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**Metabolic associated fatty liver disease and COVID-19: a double whammy?**

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## **INTRODUCTION**

The coronavirus disease 2019 (COVID-19) pandemic and the increased healthcare burden have driven the pursuit of knowledge in COVID-19 and its relationship with chronic diseases. Metabolic disorders, in particular, have been of interest in recent weeks as the need for risk management and appropriate resource allocation increases. The high prevalence of metabolic associated fatty liver disease (MAFLD) has elicited interest in establishing the interaction between MAFLD and COVID-19 infection. MAFLD, previously known as non-alcoholic fatty liver disease, is one of the most common liver disorders, affecting up to 24% of the population globally.<sup>(1)</sup> It stems from the underlying state of systemic metabolic dysfunction independent of other chronic liver diseases;<sup>(2)</sup> hence, it is a diagnosis of inclusion and does not warrant the exclusion of other liver diseases.<sup>(2)</sup> Diagnosis of MAFLD is based on evidence of hepatic steatosis and one of the following: (a) overweight or obesity; (b) type 2 diabetes mellitus; or (c) evidence of metabolic dysregulation.<sup>(2)</sup> Although there are only limited studies of patients with MAFLD and COVID-19, all of which showed a possible link between MAFLD and severity of COVID-19.

## **LIVER INJURY, MAFLD AND COVID-19**

The incidence of liver injury in COVID-19 patients is highly variable, ranging from 14% to 53%.<sup>(3,4)</sup> Consistently, the majority of liver injury reported in studies are mild, with a predominance of hepatocellular (aspartate transaminase [AST]/alanine transaminase [ALT]) abnormalities. Patients with MAFLD, however, were observed to have a higher likelihood of liver derangement from admission to discharge, as compared to patients without MAFLD (70% vs. 11.1%;  $p < 0.0001$ ).<sup>(3)</sup> Furthermore, obese COVID-19 patients with MAFLD also had higher levels of AST and ALT as compared to non-obese MAFLD patient.<sup>(5)</sup> These results may suggest that obesity, rather than MAFLD, is a more dominant risk factor for liver derangement.

Current studies have consistently shown an increased risk of severe COVID-19 disease in patients with MAFLD. The presence of MAFLD was associated with a four-fold increased risk of severe COVID-19 as compared with the absence of MAFLD (unadjusted odds ratio [OR] 4.22, 95% confidence interval [CI] 1.45–12.22).<sup>(6)</sup> Additionally, patients with MAFLD are frequently obese and have other metabolic risk factors that may place them at a higher risk of severe COVID-19 infection. Obesity, for example, is associated with a three-fold increased risk of severe COVID-19 compared to non-obesity (adjusted OR 3.00, 95% CI 1.22–7.38).<sup>(7)</sup> MAFLD with obesity further increases the risk of severe COVID-19 to six-fold (adjusted OR 6.32, 95% CI 1.16–34.54,  $p = 0.03$ ) as compared to MAFLD without obesity.<sup>(8)</sup> This increased risk is independent of diabetes mellitus, dyslipidaemia and hypertension.<sup>(6)</sup> The risk of severe COVID-19 has also been shown to rise with increasing metabolic risk factors,<sup>(6)</sup> suggesting the cumulative effects of MAFLD, obesity and other metabolic disorder on severity of COVID-19.

Targher et al, using the fibrosis-4 index (FIB-4) to assess the extent of liver cirrhosis, demonstrated that patients with MAFLD and moderate-to-high liver fibrosis scores are at higher risk of severe COVID-19 infection, irrespective of their metabolic comorbidities.<sup>(9)</sup> Notably, these patients are also more likely to be older, obese, and have diabetes and higher levels of AST/ALT as compared to patients with low FIB-4 scores or without MAFLD.<sup>(9)</sup> Zhou et al demonstrated an association between age, MAFLD and severity of COVID-19; patients under 60 years old with MAFLD were observed to have a greater than two-fold increased prevalence of more severe COVID-19 disease as compared to those without MAFLD, and this association remained significant after adjusting for major confounders like overweight, diabetes mellitus, hypertension and smoking.<sup>(10)</sup>

## **PHYSIOLOGY OF LIVER INJURY IN COVID-19 AND MAFLD**

The exact physiology and virology of COVID-19 and liver injury remains elusive. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects the human host via angiotensin converting enzyme 2 (ACE2) receptor,<sup>(11)</sup> which is expressed widely in endothelial cell and arterial smooth muscle. High levels of ACE2 expression is found in the lungs, kidney, oesophagus, bladder, ileum and heart.<sup>(11)</sup> Interestingly, liver ACE2 expression level is relatively low,<sup>(11)</sup> suggesting that liver injury may not be due to SARS-CoV-2 invasion and cytopathic damage. A recent study by Biquard et al further supports this hypothesis;<sup>(12)</sup> the authors found that gene expression of receptors required for SARS-CoV-2 infection, including ACE2 receptor, was not different between patients with MAFLD and those with simple steatosis, and between obese and lean patients.<sup>(12)</sup> In fact, a postmortem liver biopsy has suggested a more likely immune-regulated mechanism with microvesicular steatosis and T cell overactivation.<sup>(13)</sup>

One possible viral route of entry to the hepatic reticuloendothelial system is via the ileum, where there are an abundance of ACE2 receptors<sup>(11)</sup> and a rich vascular supply to the liver. Kupfer cells are hepatic macrophages that line the sinusoids of the liver and produce potent immune modulating cytokines. Patients with MAFLD, especially those who are obese, have increased levels of cytokines such as interleukin-6 (IL-6).<sup>(14)</sup> This increased IL6 level correlates independently with increased inflammatory activity in the liver and visceral fat.<sup>(14)</sup> Hence, the presence of MAFLD with advanced fibrosis could further exacerbate the virus-induced 'cytokine storm', resulting in more severe COVID-19.<sup>(9)</sup> Another hypothesis of disease progression and severity is the dysregulation of hepatic immune response, skewing pro-inflammatory M1 macrophages to immune-suppressing M2 macrophages.<sup>(1)</sup> Furthermore, anti-inflammatory cytokines, such as adiponectin, are known to be reduced in MAFLD.<sup>(15,16)</sup> Adiponectin has several immune-suppressing properties, including the induction of anti-inflammatory cytokines IL-10 and IL-1-receptor antagonist.<sup>(15)</sup> This state of immune

imbalances may be primed to exacerbate COVID-19 infection. Other possible mechanisms for liver injury include drug hepatotoxicity, liver hypoperfusion and ischaemia resulting from pneumonia-associated hypoxia, particularly in patients with more severe COVID-19 requiring ventilatory support.

## **DISCUSSION**

The ongoing COVID-19 pandemic has placed significant threats to healthcare systems throughout the world. Knowledge surrounding pre-existing chronic illnesses and risks of COVID-19 severity and progression are crucial in risk stratification and resource allocation of the already burdened healthcare system. Limited evidence has elucidated that MAFLD is associated with increased risk of severe COVID-19 disease.

Metabolic syndrome and MAFLD, however, are rarely considered mutually exclusive. Given the metabolic associations of MAFLD and obesity as the primary aetiology, it is still plausible that the association between COVID-19 severity and MAFLD could have been a coincidence. Metabolic syndrome has been previously identified as an independent risk factor for respiratory disorders,<sup>(17,18)</sup> through the combined effects of altered hormone levels,<sup>(19,20)</sup> activation of the innate immune system leading to a chronic inflammatory state,<sup>(21)</sup> and mechanical compromise.<sup>(22)</sup> Hence, it is not surprising that patients with MAFLD, as extra-hepatic manifestations of metabolic syndrome, is at risk of disease progression.

Although possible hypotheses have been put forward to explain the mechanism of liver injury, it remains uncertain if MAFLD as a single metabolic entity contributes to COVID-19 severity and progression. It is clear, however, that COVID-19 patients with disorders of metabolism, such as MAFLD and obesity, have a significantly higher risk of disease progression and poorer outcomes. Until a definitive treatment and/or vaccine is made available,

accurately identifying these patients at risk of severe COVID-19 infection is pivotal to providing safe and optimal care with appropriate use of limited healthcare resources.

At present, there is limited knowledge surrounding the impact of each metabolic entity, including obesity and MAFLD, on the course of COVID-19 infection. As MAFLD is the most common liver disorder worldwide, research in a larger and more varied population is warranted to further understand this heterogeneous disorder.

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