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The Association of Metabolic-Associated Fatty Liver Disease with Clinical Outcomes of COVID-19: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction. Metabolic-associated fatty liver disease (MAFLD) is a hepatic manifestation of metabolic syndrome (MS). MAFLD patients have a higher prevalence of COVID-19. MAFLD also is associated with worse clinical outcomes of COVID-19, such as disease severity, intensive care unit (ICU) admission rate, and higher mortality rates. However, this evidence has not been well characterized in the literature. This meta-analysis aimed to determine the clinical outcomes of COVID-19 among MAFLD patients compared to the non-MAFLD group.

Methods. A comprehensive search was conducted in the Cumulative Index of Nursing and Allied Health (CINAHL), PubMed/Medline, and Embase for studies reporting MAFLD prevalence among COVID-19 patients and comparing clinical outcomes such as severity, ICU admission, and mortality among patients with and without MAFLD. The pooled prevalence of MAFLD among COVID-19 patients and the pooled odds ratios (OR) with 95% confidence intervals (CI) for clinical outcomes of COVID-19 were calculated.

Results. Sixteen observational studies met inclusion criteria involving a total of 11,484 overall study participants, including 1,746 MAFLD patients. The prevalence of COVID-19 among MAFLD patients was 0.29 (95% CI: 0.19-0.40). MAFLD was associated with the COVID-19 disease severity OR 3.07 (95% CI: 2.30-4.09). Similarly, MAFLD was associated with an increased risk of ICU admission compared to the non-MAFLD group OR 1.46 (95% CI: 1.12-1.91). Lastly, the association between MAFLD and COVID-19 mortality was not statistically significant OR 1.45 (95% CI: 0.74-2.84).

Conclusions. In this study, a high percentage of COVID-19 patients had MAFLD. Moreover, MAFLD patients had an increased risk of COVID-19 disease severity and ICU admission rate.

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INTRODUCTION

The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) is the cause of coronavirus disease (COVID-19), a pandemic that represents a global health challenge. COVID-19 is usually a self-limiting disease; however, it is associated with a significant (3-7%) mortality rate.[1] The excessive production of pro-inflammatory cytokines because of SARS-CoV-2 infection mainly is associated with high mortality due to multiple organ failure.[2] Acute respiratory distress syndrome (ARDS) resulting from the cytokine storm is the primary cause of mortality among COVID-19 patients.

Advanced age and specific co-morbidities, such as cardiovascular diseases (CVD), chronic obstructive pulmonary disease (COPD), diabetes mellitus type 2 (DM2), and hypertension, were the main risk factors for the development of COVID-19 and increased mortality.[1,3-5] Patients who have metabolic syndromes (MS) components such as hyperlipidemia, diabetes mellitus, and obesity were more likely to develop COVID-19 infection and have a higher mortality rate.[6,7] Chronic low-grade inflammation associated with the metabolic syndrome has been known to cause compromised body immune system, resulting in microvascular endothelial dysfunction, contributing to poor health outcomes among COVID-19 patients.[8,9]

Metabolic-associated fatty liver disease (MAFLD) is the most common cause of the chronic liver disease (CLD) and affects approximately 30-40% of the world population.[10] MAFLD is also a well-known risk factor for cardiovascular disease and diabetes mellitus, resulting in higher morbidity and mortality.[4,10] Lately, a consensus of international experts has proposed to change the disease acronym from NAFLD (i.e., non-alcoholic fatty liver disease) to MAFLD due to the strong association of NAFLD with the metabolic syndrome components.[10] The criteria to diagnose MAFLD are based on the presence of hepatic steatosis and three other measures, including the presence of DM2, obesity, and evidence of body metabolic dysregulation. Pre-existing liver disease, such as metabolic-associated fatty liver disease, could increase the risk of hospitalization and severity of COVID-19.[11] Moreover, the presence of MAFLD could release more pro-inflammatory cytokines to exacerbate the SARS-CoV-2 induced inflammatory response in COVID-19 patients. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE 2) receptors for cellular entry, and the patients with MAFLD had increased expression of ACE 2 receptors, leading to more severe COVID-19 disease.[12] Furthermore, the increased production of reactive oxygen species among the MAFLD patients further stirs the inflammatory storm leading to the severity of the infection in certain patients.[13]

Recent observational studies have demonstrated that not only the presence of liver disease such as MAFLD may influence the COVID-19 disease course, SARS-CoV-2 infections also can affect the progression of liver disease (e.g., MAFLD, nonalcoholic steatohepatitis).[14,15] Other studies have reported that the existing hepatic steatosis was associated with further significant liver injury and disease severity among

COVID-19 patients.[16] Similarly, metabolic diseases also were associated with adverse COVID-19 outcomes.[17] However, limited data were available on how MAFLD was associated with the increased prevalence, severity, hospital course, and mortality of COVID-19. Therefore, this meta-analysis evaluated the prevalence of MAFLD among COVID-19 patients and how MAFLD influenced the hospitalization course and severity of COVID-19. The effect of MAFLD on the rate of intensive care unit (ICU) admission and mortality outcomes among COVID-19 patients also was evaluated.

METHODS

Study Search and Selection. The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.[18] The study search was conducted in the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed/Medline, Google Scholar, LILACs, and Embase from the database inception through May 28th, 2021. Potentially relevant articles also were identified by the manual search of the references of the selected articles. The search strategy was designed using keywords to retrieve the articles that demonstrated the association between MAFLD and COVID-19. Moreover, the bibliographies of relevant and review articles were searched manually to include any other studies of interest. The literature search was restricted to the English language articles. The initial screening of the retrieved articles was conducted based on their title and abstracts for possible eligibility. Furthermore, title and abstract-based retrieved articles were assessed for inclusion based on their full-text review. Covidence software (Covidence systematic review software; Veritas Health Innovation: Melbourne, Australia) was used by the two independent researchers (UH, MZA) to assess the eligibility of articles for final inclusion.

Inclusion Criteria. The studies were included in the final meta-analysis if they met the following inclusion criteria: (a) epidemiological studies involving patients older than 18 years of age, (b) reported laboratory-confirmed COVID-19 cases, (c) reported prevalence of MAFLD among the COVID-19 patients, (d) reported possible association risk between MAFLD and COVID-19 disease severity, ICU admission, and mortality. The following keywords were used for search strategy in PubMed, CINAHL, and Embase: "COVID-19" or "COVID-19/mortality", and "COVID-19" or "coronavirus", and "NAFLD" or "non-alcoholic fatty liver disease", and "MAFLD" or "metabolic associated fatty liver disease", and "fatty liver" and "metabolic fatty liver disease".

MAFLD was defined by the presence of hepatic steatosis and three other measures, including the presence of DM2, obesity, and evidence of body metabolic dysregulation. COVID-19 patients were considered to have the severe disease when they met the following criteria: (1) hypoxia (oxygen saturation less than 92%), (2) increased respiratory rate (greater than 35 per minute), (3) decreased consciousness: somnolence, apathy, convulsions, and coma, (4) certain specific manifestations, such as bleeding, coagulation disorders (deep venous thrombosis, pulmonary embolism), cardiovascular manifestation such as myocardial infarction, abnormally raised liver enzymes, rhabdomyolysis, and gastrointestinal dysfunction such as severe diarrhea.

Exclusion Criteria. The studies with patients younger than 18 years, pregnant patients, and those lacking informed consent were excluded. Also, those studies with a secondary cause of fatty liver diseases, such as alcoholic liver disease, autoimmune liver disease, drug-induced liver injury, cholestatic liver disease, and viral hepatitis, were excluded. Furthermore, interventional trials, animal studies, reviews, case reports, genetic studies, commentary, and study protocols were excluded. Lastly, this meta-analysis did not include the studies with incomplete literature data or information, study definitions, or unclear descriptions of outcomes.

Data Extraction. The following data were collected from each publication selected: (1) the characteristics of the study population including age, sex, body mass index (BMI), MAFLD and COVID-19 assessment methods, and population co-morbidities, (2) author name, study year, country of publication, trial registration, type of observational studies, source of the included database, duration of study follow-up, and the proportion of COVID-19 study population with metabolic associated fatty liver disease, and (3) study outcomes such as effect estimates of odds ratio (OR), risk ratio (RR), and hazard ratio (HR) were reported. To conform with the newer MAFLD definition, unadjusted ORs (not adjusted for other covariates such as age, sex, ethnicity, race, BMI, and other co-morbidities (e.g., hypertension, diabetes mellitus, obesity smoking, cardiovascular diseases, hepatocellular carcinoma (HCC), dyslipidemia, COPD, and alcohol consumption)) were used from those studies which reported the association between NAFLD and COVID-19 clinical outcomes. The absolute number of COVID-19 patients within the MAFLD and non-MAFLD group, along with the study conclusion, also were extracted. Any conflicts in the initial study screening process and data extraction phase were resolved by consensus and discussion with the senior author (MA).

Quality Assessment. The included studies were assessed for quality. The Newcastle-Ottawa scale (NOS) was used.[19] Three parameters of the scale, such as selection, comparability, and outcome/exposure, were applied to assess the quality of the publications. The studies were classified as low, medium, or high quality according to the NOS scale achieved based on the three parameters (e.g., selection, comparability, and outcome/exposure). The quality assessment was performed by two authors (UH, MZA) independently, and any discrepancies were resolved through mutual consensus. All studies with a higher NOS score (based on selection, comparability, and outcome/exposure) were selected. A high score indicates a high study quality.

Statistical Analysis. Meta-analysis was performed using the RStudio software (RStudio, v4.1.0; University of Auckland, New Zealand). The pooled prevalence of MAFLD among COVID-19 patients was calculated. The study used the published studies' available effect estimates of OR, HR, and RR. Absolute numbers were used to calculate the unadjusted ORs if the effect estimate was not reported. Pooled OR with 95% confidence intervals (CI) were calculated to assess the pooled estimates of odds of COVID-19 disease severity, ICU admission rate, and mortality (reference group: patients without MAFLD). A random-effect model was used to pool the effect estimates, based on the heterogeneity assessment of the individual study effect

estimate. A p value of < 0.05 was considered statistically significant for the pooled effect estimates. Forest plots were utilized to demonstrate the results of the meta-analysis.

Heterogeneity between the studies was tested with I^2 and X^2 tests for Cochran Q statistics. According to Cochran's handbook, I^2 value of (0-40%) was interpreted as "might not be important," (30-60%) as "moderate," (50-90%) as substantial, and (70-100%) as considerable heterogeneity.[20,21] The statistical review of this study was conducted by author UH.

RESULTS

The search results covered the period of database inception from December 2019 through May 2021. The total search results were 244 items, and after removing duplicates, it was reduced to 203. Fifty-eight studies were included in the full-text review process (by UH and MZA). After a full-text review of the extracted articles, sixteen studies were selected for the final meta-analysis, involving 11,484 overall study participants, including 1,746 MAFLD patients (Figure 1).

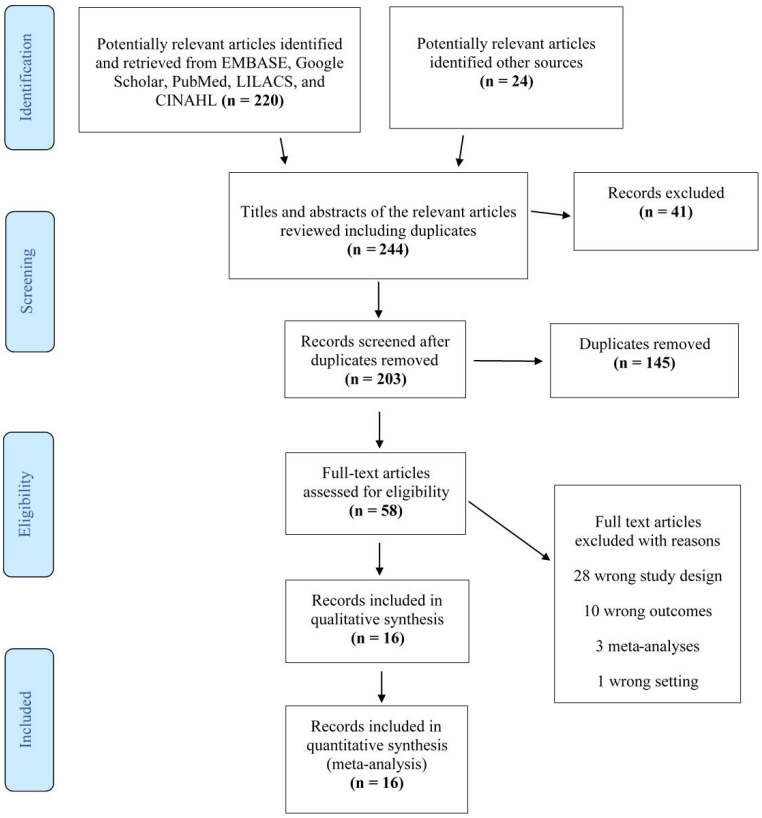

Figure 1. PRISMA flow chart of the studies.

Characteristics of the Studies Included. Three studies were cross-sectional or case-control studies,[23-25] and 13 articles were retrospective cohort studies,[22,26,28-33,35,37-40] Eight studies were reported from China,[24-26,29,31,41,43] three were from the U.S.,[21,29,36] two from the UK,[32,35] one from Turkey,[35] one from Mexico,[38] and one from Israel.[23] All studies were conducted between December 2019 and May 2021. The data sources for all studies were mainly electronic medical records/health records (EMR/HR).

Of the total, eight studies confirmed fatty liver disease based on ultrasound or computer tomography (CT).[23,24,26,28,30,31,35,36] Three studies used new consensus definition of MAFLD for diagnosis,[23,26,30] four studies used hepatic steatosis index (HIS),[29,38-40] one study used international classification disease code (ICD).[21] Two studies reported MAFLD based on the confirmed diagnosis of DM2 and obesity.[25,32] One study reported MAFLD based on EMR/HR.[33] The significant co-morbidities reported across all the included studies were obesity, DM2, hypertension, dyslipidemia, ischemic heart disease, chronic lung disease, chronic kidney disease (CKD), and metabolic dysregulation (see Tables 1 and 2 available online only at journals.ku.edu/kjm). Ten studies used reverse transcriptase-polymerase chain reaction (RT-PCR) to diagnose COVID-19 infection.[23,26,29-33,35,36,38] Six studies used laboratory-confirmed cases of COVID-19 infection.[22,24,25,28,39,40] One study did not provide clear information about the COVID-19 diagnosis method.[26]

MAFLD prevalence in COVID-19 patients. All sixteen studies reported the MAFLD prevalence in COVID-19 patients. The pooled prevalence of COVID-19 among MAFLD patients was 0.29 (95% CI: 0.19-0.40; p < 0.001; Figure 2).

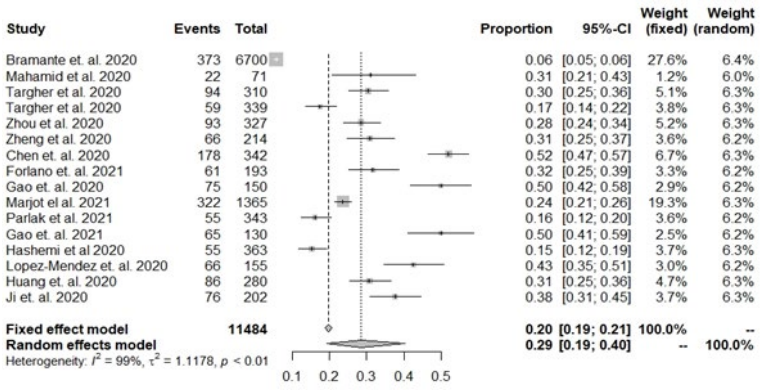

Figure 2. Forest plot of the pooled prevalence of the MAFLD among COVID-19 patients. OR, odds ratio; CI, confidence interval.

Clinical Outcomes

COVID-19 Severity in Patients with MAFLD. Twelve studies reported the severity of the COVID-19 symptoms related to MAFLD.[22-26,28-30,32,35,39,40] The pooled OR for severe COVID-19 symptoms in patients with MAFLD was 3.07 (95% CI: 2.30-4.09; p = 0.04) compared to those without MAFLD (Figure 3). Six studies reported the disease outcome as the severity of COVID-19 in MAFLD patients compared to those without MAFLD.[29-31,33,38,42] Another six studies reported the outcome as COVID-19 severity among NAFLD patients.[22,23,24,26,39,40] One study reported the association of obesity and metabolic dysregulation with COVID-19 severity.[35] Targher et al.[24] determined the association of COVID-19 severity with both low and high FIB-4 (hepatic fibrosis) scores. Also, Zhou et al.[26] reported the association of COVID-19 severity with NAFLD in both young and older patients separately.

COVID-19 Rate of ICU Admission in Patients with MAFLD. Overall, four studies reported the association between MAFLD and the rate of ICU admission among COVID-19 patients.[29,31,36,38] There was a significant increase in the rate of ICU admission among patients with MAFLD compared to those without. The pooled estimated OR was 1.46 (95% CI: 1.12-1.91; p = 0.28; Figure 4). The statistical heterogeneity for this analysis measured by I^2 was 22%. The clinical characteristics and quality assessment of the included studies have been described in Table 1 (available online only at journals.ku.edu/kjm).

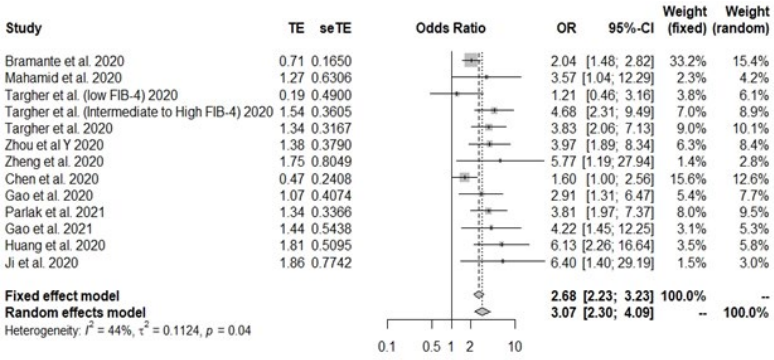

Figure 3. Forest plot of the pooled odds ratio of the association between MAFLD and COVID-19 severity. TE, treatment effect; seTE, standard error of treatment effect; OR, odds ratio; CI, confidence interval.

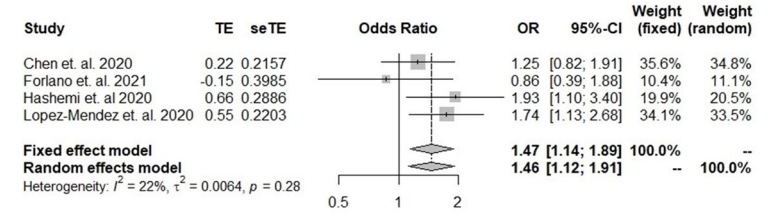

Figure 4. Forest plot of the pooled odds ratio of the association of MAFLD and ICU admission rate among COVID-19 patients. TE, treatment effect; seTE, standard error of treatment effect; OR, odds ratio; CI, confidence interval.

COVID-19 Mortality in MAFLD. Seven studies reported the COVID-19 mortality among MAFLD patients compared to those without MAFLD.[22,29,31,33,35,36,38] There was no observed statistical difference in the COVID-19 mortality among MAFLD patients compared to those without (OR 1.45; 95% CI: 0.74-2.84; p = < 0.01; Figure 5). The clinical characteristics and quality assessment of the included studies have been described in Table 1 (available online only at journals.ku.edu/kjm).

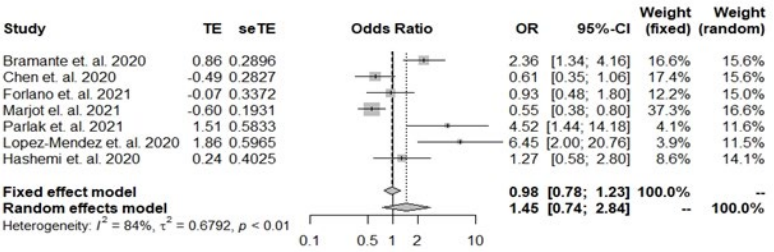

Figure 5. Forest plot of the pooled odds ratio of the association of MAFLD and COVID-19 mortality. TE, treatment effect; seTE, standard error of treatment effect; OR, odds ratio; CI, confidence interval.

The Assessment of Publication Bias. Based on the quality assessment criteria (i.e., NOS), all the included studies were observational and were moderate to high quality. The observational nature of the studies should be factored into in interpreting the results. Also, there was significant heterogeneity among the studies evaluating the COVID-19 prevalence among MAFLD patients (I^2 > 90%). There were several factors leading to this high heterogeneity. First, the studies included in this review have been conducted in different countries with different patient population demographics. Some countries were hit harder by the pandemic than others, leading to disparities in infection prevalence. Second, different data analysis parameters were used to adjust for confounders by different studies that might be the source of heterogeneity. Third, Bramante et al.[22] have the most skewed effect size in this analysis. It might be a source of high heterogeneity as their study has the highest study population among the studies included in this review. However, the point estimate effect was calculated by random effect model, taking on the higher heterogeneity between the studies, making the results significant. The publication bias was assessed using Egger's regression test methodology.[41] The p value was 0.025, suggesting the absence of publication bias in COVID-19 severity outcome. Egger's regression test was not performed for ICU admission and mortality outcomes because of the meta-analysis's limited number of studies (i.e., less than 10).

Both funnel plot and the ROBINS-E tool (The Risk of Bias in Non-randomized Studies of Exposures) were used to assess bias in the studies which reported the association of MAFLD with COVID-19 clinical outcomes (COVID-19 ICU admission and mortality). There are seven domains of bias assessment in this tool. These domains include the presence of confounding factors, selection of study participants, exposure classification, a patient departure from exposure, missing data, outcome measurement, and selection of the results reported in the study.[42] The individual judgments of each domain were taken and summarized to get an overall risk of bias assessment for the individual study. All those studies with a low risk of bias were selected and included in this meta-analysis. Two authors (UH, MZA) conducted the bias assessment and discussed any ambiguities with a senior author (HO).

DISCUSSION

The meta-analysis and systemic review have demonstrated the MAFLD prevalence and outcomes of COVID-19 among patients with MAFLD compared to those without. The study findings have established a high risk of COVID-19 disease severity and ICU admission among the patients with MAFLD than those without MAFLD. Moreover, there was an increased risk of COVID-19 mortality among MAFLD patients than those without MAFLD; however, this finding did not reach statistical significance.

COVID-19 is caused by SARS-CoV-2, which is genetically related to other coronavirus families such as SARS-CoV and Middle Eastern respiratory syndrome coronavirus (MERS-CoV).[43] These coronaviruses are known to affect liver function by different mechanisms. The direct effect of these viruses through translocation from the gut to the liver can spoil liver function. SARS-CoV-2 binds to the liver cells through angiotensin-converting enzyme receptors and causes direct toxicity through active viral replication within the hepatic cells. Furthermore, SARS-CoV-2 also can affect liver function through indirect mechanisms (e.g., causing ischemia, inflammation).[44] According to the cytokine storm hypothesis, SARS-CoV-2 infection can cause a severe immune-mediated cytokine storm because of inflammation that can damage the hepatocytes. This hypothesis was supported by the rise of the blood levels of the pro-inflammatory markers IL-2, IL-4, low-density lipoprotein, C-reactive protein, and serum ferritin in COVID-19 patients.[45] Among the other possible mechanisms of liver injury included drug-induced liver damage. Most of these patients were treated with antiviral drugs that can have harmful effects on hepatocytes, resulting in a rise in ALT and AST.[43,45]

The liver has an abundance of innate immune cells (e.g., macrophages, natural killer T cells, and γδ T cells).[46] Comorbid conditions such as obesity and MAFLD have been associated with the increased production of pro-inflammatory cytokines like tumor necrosis factor-α from Kupffer and adipose cells.[47] In MAFLD, free fatty acids flux in the hepatocytes and adipose tissue insulin resistance activates the liver macrophages. The dysregulated macrophages response in the liver of MAFLD patients promotes inflammation leading to the progression and severity of COVID-19.[4]

The presented meta-analysis revealed the high pooled prevalence of MAFLD among COVID-19 patients. This finding was comparable with the previously reported literature. In a meta-analysis of four studies, Pan et al.[50] reported a pooled prevalence of 0.31 (95% CI: 0.28-0.35) of MAFLD among COVID-19 patients. Moreover, the current study revealed a higher risk of COVID-19 disease severity among MAFLD patients than those without MAFLD. These findings were in alignment with other published studies. Hegyi et al.[51] reported an association of MAFLD with COVID-19. They demonstrated that MAFLD was associated with an increased risk of COVID-19 disease severity compared to the non-MAFLD group (OR = 2.61[95% CI: 1.75-3.91]).

Similarly, Singh et al.[52], in a pooled analysis, found that the presence of MAFLD among COVID-19 patients to be associated significantly with a higher risk of COVID-19 severity and ICU admission. Another study reported that obesity alone was associated with a significantly increased risk of COVID-19 disease severity even after adjusting for other confounders and co-morbidities.[53] The current meta-analysis revealed the effect of MAFLD on COVID-19 severity by using a large cohort of studies.

This study had limitations that need to be considered while interpreting the results. First, the respective studies included in this meta-analysis lacked a robust and consistent definition of COVID-19 disease severity. However, this limitation can be recommended for future epidemiological studies to contemplate while determining an association between COVID-19 outcomes and MAFLD. Furthermore, the various included studies did not adjust for confounding factors such as age, race, sex, and certain other co-morbidities, which can affect the study findings. Moreover, the study population had several co-morbidities, such as hypertension, obesity, DM2, CVD, and CKD, making it challenging to dissect the contribution of each co-morbidity towards COVID-19 outcomes, as previous studies have shown the negative association of these co-morbidities with COVID-19.[54] Lastly, fewer studies were included in the sub-group analysis of the effect of MAFLD on COVID-19 ICU admission rate and mortality, which made it challenging to analyze publication bias (less than ten articles). Despite the limitations, this study merits consideration. Foremost, to the best of our knowledge, this was the first study to report the MAFLD prevalence and COVID-19 outcomes together in a large-scale MAFLD population. In addition, this study is the first to report the COVID-19 mortality among MAFLD patients in a large cohort of studies.

CONCLUSIONS

In conclusion, MAFLD was more prevalent among patients with COVID-19. This meta-analysis and systemic review revealed a higher risk of COVID-19 disease severity and ICU admission in patients with MAFLD than their counterparts; however, the association between MAFLD and COVID-19 mortality was not significant. These findings suggested that the MAFLD patients should be followed closely for these complications if they develop COVID-19. The potential mechanism of COVID-19 severity among MAFLD patients remains illuminated by future studies. Furthermore, extensive prospective cohort studies are needed to include ICU admission rate and mortality outcomes in COVID-19 patients to elucidate the impact of MAFLD further.

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