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Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19

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ABSTRACT

Background and aims: Liver involvement is common in COVID-19. Elevated aspartate and alanine amino transaminase (AST/ALT) and borderline increase in serum bilirubin and serum alkaline phosphatase (ALP) are the commonest findings. Patients with associated co morbid conditions like obesity, cardiovascular disease, renal disease, malignancy, hypertension and old age are prone to develop severe disease. Limited data is available in patients with COVID-19 and metabolic dysfunction associated fatty liver disease (MAFLD). The aim of this review is to analyse the effect of MAFLD on severity of COVID-19.

Methods: We systematically searched the PubMed database till May 20, 2020 and retrieved all the articles published on COVID-19 and fatty liver/MAFLD/NAFLD.

Results: Limited studies done had shown four to six fold high risk of severe COVID-19 in patients with MAFLD. Patients with MAFLD and associated obesity, severe fibrosis and age <60 yrs are more prone to develop severe COVID-19.

Conclusion: MAFLD is associated with 4–6 fold increase in severity of COVID-19 compared to non MAFLD patients. Physician and hepatologist should follow these patients cautiously and preventive measures to be taken strictly in these high risk patients.

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1. Introduction

Corona viruses are a family of viruses that affects both humans and animals. COVID-19 declared pandemic by WHO in 2020. Upper respiratory tract infections are predominant symptoms though it can affect liver and intestine also [1]. Majority of the infections are mild and self limiting however severe infections are seen in patients with old age, diabetes, obesity, hypertension, cardiovascular disease, chronic liver disease, renal disease and patients with malignancy. COVID-19 associated liver injury with raised aspartate aminotransferase (AST), alanine aminotransferase (ALT), and mildly elevated bilirubin which range from 14% to 53%. These enzymes are more raised in males, symptomatic patients and in patients who are critical sick and are admitted in intensive care unit [2–8].

There are limited studies in patients with underlying liver disease and COVID-19 and results favour that underlying liver disease predisposes to severe COVID-19 [9,10]. Patients with metabolic dysfunction associated fatty liver disease (MAFLD) which was formerly known as non-alcoholic fatty liver disease (NAFLD). These patients are often overweight and have additional metabolic risk factors like hypertension, diabetes and dyslipidemia which may contribute to a greater risk in COVID-19. This short review will assess the effect of MAFLD on the severity of COVID-19.

1.1. Burden of MAFLD

The global prevalence of MAFLD in a metanalysis is currently estimated to be 24% [11]. Prevalence varies from country to country and in different regions of same country. It depend upon age, gender, ethnicity, dietary patterns and mode of investigation for MAFLD [11–13]. MAFLD is now considered a diagnosis of inclusion rather than excluding other causes like viral, genetic and alcohol. Prevalence of MAFLD is increasing due to change in life style and dietary pattern of persons. Recently, a consensus of international experts proposed that the disease acronym be changed from NAFLD to metabolic (dysfunction) associated fatty liver disease (MAFLD) due to strong association with different component of metabolic syndrome [14]. As MAFLD is now one of the commonest liver diseases all over the world it is expected that physicians will see more
patients who have both MAFLD and COVID-19.

1.2. MAFLD and COVID-19 studies

MAFLD is extra-hepatic manifestations of metabolic syndrome and one of the commonest liver disorders. There are limited studies in patients with MAFLD and COVID-19 and the results of all reflect MAFLD increases the severity of COVID-19 in these patients.

In a retrospective study by Ji D et al. [15], 202 consecutive patients with COVID-19 and MAFLD were studied. Majority of patients had mild disease and 14% had severe disease. Liver injury was observed in 101 (50%) and 152 (75.2%) patients on admission and during hospitalization, respectively. Almost all liver injury was mild with hepatocellular pattern, only 3% had ductular or mixed pattern. Sixty-seven (33.2%) patients had persistent abnormal liver function from admission to last follow-up. Total bilirubin was elevated in 8%, serum alkaline phosphatase (ALP2.5%) gamma glutamyl transpeptidase (GGT2.3%), ALT(50%) and AST(17%). Thirty-nine (19.3%) and 163 (80.7%) had progressive and stable disease, respectively. Patients with progressive disease were older, had higher BMI, and a higher percentage of comorbidity and MAFLD. Patients with MAFLD had a higher risk of disease progression, higher likelihood of abnormal liver function from admission to discharge and longer viral shedding time compared to patients without NAFLD.

In another study by Zheng et al. [16] 66 patients [obese,n = 45 and non obese,n = 21] with COVID-19 and MAFLD were included. Of these 47 (71.2%) patients had non-severe and 19 (28.8%) had severe COVID-19. Patients who were obese and had MAFLD had significantly higher AST and ALT compared to non obese MAFLD patient. Patients with severe disease were more obese (89.5% vs. 59.6%, p = 0.021) and presence of obesity in MAFLD patients was associated with a 6-fold increased risk of severe COVID-19 illness independent to hypertension, diabetes and dyslipidemia.

Targher et al. [17] enrolled 94 (30%) patient of MAFLD out of 310 COVID-19 patients. Fibrosis-4 (FIB-4) was used as a criterion for assessing fibrosis. Forty four patients had FIB-4<1.3, thirty six patients had FIB-4(1.3–2.6) and 14 patients had FIB-4>2.6. Patients with MAFLD and intermediate or high FIB-4 scores were more likely to be older, obese, diabetic and had higher NFS (NAFLD fibrosis score), higher liver enzymes, higher C reactive protein, as well as lower levels of lymphocyte count, platelet count, triglycerides and high-density lipoprotein cholesterol compared with their counterparts with low FIB-4 score or those without MAFLD. Notably, the severity of COVID-19 illness markedly increased among patients with MAFLD with intermediate or high FIB-4 scores. This data demonstrate that patients with MAFLD with increased FIB-4 or NFS are at higher likelihood of having severe COVID-19 illness, irrespective of metabolic comorbidities.

Patients age as a risk factor for the severity of COVID-19 in MAFLD was assessed by Zhou et al. [18]. Ninety three (29%) of 327 patients with COVID-19 had MAFLD. In patients aged younger than 60 years, a more than two-fold higher prevalence of severe COVID-19 was observed in MAFLD patients compared to those without; this association remained significant after adjusting for age, sex, smoking status, overweight, diabetes, and hypertension (adjusted OR 2.67, 95%CI 1.13–6.34, P = 0.03).

Gao F et al. [19] in 65 patients with MAFLD and no diabetes concluded that in non-diabetic patients with COVID-19, the presence of MAFLD was associated with a 4-fold increased risk of severe COVID-19; the risk increased with increasing numbers of metabolic risk factors. The association with COVID-19 severity persisted after adjusting for age, sex and existing morbid conditions.

These studies suggests patients with MAFLD had higher chances of severe COVID-19, more likely to have abnormal AST and ALT, had higher viral shedding time, likely to have more liver injury during hospital stay compared to non MAFLD patients. Associated significant fibrosis with MAFLD is another risk factor for severity of COVID-19 compared to intermediate or no fibrosis patients with MAFLD.

Recently done studies showed MAFLD to be present in app. 30% of the total COVID-19 patients [16,17]. Most of the MAFLD patients are asymptomatic and had no obvious liver related problem so these patients go unnoticed in early stages of the disease. Probable reasons of increased severity of COVID-19 in patients with MAFLD are multiple but none seems to be satisfactory till now.

2. Mechanism of liver injury in COVID-19 and MAFLD

Different mechanisms have been postulated for liver injury. Direct cytotoxicity due to active viral replication in hepatic cells and cholangiocytes: SARS-CoV-2 binds to target cells through angiotensin converting enzyme (ACE2) receptors however normal ALP in majority of patients is against this hypothesis. Cytokine storm hypothesis: immune mediated damage due to the severe inflammatory response following COVID-19 infection as markers of inflammation like C reactive protein (CRP), serum ferritin, LDH, IL-6, IL-2, were significant elevated. This form of injury is the most probable reason as other viral infection like influenza also affects the liver in the same way. Ischemic damage: majority of sick patients are on ventilator and inotropic support. As AST and ALT are raised one to two times the upper limit of normal which is against the ischemic or hypoxic liver injury and the final probable hypothesis is drug induced liver injury (DILI): Majority of the patients are on number of drugs like lopinavir/ritonavir, remdesivir, chloroquine, tocilizumab and Chinese traditional medicine, which have some hepatotoxic effects [20,21].

ACE-2 receptors have been shown to present in liver in cholangiocytes and on hepatocytes. SARS-CoV-2 targets these receptors for its entry and it is hypothesized that this leads to injury of cholangiocytes and hepatocytes [22]. In a recent paper by Biquard L et al. [23] concluded that the MAFLD is not associated with increased expression of genes encoded for proteins receptors needed for SARS-CoV-2 infection and mRNA expression of SARS-CoV-2 infection critical genes, such as angiotensin converting enzyme 2 (ACE2), transmembrane Protease Serine 2 (TMPRSS2), phosphatidylinositol 3-phosphate 5-kinase (PIKfyve), cathepsin L cathepsin in human liver biopsy, were not found to be enhanced in patients with MAFLD or obesity. Hence increased expression of ACE-2 receptors in MAFLD patients is an unlikely explanation of increased liver injury or severity in these patients.

The liver is enriched with innate immune cells (such as macrophages, natural killer, natural killer T, and γδ T cells) [24]. Obesity and MAFLD have been associated with increased production of pro-inflammatory cytokines like TNF-α by adipose cells and Kupffer cells. Adipose tissue insulin resistance and free fatty acid flux to liver activates hepatic macrophages in MAFLD independent of obesity and diabetes [25,26]. Stimulated macrophage can have two types of response and classified as M1 and M2. M1 macrophages initiate inflammatory processes in contrast, M2 macrophages have anti-inflammatory and reparative functions with high expression of different chemokines and thus have opposite action to M1 response [27,28]. It is the balance of these two response which decides the clinical status of the patient. It is postulated that dysregulated hepatic innate immunity in patients with MAFLD contributes to the pathogenesis. Probably the polarization status of hepatic macrophages is skewed from inflammation-promoting M1 macrophages to inflammation suppressing M2 macrophages, leading to progression of COVID-19. MAFLD with significant/advanced fibrosis might exacerbate the virus-induced cytokine ‘storm’, possibly through the hepatic release of multiple proinflammatory cytokines,
thereby contributing mechanistically to severe COVID-19.

3. Conclusion

MAFLD is a common problem all over the world and approxim-ately one third of world population is affected. Limited studies data has confirmed that MAFLD is associated with 4–6 fold increased risk of severe disease, more deranged liver function, increased viral shedding duration compared to patients with no MAFLD. Younger patients with age less than 60 years also associated with increased severity of COVID-19. Multiple hypotheses has been put forward for increased liver injury however dysregulated hepatic innate response with the skewed polarization status of hepatic macrophages from inflammation-promoting M1 macrophages to inflammation suppressing M2 macrophages is a more likely cause of severe disease in these patients.

Declaration of competing interest

None.

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