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Coronavirus disease 2019 and non-alcoholic fatty liver disease

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic may present with a broad range of clinical manifestations, from no or mild symptoms to severe disease. Patients with specific pre-existing comorbidities, such as obesity and type 2 diabetes, are at high risk of coming out with a critical form of COVID-19. Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, and, because of its frequent association with metabolic alterations including obesity and type 2 diabetes, it has recently been re-named as metabolic-associated fatty liver disease (MAFLD). Several studies and systematic reviews pointed out the increased risk of severe COVID-19 in NAFLD/MAFLD patients. Even though dedicated mechanistic studies are missing, this higher probability may be justified by systemic low-grade chronic inflammation associated with immune dysregulation in NAFLD/MAFLD, which could trigger cytokine storm and hypercoagulable state after severe acute respiratory syndrome coronavirus 2 infection. This review focuses on the predisposing role of NAFLD/MAFLD in favoring severe COVID-19, discussing the available information on specific risk factors, clinical features, outcomes, and pathogenetic mechanisms.

Key Words: Non-alcoholic fatty liver disease; Metabolic-associated fatty liver disease; COVID-19; SARS-CoV-2; Liver injury; Immune dysregulation

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Core Tip: Non-alcoholic fatty liver disease is the most widespread hepatic disorder. Recently re-named as metabolic-associated fatty liver disease, it has been lately pointed out as a predisposing factor for severe coronavirus disease 2019 (COVID-19). We herein discuss the epidemiology and possible underlying pathways predisposing severe COVID-19 in non-alcoholic fatty liver disease/metabolic-associated fatty liver disease patients.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) was declared as a global pandemic by the World Health Organization (WHO) on March 11, 2020[1]. Indeed, after the first diagnosis of COVID-19 case in Wuhan (China) in December 2019, the virus spread quickly, affecting 220 countries and territories[2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative virus of COVID-19, whose most likely origin is natural selection in an animal host followed by zoonotic transfer[3]. Features of SARS-CoV-2 infectivity and transmissibility, as well as multiple clinical presentations of COVID-19, represent burning research topics, especially with the alarming rise of new variants. Severe COVID-19 most frequently presents with acute respiratory failure, even though several non-respiratory manifestations may characterize both the acute phase of the disease and the post-COVID syndrome (or long COVID)[4].

COVID-19 patients may show hepatic injury – largely characterized by a mild increase in serum aminotransferase levels – or may experience worsening of a pre-existing liver disease[5]. Most patients presenting with moderate-severe COVID-19 are old and/or affected by metabolic comorbidities, such as diabetes mellitus and obesity [6]. These conditions are also strongly associated with unrecognized underlying liver disease, mostly non-alcoholic fatty liver disease (NAFLD)[7,8]. Affecting almost 1 billion people, NAFLD is considered as the most common chronic liver disease all over the world, and its prevalence is estimated to become higher together with the epidemics of type 2 diabetes and obesity[9]. Recent international consensus panel proposed to rename NAFLD to metabolic-associated fatty liver disease (MAFLD), giving importance to the underlying systemic metabolic dysfunction rather than alcohol abstinence[10]. Of interest, NAFLD/MAFLD patients are more likely to develop liver damage when infected by SARS-CoV-2[11].

To date, the available reviews on this topic focused on the impact of COVID-19 infection on NAFLD/MAFLD worsening and progression. The present review aims to consider the ongoing relationship between COVID-19 and NAFLD/MAFLD, targeting the predisposing role of NAFLD/MAFLD in favoring severe COVID-19. The available information since the beginning of pandemic, specific risk factors, clinical features, outcomes, and pathogenetic mechanisms will be analyzed and discussed.

EPIDEMIOLOGY

Epidemiology of NAFLD/MAFLD

NAFLD/MAFLD is characterized by steatosis in > 5% of liver parenchyma, in association with metabolic alterations (mostly type 2 diabetes and obesity), without any chronic liver disease, and with ethanol intake not exceeding 30 g/d for men and 20 g/d for women[12]. In the histological spectrum of NAFLD/MAFLD, steatosis may be accompanied by mild inflammation (non-alcoholic fatty liver) or necro-inflammation with hepatocyte ballooning (non-alcoholic steatohepatitis, NASH)[13].

Being the most widespread chronic liver disease worldwide, NAFLD/MAFLD prevalence ranges from 13.5% in Africa to 31.8% in the Middle East, consistent with differences in genetic predisposition, caloric intake, physical activity, body fat distribution, and socio-economic status[14]. In the general population, NAFLD/MAFLD prevalence increases with age, and it is higher in men than women (particularly in the pre-menopausal period)[15,16]. NAFLD/MAFLD is diagnosed in 47.3%-63.7% of type 2 diabetes patients and up to 80% of obese people[17,18]. Type 2 diabetes is rising worldwide, affecting more than 400 million people and representing the ninth main cause of death[19]. Even though type 2 diabetes is closely related to obesity, its significance in NAFLD is two-fold. Indeed, other than a high prevalence of NAFLD in these patients, type 2 diabetes accelerates NAFLD progression and is a predictor of advanced fibrosis and mortality[20]. Similar to type 2 diabetes, obesity prevalence has doubled in the last 40 years, so that approximately a third of the population can be classified as overweight or obese[21]. Even though its prevalence is higher in older

people, obesity rates increased in all ages and both sexes, regardless of country, ethnicity, or socioeconomic status[21].

Epidemiology of COVID-19

COVID-19 has been declared as a global pandemic by the WHO in March 2020, since cases are reported in all continents[1]. To date, there have been 168509636 confirmed cases of COVID-19, including 3505534 deaths, reported to WHO[22]. Nevertheless, the reported case counts undervalue the global burden of COVID-19, since only a small percentage of acute infections is diagnosed[23]. COVID-19 severity is related with increasing age, male sex, and pre-existing medical diseases[24,25]. Severe COVID-19, defined as intensive care unit or hospital admission, mechanical ventilation, or death, is associated with underlying conditions as diabetes mellitus and obesity[26,27]. Indeed, prevalence studies are not conclusive on increased risk of SARS-CoV-2 infection in patients affected by diabetes mellitus, but this condition may worsen the outcome of COVID-19[28]. Similarly, investigations do not show that obesity increases the risk of contracting COVID-19, but that it may exacerbate the disease severity[27].

NAFLD/MAFLD in COVID-19 patients

The diagnosis of NAFLD/MAFLD requires: (1) the presence of hepatic steatosis detected by liver imaging or histology; and (2) exclusion of significant alcohol intake, other causes of steatosis, or chronic liver disease[29]. Even though liver histology is the gold standard for the diagnosis of NAFLD/MAFLD, to differentiate NASH from simple steatosis and to assess fibrosis, liver biopsy is limited to selected patients due to its invasiveness and costs[29]. Thus, available data on NAFLD/MAFLD prevalence in COVID-19 patients are limited to non-invasive diagnosis.

The frequency of hepatic steatosis fortuitously detected by chest computed tomography in COVID-19 patients was 4.7 times higher than that in age- and sex-matched non-infected patients (31.9% *vs* 7.1%)[30]. This result is confirmed by further studies in which NAFLD/MAFLD was diagnosed by the hepatic steatosis index in 30.7%-37.6% COVID-19 patients from China, even though (differently from the previous investigation) associated with higher risk of disease progression[11,31]. Other studies from China demonstrated that the presence of NAFLD/MAFLD is independently associated with severe COVID-19[32,33]. These latter observations suggest that a huge percentage of patients is at risk of developing the severe form of COVID-19 due to the increasing worldwide occurrence of NAFLD/MAFLD. Nevertheless, results from a study performed in Qatar could not demonstrate that NAFLD/MAFLD was an independent predictor of mortality or COVID-19 severity [34]. A further study conducted at the Imperial College Healthcare NHS Trust in London assessed that NAFLD/MAFLD *per se* was not associated with adverse outcomes in COVID-19 patients[35]. Two systematic reviews with meta-analysis considered several studies to conclude that NAFLD/MAFLD was associated with increased risk of severe COVID-19[36,37].

To answer the question whether NAFLD/MAFLD could increase the risk of contracting COVID-19, the impact of genetic risk score was analyzed in hospitalized participants of the UK Biobank cohort, resulting in no evident association between genetic predisposition of NAFLD/MAFLD and severe COVID-19[38]. A review on data from a huge commercial database including electronic records from 26 national healthcare systems demonstrated that the diagnosis of NASH increases 4.93 times the risk of COVID-19[6].

Several studies tried to point out if there are any risk factors predictive of severe COVID-19 in NAFLD/MAFLD patients (summarized in Table 1). According to the results of a pooled analysis, the risk of severe disease in COVID-19 patients affected by NAFLD/MAFLD seems independent of obesity[39]. Nevertheless, a systematic review showed that obesity, together with hepatic fibrosis and younger age, are associated with increased risk of severe COVID-19[40]. A subsequent study performed in a tertiary care center from Mexico showed that the presence of liver fibrosis in NAFLD/MAFLD patients is associated with severe COVID-19[41]. A further study from three Chinese hospitals suggested that high serum interleukin-6 (IL-6) levels at admission represents an independent risk factor for severe COVID-19 in NAFLD/MAFLD patients[42]. In NAFLD/MAFLD patients, male sex and a noticeable inflammatory response were associated with high COVID-19-related mortality[35]. A retrospective study showed that NAFLD/MAFLD rose the risk of hospitalization in all racial subgroups, even though the highest increase was observed among black people [43].

Table 1 Risk factors associated with severe coronavirus disease 2019 in patients with non-alcoholic fatty liver disease/metabolic-associated fatty liver disease

Risk factors	Ref.
Obesity	[40]
Younger age	[40]
Black race	[43]
Liver fibrosis	[40,41]
High serum IL-6 at admission	[42]
Male sex	[35]
High ferritin at admission	[35]
High EWS at admission	[35]

EWS: Early warning score; IL-6: Interleukin-6.

COVID-19 AND NAFLD/MAFLD: PATHOGENETIC LINKS

As the risk of severe COVID-19 increases in patients affected by NAFLD/MAFLD, it is conceivable that specific joint pathogenic mechanisms could be involved (Figure 1).

SARS-CoV-2 virus entry and cleavage

During the initial phase of COVID-19 infection, pathogenesis of the disease relies on binding of spike SARS-CoV-2 protein to angiotensin I converting enzyme 2 (ACE2) receptors, through which the virus enters target cells[44-46]. Even though ACE2 receptors are mainly expressed in epithelial cells of the upper respiratory tract, in type 2 alveolar epithelial cells, and in ciliated cells, they can also be found on the brush border of enterocytes and in cholangiocytes[45]. Following the binding with ACE2 receptor, the SARS-CoV-2 spike protein undergoes a cleavage by the host's *FURIN* serine protease, a critical process in promoting spike-mediated entry of the virus[47]. Likewise, cleavage of SARS-CoV-2 spike protein by the serine protease two key host factors of SARS-CoV-2 (transmembrane serine protease 2, *TMPRSS2*) is determinant for its fusogenic activity[46]. Of great interest, it has been evidenced that patients with NAFLD/MAFLD present with an increased expression of *ACE2*, *FURIN*, and *TMPRSS2* genes[48]. The enhanced expression of receptors that mediate SARS-CoV-2 cellular entry can explain the increased susceptibility of NAFLD/MAFLD to COVID-19. Moreover, increased levels of *FURIN* and *TMPRSS2* may boost the processing of SARS-CoV-2 spike, further improving its cellular entry. It is worth to note that analysis of data from rodent models and NAFLD/MAFLD patients could not show any increased hepatic expression of *ACE2*, *FURIN*, and *TMPRSS2* genes[49]. On the contrary, the upregulation of these genes in multiple tissues probably represents an additional mechanism of increased susceptibility to severe COVID-19 in NAFLD/MAFLD patients[50].

Immune cell response

Several authors suggested that individuals with NAFLD/MAFLD may present with a dysregulation of both innate and adaptive immune response, which could predispose to worse outcomes in COVID-19. Innate immune response is particularly mediated by Kupffer cells in the liver, which represent the major number of resident macrophages in a single organ[51,52]. Kupffer cells are located within the hepatic sinusoids as part of the reticuloendothelial system, constituting the first line of defense against microorganisms, and regulating immune homeostasis in the liver with the involvement of other immune cells such as neutrophils[53]. In NAFLD/MAFLD, macrophages are polarized towards a pro-inflammatory (M1, or classically activated) rather than anti-inflammatory (M2, or alternatively activated) phenotype[54]. Activation and hyperplasia of Kupffer cells was documented in patients with COVID-19 by several histopathological findings[55,56]. Nevertheless, the impact of COVID-19 on Kupffer cell polarization has not been fully characterized. Of note, ACE2 receptor is detected on the surface of Kupffer cells, leading to hypothesize that hepatic macrophages could be infected by SARS-CoV-2, triggering the primary defense response to the host[57]. This response is mostly mediated by type-I and type-III interferons, leading to the

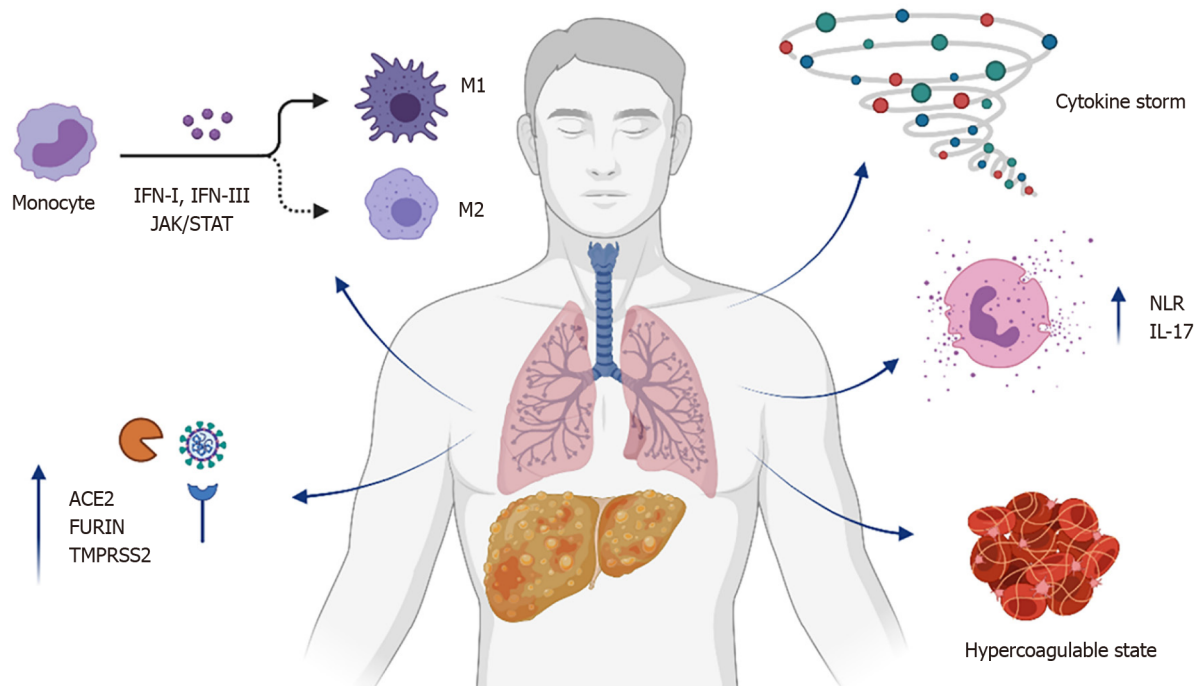


Figure 1 Mechanisms supporting severe coronavirus disease 2019 in non-alcoholic (or metabolic-associated) fatty liver disease. Non-alcoholic fatty liver disease/metabolic-associated fatty liver disease may present with systemic overexpression of genes involved in severe acute respiratory syndrome coronavirus 2 entry and cleavage (such as angiotensin I converting enzyme 2, Furin, and transmembrane serine protease 2), interferon-mediated polarization of macrophages toward a pro-inflammatory M1 phenotype, elevated circulating levels of pro-inflammatory cytokines, increased neutrophil-to-lymphocyte ratio with activation of the pro-interleukin-17 axis, and enhanced production of pro-coagulant molecules. Taken together, these pathways increase susceptibility of severe coronavirus disease 2019 in non-alcoholic fatty liver disease/metabolic-associated fatty liver disease patients. ACE2: Angiotensin I converting enzyme 2; IFN: Interferon; IL-17: Interleukin-17; JAK/STAT: Janus kinase/signal transducer and activator of transcription; NLR: Neutrophil-to-lymphocyte ratio; TMPRSS2: Transmembrane serine protease 2.

activation of janus kinase (JAK)-signal transducer and activator of transcription (STAT)-driven transcription of cytokines[58,59]. The expression of both *JAK1* and *STAT1*, as well as interferon-encoding genes, are increased in NAFLD/MAFLD patients[48]. Of interest, a significant relationship between ACE2 and JAK-STAT signaling was described, suggesting that this pathway may be involved in the downstream action of ACE2 overexpression[60].

Cytokine storm

The progression from a mild to a severe form of COVID-19 is associated with a cytokine storm, characterized by elevated IL-6, IL-8, and tumor necrosis factor (TNF) levels[61]. Several cytokines are involved in NAFLD/MAFLD, determining a low-grade systemic inflammation that favors disease progression and comorbidities[62]. Circulating IL-6 is high in several chronic conditions, including metabolic syndrome, cardiovascular diseases, and chronic inflammatory airways diseases[63]. Furthermore, fatty liver is independently associated with elevated IL-6 levels[64]. Serum IL-6 is strongly and independently associated with COVID-19 severity, and treatment with a monoclonal antibody directed against IL-6 receptor (tocilizumab) improves clinical outcomes in patients affected by serious disease[65]. Indeed, while in physiological conditions the hepatic production of cytokines is nonexistent or mild, lipid accumulation leads to the release of pro-inflammatory molecules as TNF and IL-6 by hepatocytes, Kupffer cells, and adipose tissue, with reduced levels of the anti-inflammatory cytokine IL-10[66]. It is worth to note that adipose tissue is mainly characterized by dysfunctional and inflammatory immune response in patients affected by morbid obesity. In particular, both adipose and mesenchymal stem cells from obese patients are characterized by increased secretion of pro-inflammatory cytokines, including IL-6, IL-8, and TNF[67]. This may contribute to explain the increased probability of severe SARS-CoV-2 infections in NAFLD/MAFLD patients, but further studies are required to improve knowledge about the pathogenetic link between the altered innate liver immunity and COVID-19.

Neutrophils and IL-17

The neutrophil-to-lymphocyte ratio (NLR) is a biomarker of cellular immune imbalance in NAFLD/MAFLD[68]. A high NLR is associated with severity of disease, worse outcomes, and mortality in NAFLD/MAFLD patients[69,70]. Of interest, the presence of NAFLD/MAFLD and a NLR > 2.8 is associated with higher risk of severe COVID-19 with respect to patients not affected by NAFLD/MAFLD and normal NLR [33]. It is worth to note that NLR is also an easy-to-use prognostic biomarker in the early stage of SARS-CoV-2 infection[71]. Neutrophils are a crucial source of IL-17, especially in the liver but also in the airway[72,73]. The pro-inflammatory IL-17 axis may drive the progression of NAFLD/MAFLD, and also COVID-19 severity[74,75]. Activation of the IL-17 axis in NAFLD/MAFLD, other than complemented with the increase of additional pro-inflammatory cytokines as IL-6 and TNF, occurs with the imbalance of T helper lymphocyte subsets[76]. Hospitalized COVID-19 patients show a dysregulation in the balance of T lymphocytes, characterized by a reduced proportion of Treg cells as compared to non-hospitalized individuals[77]. Taken together, these observations suggest that the cellular immune imbalances described in NAFLD/MAFLD could predispose to severe COVID-19, even though further research is needed to clarify this aspect.

Hypercoagulable state

Cytokine release by pro-inflammatory cells may lead to enhanced production of pro-coagulant molecules such as the tissue factor and the von Willebrand factor, with consequent hypercoagulable state and resulting widespread micro-/macrovascular thrombosis[78,79]. NAFLD/MAFLD patients exhibit coagulation disorders, including elevated circulating levels of both tissue factor and von Willebrand factor, as well as increased platelet activation and plasmat concentration of plasminogen activator inhibitor type 1[80-82]. COVID-19 patients affected by NAFLD/MAFLD present with higher level of circulating D-dimer with respect to those without NAFLD/MAFLD, suggesting that the NAFLD/MAFLD-associated pro-coagulant state may contribute to COVID-19 severity[83]. Results from a retrospective study on a cohort of COVID-19 patients revealed that the prevalence of NAFLD/MAFLD was higher in individuals presenting with Doppler ultrasound documented deep vein thrombosis[84]. Furthermore, mean admission and peak serum D-dimer concentration was more elevated in COVID-19 patients with NAFLD/MAFLD with respect to those without NAFLD/MAFLD[84]. It is conceivable that COVID-19 may further increase production of pro-inflammatory cytokines in NAFLD/MAFLD subjects, with consequent activation of the coagulation cascade and thrombosis. Indeed, histologic study of pulmonary vessels described widespread thrombosis with microangiopathy in COVID-19 patients, who also presented with hepatic steatosis involving 50%-60% of liver parenchyma[85]. To confirm this report, an Italian post-mortem analysis found hepatic steatosis and pulmonary thrombi in 55% and 73% COVID-19 patients, respectively[86]. These observations strongly suggest that these diseases are interlinked; the proinflammatory hypercoagulable state representing a mutual pathogenetic pathway to severe COVID-19, contributing to thrombosis and disease progression.

CONCLUSION

Since COVID-19 may present with severe disease and high mortality rate, several studies addressed predisposing factors and underlying pathways to identify patients at high risk. The severe form of SARS-CoV-2 infection occurs in individuals preliminary affected by metabolic diseases, including NAFLD/MAFLD. Chronic low-grade inflammation is suggested as the main leading process to trigger immune dysregulation, cytokine storm, and hypercoagulability in NAFLD/MAFLD patients with COVID-19. Other than being considered for specific therapeutic approaches against COVID-19, subjects affected by NAFLD/MAFLD should be acknowledged among groups with high-risk medical conditions in SARS-CoV-2 vaccination programs. Even though several concerns were raised about SARS-CoV-2 vaccine responses, vaccination with the alum-adsjuvanted inactivated COVID-19 vaccine (Beijing Institute) resulted as effective and safe in NAFLD/MAFLD patients[87]. Nevertheless, further investigations are necessary to clarify whether NAFLD/MAFLD patients should be prioritized for SARS-CoV-2 vaccination.

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