**: 1017-1029 [PMID: 26354800 DOI: 10.1111/obr.12320]

74 **Kang Z**, Luo S, Gui Y, Zhou H, Zhang Z, Tian C, Zhou Q, Wang Q, Hu Y, Fan H, Hu D. Obesity is a potential risk factor contributing to clinical manifestations of COVID-19. *Int J Obes (Lond)* 2020; **44**: 2479-2485 [PMID: 32921796 DOI: 10.1038/s41366-020-00677-2]

75 **Bramante C**, Tignanelli CJ, Dutta N, Jones E, Tamariz L, Clark JM, Usher M, Metlon-Meaux G, Ikramuddin S. Non-alcoholic fatty liver disease (NAFLD) and risk of hospitalization for Covid-19. *medRxiv* 2020 [PMID: 32909011 DOI: 10.1101/2020.09.01.20185850]

76 **Lopez-Mendez I**, Aquino-Matus J, Gall SM, Prieto-Nava JD, Juarez-Hernandez E, Uribe M, Castro-Narro G. Association of liver steatosis and fibrosis with clinical outcomes in patients with SARS-CoV-2 infection (COVID-19). *Ann Hepatol* 2021; **20**: 100271 [PMID: 33099028 DOI: 10.1016/j.aohep.2020.09.015]

77 **Forlano R**, Mullish BH, Mukherjee SK, Nathwani R, Harlow C, Crook P, Judge R, Soubieres A, Middleton P, Daunt A, Perez-Guzman P, Selvapatt N, Lemoine M, Dhar A, Thursz MR, Nayagam S, Manousou P. In-hospital mortality is associated with inflammatory response in NAFLD patients admitted for COVID-19. *PLoS One* 2020; **15**: e0240400 [PMID: 33031439 DOI: 10.1371/journal.pone.0240400]

78 **Mushtaq K**, Khan MU, Iqbal F, Alsoub DH, Chaudhry HS, Ata F, Iqbal P, Elfert K, Balaraju G, Almaslamani M, Al-Ejji K, AlKaabi S, Kamel YM. NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression - The debate continues. *J Hepatol* 2021; **74**: 482-484 [PMID: 33223215 DOI: 10.1016/j.jhep.2020.09.006]

79 **Targher G**, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QF, Pan KH, Zheng KI, Chen YP, Eslam M, George J, Zheng MH. Detrimental effects of metabolic dysfunction-associated fatty liver disease and increased neutrophil-to-lymphocyte ratio on severity of COVID-19. *Diabetes Metab* 2020; **46**: 505-507 [PMID: 32505652 DOI: 10.1016/j.diabet.2020.06.001]

80 **Sachdeva S**, Khandait H, Kopel J, Aloysius MM, Desai R, Goyal H. NAFLD and COVID-19: a Pooled Analysis. *SN Compr Clin Med* 2020: 1-4 [PMID: 33173850 DOI: 10.1007/s42399-020-00631-3]

81 **Hashemi N**, Viveiros K, Redd WD, Zhou JC, McCarty TR, Bazarbashi AN, Hathorn KE, Wong D, Njie C, Shen L, Chan WW. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: A multicentre United States experience. *Liver Int* 2020; **40**: 2515-2521 [PMID: 32585065 DOI: 10.1111/liv.14583]

82 **Gao F**, Zheng KI, Wang XB, Yan HD, Sun QF, Pan KH, Wang TY, Chen YP, George J, Zheng MH. Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in nondiabetic patients. *J Gastroenterol Hepatol* 2021; **36**: 204-207 [PMID: 32436622 DOI: 10.1111/jgh.15112]

83 **Huang R**, Zhu L, Wang J, Xue L, Liu L, Yan X, Huang S, Li Y, Yan X, Zhang B, Xu T, Li C, Ji F, Ming F, Zhao Y, Cheng J, Wang Y, Zhao H, Hong S, Chen K, Zhao XA, Zou L, Sang D, Shao H, Guan X, Chen X, Chen Y, Wei J, Zhu C, Wu C. Clinical features of COVID-19 patients with non-alcoholic fatty liver disease. *Hepatol Commun* 2020 [PMID: 32838108 DOI: 10.1002/hep4.1592]

84 **Mahamid M**, Nseir W, Khoury T, Mahamid B, Nubania A, Sub-Laban K, Schifter J, Mari A, Sbeit W, Goldin E. Nonalcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study. *Eur J Gastroenterol Hepatol* 2020 [PMID: 32868652 DOI: 10.1097/MEG.0000000000001902]

85 **Zhou YJ**, Zheng KI, Wang XB, Yan HD, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Younger patients with MAFLD are at increased risk of severe COVID-19 illness: A multicenter preliminary analysis. *J Hepatol* 2020; **73**: 719-721 [PMID: 32348790 DOI: 10.1016/j.jhep.2020.04.027]

86 **Chen VL**, Hawa F, Berinstein JA, Reddy CA, Kassab I, Platt KD, Hsu CY, Steiner CA, Louissaint J, Gunaratnam NT, Sharma P. Hepatic Steatosis Is Associated with Increased Disease Severity and Liver Injury in Coronavirus Disease-19. *Dig Dis Sci* 2020 [PMID: 32980956 DOI: 10.1007/s10620-020-06618-3]

87 **Zhou YJ**, Zheng KI, Wang XB, Sun QF, Pan KH, Wang TY, Ma HL, Chen YP, George J, Zheng MH. Metabolic-associated fatty liver disease is associated with severity of COVID-19. *Liver Int* 2020; **40**: 2160-2163 [PMID: 32573883 DOI: 10.1111/liv.14575]

88 **Pan L**, Huang P, Xie X, Xu J, Guo D, Jiang Y. Metabolic associated fatty liver disease increases the severity of COVID-19: A meta-analysis. *Dig Liver Dis* 2021; **53**: 153-157 [PMID: 33011088 DOI: 10.1016/j.dld.2020.09.007]

89 **Sonzogni A**, Previtali G, Seghezzi M, Grazia Alessio M, Gianatti A, Licini L, Morotti D, Zerbi P, Carsana L, Rossi R, Lauri E, Pellegrinelli A, Nebuloni M. Liver histopathology in severe COVID 19 respiratory failure is suggestive of vascular alterations. *Liver Int* 2020; **40**: 2110-2116 [PMID: 32654359 DOI: 10.1111/liv.14601]

90 **Lagana SM**, Kudose S, Iuga AC, Lee MJ, Fazlollahi L, Remotti HE, Del Portillo A, De Michele S, de Gonzalez AK, Saqi A, Khairallah P, Chong AM, Park H, Uhlemann AC, Lefkowitch JH, Verna EC. Hepatic pathology in patients dying of COVID-19: a series of 40 cases including clinical, histologic, and virologic data. *Mod Pathol* 2020; **33**: 2147-2155 [PMID: 32792598 DOI: 10.1038/s41379-020-00649-x]

91 **Bradley BT**, Maioli H, Johnston R, Chaudhry I, Fink SL, Xu H, Najafian B, Deutsch G, Lacy JM, Williams T, Yarid N, Marshall DA. Histopathology and ultrastructural findings of fatal COVID-19 infections in Washington State: a case series. *Lancet* 2020; **396**: 320-332 [PMID: 32682491 DOI: 10.1016/S0140-6736(20)31305-2]

92 **Falasca L**, Nardacci R, Colombo D, Lalle E, Di Caro A, Nicastri E, Antinori A, Petrosillo N, Marchioni L, Biava G, D'Offizi G, Palmieri F, Goletti D, Zumla A, Ippolito G, Piacentini M, Del Nonno F. Postmortem Findings in Italian Patients With COVID-19: A Descriptive Full Autopsy Study of Cases With and Without Comorbidities. *J Infect Dis* 2020; **222**: 1807-1815 [PMID: 32914853 DOI: 10.1093/infdis/jiaa578]

93 **Browning JD**, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; **40**: 1387-1395 [PMID: 15565570 DOI: 10.1002/hep.20466]

94 **Suzuki T**, Shinjo S, Arai T, Kanai M, Goda N. Hypoxia and fatty liver. *World J Gastroenterol* 2014; **20**: 15087-15097 [PMID: 25386057 DOI: 10.3748/wjg.v20.i41.15087]

95 **Rankin EB**, Rha J, Selak MA, Unger TL, Keith B, Liu Q, Haase VH. Hypoxia-inducible factor 2 regulates hepatic lipid metabolism. *Mol Cell Biol* 2009; **29**: 4527-4538 [PMID: 19528226 DOI: 10.1128/MCB.00200-09]

96 **National Institute of Diabetes and Digestive and Kidney Diseases**. Corticosteroids. 2012. Available from: https://www.niddk.nih.gov/

97 **Negro F**. Mechanisms and significance of liver steatosis in hepatitis C virus infection. *World J Gastroenterol* 2006; **12**: 6756-6765 [PMID: 17106922 DOI: 10.3748/wjg.v12.i42.6756]

98 **Portincasa P**, Krawczyk M, Smyk W, Lammert F, Di Ciaula A. COVID-19 and non-alcoholic fatty liver disease: Two intersecting pandemics. *Eur J Clin Invest* 2020; **50**: e13338 [PMID: 32589264 DOI: 10.1111/eci.13338]

99 **Wong GL**, Wong VW, Thompson A, Jia J, Hou J, Lesmana CRA, Susilo A, Tanaka Y, Chan WK, Gane E, Ong-Go AK, Lim SG, Ahn SH, Yu ML, Piratvisuth T, Chan HL; Asia-Pacific Working Group for Liver Derangement during the COVID-19 Pandemic. Management of patients with liver derangement during the COVID-19 pandemic: an Asia-Pacific position statement. *Lancet Gastroenterol Hepatol* 2020; **5**: 776-787 [PMID: 32585136 DOI: 10.1016/S2468-1253(20)30190-4]

100 **Ibáñez-Samaniego L**, Bighelli F, Usón C, Caravaca C, Fernández Carrillo C, Romero M, Barreales M, Perelló C, Madejón A, Marcos AC, Albillos A, Fernández I, García-Samaniego J, Calleja JL, Bañares R. Elevation of Liver Fibrosis Index FIB-4 Is Associated With Poor Clinical Outcomes in Patients With COVID-19. *J Infect Dis* 2020; **222**: 726-733 [PMID: 32563190 DOI: 10.1093/infdis/jiaa355]

101 **Eslam M**, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, Zelber-Sagi S, Wai-Sun Wong V, Dufour JF, Schattenberg JM, Kawaguchi T, Arrese M, Valenti L, Shiha G, Tiribelli C, Yki-Järvinen H, Fan JG, Grønbæk H, Yilmaz Y, Cortez-Pinto H, Oliveira CP, Bedossa P, Adams LA, Zheng MH, Fouad Y, Chan WK, Mendez-Sanchez N, Ahn SH, Castera L, Bugianesi E, Ratziu V, George J. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *J Hepatol* 2020; **73**: 202-209 [PMID: 32278004 DOI: 10.1016/j.jhep.2020.03.039]

102 **Xu B**, Xing Y, Peng J, Zheng Z, Tang W, Sun Y, Xu C, Peng F. Chest CT for detecting COVID-19: a systematic review and meta-analysis of diagnostic accuracy. *Eur Radiol* 2020; **30**: 5720-5727 [PMID: 32415585 DOI: 10.1007/s00330-020-06934-2]

103 **Wells MM**, Li Z, Addeman B, McKenzie CA, Mujoomdar A, Beaton M, Bird J. Computed Tomography Measurement of Hepatic Steatosis: Prevalence of Hepatic Steatosis in a Canadian Population. *Can J Gastroenterol Hepatol* 2016; **2016**: 4930987 [PMID: 27446844 DOI: 10.1155/2016/4930987]

104 **Kotronen A**, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, Lundbom N, Rissanen A, Ridderstråle M, Groop L, Orho-Melander M, Yki-Järvinen H. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. *Gastroenterology* 2009; **137**: 865-872 [PMID: 19524579 DOI: 10.1053/j.gastro.2009.06.005]

105 **Long MT**, Pedley A, Colantonio LD, Massaro JM, Hoffmann U, Muntner P, Fox CS. Development and Validation of the Framingham Steatosis Index to Identify Persons With Hepatic Steatosis. *Clin Gastroenterol Hepatol* 2016; **14**: 1172-1180.e2 [PMID: 27046482 DOI: 10.1016/j.cgh.2016.03.034]

106 **McHenry S**, Park Y, Browning JD, Sayuk G, Davidson NO. Dallas Steatosis Index Identifies Patients With Nonalcoholic Fatty Liver Disease. *Clin Gastroenterol Hepatol* 2020; **18**: 2073-2080.e7 [PMID: 31982611 DOI: 10.1016/j.cgh.2020.01.020]

107 **Kulkarni AV**, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, Talukdar R, Sharma M, Qi X, Rao PN, Reddy DN. Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. *Aliment Pharmacol Ther* 2020; **52**: 584-599 [PMID: 32638436 DOI: 10.1111/apt.15916]

108 **Effenberger M**, Grander C, Fritsche G, Bellmann-Weiler R, Hartig F, Wildner S, Seiwald S, Adolph TE, Zoller H, Weiss G, Tilg H. Liver stiffness by transient elastography accompanies illness severity in COVID-19. *BMJ Open Gastroenterol* 2020; **7** [PMID: 32665398 DOI: 10.1136/bmjgast-2020-000445]

109 **Centers for Disease Control and Prevention**. Certain Medical Conditions and Risk for Severe COVID-19 Illness. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

110 **Marjot T**, Webb GJ, Barritt AS, Ginès P, Lohse AW, Moon AM, Pose E, Trivedi P, Barnes E. SARS-CoV-2 vaccination in patients with liver disease: responding to the next big question. *Lancet Gastroenterol Hepatol* 2021; **6**: 156-158 [PMID: 33444545 DOI: 10.1016/S2468-1253(21)00008-X]

111 **Polack FP**, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**: 2603-2615 [PMID: 33301246 DOI: 10.1056/NEJMoa2034577]

112 **Voysey M**, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, Angus B, Baillie VL, Barnabas SL, Bhorat QE, Bibi S, Briner C, Cicconi P, Collins AM, Colin-Jones R, Cutland CL, Darton TC, Dheda K, Duncan CJA, Emary KRW, Ewer KJ, Fairlie L, Faust SN, Feng S, Ferreira DM, Finn A, Goodman AL, Green CM, Green CA, Heath PT, Hill C, Hill H, Hirsch I, Hodgson SHC, Izu A, Jackson S, Jenkin D, Joe CCD, Kerridge S, Koen A, Kwatra G, Lazarus R, Lawrie AM, Lelliott A, Libri V, Lillie PJ, Mallory R, Mendes AVA, Milan EP, Minassian AM, McGregor A, Morrison H, Mujadidi YF, Nana A, O'Reilly PJ, Padayachee SD, Pittella A, Plested E, Pollock KM, Ramasamy MN, Rhead S, Schwarzbold AV, Singh N, Smith A, Song R, Snape MD, Sprinz E, Sutherland RK, Tarrant R, Thomson EC, Török ME, Toshner M, Turner DPJ, Vekemans J, Villafana TL, Watson MEE, Williams CJ, Douglas AD, Hill AVS, Lambe T, Gilbert SC, Pollard AJ; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; **397**: 99-111 [PMID: 33306989 DOI: 10.1016/S0140-6736(20)32661-1]

113 **Baden LR**, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021; **384**: 403-416 [PMID: 33378609 DOI: 10.1056/NEJMoa2035389]

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**Figure Legends**

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**Figure 1 Total coronavirus disease 2019 cases and nonalcoholic fatty liver disease prevalence.** United States of America 25,439,570, India 10,689,527, Brazil 8,933,356, Russia 3,716,228, United Kingdom 3,700,268, France 3,138,498, Spain 2,629,817, Italy 2,485,956, Turkey 2,442,350, Germany 2,164,043.

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**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.

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**Figure 3 Number of deaths from coronavirus disease 2019 per 100,000 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.

**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 *et al*[61] | Cohort*n =* 130 ptsChina | 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 *et al*[52] | Cohort *n =* 202 ptsChina | 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 *et al*[53] | Cohort*n =* 310 ptsChina | 94/216 | Hepatic steatosis by CT and MAFLD consensus criteria | FIB-4NFS | 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 *et al*[83] | Cohort*n =* 280 ptsChina | 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 *et al*[84] | Case control*n =* 71 ptsIsrael | 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 *et al*[85] | Cohort *n =* 327 ptsChina | 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 *et al*[86] | Cohort *n =* 342 ptsUnited 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 *et al*[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 *et al*[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, *I2* = 38.8%, *P =* 0.1799). Increased risk of severe COVID-19 (OR 2.93, 95%CI: 1.87-4.60, *I2* = 34.3%, *P =* 0.166) |
| Bramante *et al*[75] | Cohort*n =* 6700 ptsUnited States | 373 | ICD codes for NAFLD or NASH or BMI ≥ 30 kg/m2 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 *et al*[76] | Cross sectional*n =* 155 ptsMexico | 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 *et al*[77] | Cohort*n =* 193 ptsUnited 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 fibrosis) |
| Mushtaq *et al*[78] | Cross sectional | 320/269 | HSI > 36 points | N/A | Mortality, COVID-19 severity, COVID-19 progression and liver injury | MAFLD: Increased risk of mild (OR 2.99, 95%CI: 1.62-4.37, *P =* 0.000) and moderate (OR 5.104, 95%CI: 3.21-6.99, *P =* 0.000) liver injury. No difference in disease severity, progression or mortality |
| Targher *et al*[79] | Cohort*n =* 589 ptsQatar | 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, *P =* 0.053), non-MAFLD+NLR > 2.8 (OR 17.7, 95%CI: 3.89-80.6, *P <* 0.001), MAFLD+NLR>2.8 (OR 25.9, 95%CI: 5.32-127, *P <* 0.001) compared to those with non-MAFLD+NLR≤2.8. Patients with MAFLD and high NLR values have increased risk of severe COVID-19  |
| Ji *et al*[46] | Cohort*n =* 200 ptsChina | 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 μg/mL, *P =* 0.003) and peak levels (1.81 *vs* 0.63 μg/mL, *P =* 0.003) |
| Ji *et al*[46] | Cohort*n =* 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%, *P =* 0.01) |
| Sachdeva *et al*[80] | Systematic review and meta-analysis*n =* 8142 pts8 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, *P <* 0.001) |
| Hashemi *et al*[81] | Cohort*n =* 363 ptsUnited 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, *P =* 0.03) and need of mechanical ventilation (OR 2.15, 95%CI: 1.18-3.91, *P =* 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.**Table 2 Histological findings from liver biopsies of coronavirus disease 2019 patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Inclusion criteria** | **Population characteristics *n* (%)** | **Histopathological results** |
| Sonzogni *et al*[89] | Postmortem SARS-CoV-2- positive patients.(*n =* 48)1 Male/Female (*n*): 35/131Age (yr): 71 (32-86) | No comorbidities: 6 (13.3) Hypertension 24 (53.3) Cardiovascular Disease (different than hypertension) 17 (37.8) Diabetes13 (28.9) Obesity 7 (15.6) Kidney disease10 (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 *et al*[90] |  Patients who died from illness related to COVID-19.(*n =* 40)1Male/Female (*n*): 28/121Age (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 *et al*[91] | Patients with a positive antemortem or post- mortem SARS-CoV-2.(*n =* 14)1Male/Female: 6/81Age (yr): 73.5 (42-84) | - | Periportal lymphocytic inflammation | 2 (14%) |
| Centrilobular necrosis | 4 (28%) |
| Steatosis | 9 (64%) |
| Congestion | 11 (78%) |
| Falasca *et al*[92] | Postmortem SARS-CoV-2- positive patients.(*n =* 22)1Male/Female: 15/71Age (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.