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Association of non-alcoholic fatty liver and metabolic-associated fatty liver with COVID-19 outcomes: A systematic review and meta-analysis

Jagirdhar GSK *et al*. NAFLD and COVID-19

Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) and metabolic associated fatty liver disease (MAFLD) are on rise like any other liver disease and tends to affect 25% of the U.S. population. The impact of NAFLD and MAFLD among coronavirus disease 2019 (COVID-19) patients remains unclear.

AIM

To identify the association of NAFLD and MAFLD with mortality, hospitalization, hospital length of stay, and supplemental oxygen utilization in COVID-19 patients.

METHODS

A systematic review of literature on Cochrane, Embase, PubMed, ScienceDirect, and Web of Science databases was conducted from January 2019 to July 2022. Studies that evaluated NAFLD/MAFLD using laboratory methods, non-invasive imaging, or liver biopsy were included. The study protocol was registered in PROSPERO (ID CRD42022313259) and PRISMA guidelines were followed. The NIH quality assessment tool was used to assess the quality of the studies. Pooled analysis was conducted using the software Rev Man version 5.3. The stability of the results was assessed using sensitivity analysis.

RESULTS

Thirty-two studies with 43388 patients were included in the meta-analysis of which 8538 (20%) patients were observed to have NAFLD. There were 42254 patients from twenty-eight studies included in the mortality analysis. A total of 2008 patients died from COVID-19; 837 (10.52%) in the NAFLD group and 1171 (3.41%) in the non-NAFLD group. The odds ratio was 1.38 for mortality, and a 95% confidence interval (95%CI) of 0.97-1.95 and a $P = 0.07$. A total of 5043 patients from eight studies were included in the hospital length of stay analysis. There were 1318 patients in the NAFLD group and 3725

patients in the non-NAFLD group. A qualitative synthesis showed that the mean difference in the hospital length of stay was about 2 d between the NAFLD and non-NAFLD groups and a 95%CI of 0.71-3.27 and P = 0.002. For hospitalization rates, the odds ratio is 3.25 with a 95%CI of 1.73-6.10 and a P = 0.0002. For supplemental oxygen utilization, the odds ratio was 2.04 with a 95%CI of 1.17-3.53, and a P = 0.01.

CONCLUSION

Our meta-analysis suggests that there are increased odds of hospitalization, longer hospital length of stay, and increased use of supplemental oxygen in NAFLD/MAFLD patients.

Key Words: Non-alcoholic fatty liver; Fatty liver; Coronavirus; COVID-19; Metabolic associated fatty liver

Jagirdhar GSK, Qasba RK, Pattnaik H, Rama K, Banga A, Reddy ST, Flumignan Bucharles AC, Kashyap R, Elmati PR, Bansal V, Bains Y, DaCosta T, Surani S. Association of non-alcoholic fatty liver and metabolic-associated fatty liver with COVID-19 outcomes: A systematic review and meta-analysis. *World J Gastroenterol* 2023; In press

Core Tip: Metabolic-associated fatty liver disease (MAFLD) is like non-alcoholic fatty liver disease (NAFLD) and is a hepatic presentation of metabolic syndrome. NAFLD and MAFLD and widely prevalent. It is estimated that 25% of the United States population have this condition. The association and effect size between fatty liver disease and coronavirus disease 2019 (COVID-19) infection is still unconfirmed. The discrepancies in the available literature may be due to study design, confounding, small study population, and heterogeneity. We performed a systematic review and meta-analysis to study the impact of NAFLD/MAFLD on mortality, hospitalization, hospital length of stay, and supplemental oxygen utilization in COVID-19 patients.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the subspecies of coronavirus that is responsible for causing coronavirus disease 2019 (COVID-19), the respiratory illness responsible for the ongoing COVID-19 pandemic. Its first detected case was reported back in December of 2019 from Wuhan, China[1]. Since then, it has spread worldwide leading to a global pandemic. As of 12th December 2022, over 650 million confirmed cases have been reported with more than 6 million deaths[2]. Most COVID-19 cases are reported to be of mild to moderate forms with usual signs and symptoms varying from general fatigue, fever, and dry cough to some very unusual ones like loss of smell and taste. In severe form, it is associated with several comorbidities such as diabetes, hypertension, obesity, chronic obstructive pulmonary disease, and other cardiovascular diseases[3,4]. Patients with metabolic syndrome (MS) having obesity, hyperglycemia, dyslipidemia, and hypertension had worse outcomes in COVID-19[5,6]. A retrospective study from Cleveland Clinic, United States concluded that patients with MS were 77% more likely to be hospitalized, 56% more likely to be admitted to the intensive care unit, and 81% more likely to die from COVID-19[6]. A recent consensus of experts proposed redefining non-alcoholic fatty liver disease (NAFLD) as metabolic associated fatty liver disease (MAFLD)[7-9]. It is now considered the hepatic form of MS[10] and is one of the most common etiologies of chronic liver diseases (CLD). It has around 24% estimated global prevalence rate[11]. These patients may have a higher risk of hospitalization and severity of COVID-19 according to recently published reports. A cohort of Chinese patients indicated a higher risk of respiratory disease progression in MAFLD patients[12]. In another subsequent study, there was an increased risk for COVID-19 progression in younger patients with MAFLD[13]. However, there is still conflicting evidence addressing the severity of COVID-19 in MAFLD and NAFLD patients. Prior meta-analysis of a small number of studies did not detect worse outcomes in NAFLD/MAFLD patients with COVID-19[14-16]. Therefore, we decided to conduct this systematic review and meta-analysis to assess

the effect of NAFLD or MAFLD on mortality, hospitalization, length of hospital stay, and supplemental oxygen utilization among patients with COVID-19.

MATERIALS AND METHODS

This review is reported following the PRISMA statement[17] as indicated in the PRISMA checklist and was registered with PROSPERO (ID CRD42022313259; www.crd.york.ac.uk/prospero).

Search and selection

A literature search was performed in six bibliographic databases PubMed, Cochrane, Embase, Science Direct, and Web of Science from Jan 2020 to July 2022. Using a combination of keywords and medical subject headings, we used vocabulary related to "COVID-19" OR "SARS-CoV-2" AND "NASH" OR "NAFLD" OR "Non-alcoholic Fatty Liver Disease" OR "Fatty Liver" OR "Metabolic Syndrome".

Six authors (Jagirdhar GSK, Qasba RK, Kashyap R, Flumignan Bucharles AC, Banga A, and Reddy ST), were involved in the study selection. After removing duplicates using Endnote reference manager software, two authors did the title and abstract screening independently using the Rayyan software (https://rayyan.ai/). Studies satisfying the inclusion criteria were retrieved and screened for full-text eligibility. Conflicts between two authors on study selection were resolved among the authors or were solved by an additional third arbiter in case a consensus could not be reached. We included observational studies that studied mortality, hospitalization, hospital length of stay and supplemental oxygen utilization outcomes in COVID-19 patients. We included studies that assessed NAFLD/MAFLD using lab assessment [fibrosis-4 (FIB-4), aminotransferase/platelet ratio index, Fibrosis score, hepatic steatosis index (HIS), *etc.*], non-invasive imaging [elastography, liver ultrasound or computed tomography (CT) scan, magnetic resonance elastography, liver stiffness measurement], or liver biopsy. For studies that diagnosed NAFLD using biomarkers/lab diagnosis, we only included studies that measured NAFLD prior to index admission since acute COVID infection

can increase biomarker/lab values leading to misdiagnosis as NAFLD. We excluded studies that were: (1) Systematic reviews; (2) Meta-analyses; (3) Literature reviews; (4) Survey studies; (5) Case reports; (6) Animal studies; (7) Single arm studies; (8) Studies that do not measure NAFLD/MAFLD/fatty liver; (9) Not a retrospective or prospective study; (10) Randomized controlled trials; (11) Studies not related to COVID-19 patients; (12) Not in English language; and (13) Abstract only studies. We studied NAFLD/MAFLD patients together since recent studies are emerging that NAFLD is related to MS both mutually and bi-directionally. We included studies that compared no or mild NAFLD/MAFLD patient outcomes to moderate or severe NAFLD/MAFLD patient outcomes. We also searched systematic reviews and meta-analyses obtained from our search for eligible articles and added studies meeting our inclusion criteria. When multiple publications used overlapping study populations, we included the study with greater sample size. We grouped studies for the meta-analysis based on mortality, hospitalization, hospital length of stay, and supplemental oxygen utilization outcomes.

Data extraction

Three independent authors (Qasba RK, Banga A, Flumignan Bucharles AC) performed data extraction from all the included studies into a pre-piloted data extraction form in Microsoft Excel. A fourth author (Jagirdhar GSK) independently assessed the extracted data for validation. The following was extracted from each study: (1) General information: First author, title, digital object identifier, and year of publication; (2) Study characteristics: Study site/country, study period, number of centers, Journal, study design; (3) Participant characteristics: Number of NAFLD/MAFLD and non-NAFLD/MAFLD patients and their demographic characteristics, method of assessment of NAFLD; and (4) Outcomes: Number of patients with the events (mortality, hospital length of stay, hospitalization, and supplemental oxygen utilization) in NAFLD/MAFLD and non-NAFLD/MAFLD populations.

Statistical analysis

The Review Manager (RevMan) [Computer application] Version 5.4.1, the Cochrane Collaboration, 2020 was used to assess all results[18]. Using a random-effects model, crude odds ratios (OR) for each study with corresponding 95% confidence intervals (CI) were calculated from raw data for events and non-events from each research[19]. A *P*-value of < 0.05 was considered statistically significant for the analysis. Forest plots were generated to present the results of the meta-analyses. A previously proven technique was used to transform the median to mean to examine continuous outcomes[20]. The estimates for mean differences were then produced using the random effects model[19]. To measure study heterogeneity, the Cochrane Q and the I^2 statistics were used[19]. Low-level heterogeneity was defined as I^2 20%[19]. The stability of the results was assessed using sensitivity analysis. Egger's test and funnel plots were used to determine the likelihood of publication bias[21].

Quality assessment

The NIH scale was used to assess case control, cohort, and randomized controlled trials for appraisal of study quality. As per the scale, studies were classified into three categories: Good, fair, or Poor. Five authors (Jagirdhar GSK, Qasba RK, Banga A, Rama K, Pattnaik H) independently performed the quality assessment of the included studies, and any discrepancies were resolved through discussion.

RESULTS

Search and selection

A total of 1084 records were identified from the initial search, out of those 242 were excluded as duplicates and 842 articles were selected for the screening of title and abstract. Eighty-seven were chosen for full-text screening and a total of 32 studies met the inclusion criteria. These papers were eligible for qualitative and quantitative.

Figure 1 shows the PRISMA diagram for the study selection process. Since we included studies that compared mortality, hospitalization, hospital length of stay, and

supplemental oxygen utilization in mild or no NAFLD/MAFLD to moderate to severe NAFLD/MAFLD. We excluded studies that did not present these outcomes or those that did not mention the method of NAFLD assessment[22-28].

Characteristics of included studies

We analyzed data for a total of 43388 patients from thirty-two studies in the meta-analysis of which 8538 (20%) patients were observed to have NAFLD and 34850 did not have NAFLD. The studies observed the outcomes of patients infected with COVID-19 with and without NAFLD/MAFLD. The outcomes recorded were the rate of hospitalization, length of stay in the hospital, supplemental oxygen requirement, and mortality of patients in both groups.

All 29 of 32 studies reported mortality data for COVID-19 infection. 10 studies reported hospital length of stay, 4 studies reported need for hospitalization, and 4 reported supplemental oxygen utilization. The main characteristics of the included studies are summarized in Table 1.

NAFLD/MAFLD and mortality outcomes in COVID-19: A total of 42254 patients from twenty-eight studies were included in the qualitative analysis. A total of 2008 patients died from COVID-19; 837 (10.52%) in the NAFLD group and 1171 (3.41%) in the non-NAFLD group. The odds ratio was 1.38 for mortality with a 95%CI of 0.97-1.95, I^2 = 84%, and P = 0.07. Figure 2A shows the forest plot and meta-analysis of mortality outcomes in COVID-19 patients. Figure 2B shows the sensitivity analysis of the studies. We failed to observe an association between NAFLD/MAFLD and in-hospital mortality in COVID-19 patients. Visual inspection of the standard error plots for the mortality meta-analysis (Supplementary Figure 1) suggests symmetry without an underrepresentation of studies of any precision. No publication bias was found on Egger's test, P = 0.466.

NAFLD/MAFLD and Hospitalization in COVID-19: Four studies were taken for quantitative analysis with 28199 patients to assess the need for hospitalization in NAFLD and non-NAFLD groups with COVID-19. A total of 4302 patients were hospitalized for COVID-19: 765 (50.83%) patients from the NAFLD group and 3537 (13.25%) patients from the non-NAFLD group. The odds ratio is 3.25 with a 95%CI of 1.73-6.10, I^2 = 92%, and a P-value of 0.0002. Figure 3A shows the forest plot for hospitalization in COVID-19 patients with and without NAFLD/MAFLD. Figure 3B shows the sensitivity analysis of the studies. Visual inspection of the standard error plots for the need for hospital admission meta-analysis showed (Supplementary Figure 2) symmetry without an underrepresentation of studies of any precision. No publication bias was found (Egger's test, P = 0.254). However, as there were < 10 studies included in the analysis; thus, publication bias cannot be completely excluded.

NAFLD/ MAFLD and Hospital length of stay in COVID-19: A total of 5043 patients from ten studies were included in the qualitative analysis. A total of 1318 patients in the NAFLD group and 3725 patients in the non-NAFLD group. A qualitative synthesis showed that the mean difference in the hospital length of stay was 1.99 d between the NAFLD and non-NAFLD groups and a 95%CI of 0.71-3.27, I^2 = 70%, and P-value 0.002. This denotes an average of about 2 d of additional hospital stays among NAFLD/MAFLD patients with COVID-19. Figure 4A shows a forest plot and meta-analysis of hospital length of stay in COVID-19 patients with and without NAFLD/MAFLD. Figure 4B shows the sensitivity analysis of the studies. Visual inspection of the standard error plots for the hospital length of stay meta-analysis (Supplementary Figure 3) suggests symmetry without an underrepresentation of studies of any precision. Publication bias was found on Egger's test, P = 0.013.

NAFLD/MAFLD and supplemental oxygen utilization in COVID-19: A total of 3609 patients from four studies were included in the qualitative analysis to assess the requirement for supplemental oxygen in COVID-19 patients during their in-hospital

stay. 170 (7.30%) patients in the NAFLD group and 96 (7.48 %) in the non-NAFLD group required supplemental oxygen. The odds ratio was 2.04 with a 95%CI of 1.17-3.53, $I^2 = 56\%$, and a P value of 0.01. Figure 5A shows a forest plot and meta-analysis of supplemental oxygen utilization in COVID-19 patients with and without NAFLD/MAFLD. Figure 5B shows the sensitivity analysis of the studies. Visual inspection of the standard error plots for the need for supplemental oxygen requirement meta-analysis (Supplementary Figure 4) suggests symmetry without an underrepresentation of studies of any precision. No publication bias was found on Egger's test, $P = 0.500$. However, as there were < 10 studies included in the analysis; thus, publication bias cannot be completely excluded.

Quality assessment

Figures for quality assessment of case-control, cross-sectional, and cohort studies included in our study are attached with supplementary material. For case-control studies, the quality assessment of included studies identified three as good quality, one as fair, and no poor rated studies. None of the studies were able to recruit a concurrent control or blind the outcome assessors. Only Madan *et al*[41] discussed reasons for selecting included participants, providing a sample size justification additionally, Trivedi *et al*[48] were the only ones to include a random selection of participants. For included cohorts, nineteen were identified as good and ten as fair with no poor rated studies. Only Kim *et al*[40], Yoo *et al*[54], and Zhou *et al*[56] could provide a sample size justification additionally studies scored poorly on blinding of outcome assessors with only Marjot *et al*[42] and Zhou *et al*[56] being able to do so, Furthermore Ji *et al*[34] and Huang *et al*[38] were the only ones to measure exposure more than once for each person during the study period.

DISCUSSION

Our systematic review and meta-analysis of 32 studies and 43388 COVID-19 patients, of which 8538 (20%) patients were observed to have NAFLD/MAFLD, provided a

comprehensive assessment of mortality, need for hospitalization, hospital length of stay, and need for supplemental oxygen in COVID-19 afflicted patients with fatty liver disease. In the current meta-analysis, there was no relation between pre-existing NAFLD/MAFLD and COVID-19-related mortality. The results for the unadjusted analysis showed an increased risk of mortality, but the results were not statistically significant. Similar results were seen in a prior meta-analysis[59]. Meta-analysis of 7 studies by Hayat *et al*[58] on MAFLD and COVID-19 mortality found an OR of 1.45 and a non-significant 95%CI of 0.74-2.84, $P < 0.01$.

As per our meta-analysis, patients with NAFLD/MAFLD had higher hospitalization rates compared to non-NAFLD/MAFLD patients (OR = 2.71, 95%CI: 1.10-6.70, P = 0.03). COVID-19 is associated with increased inflammation and thrombosis, while NAFLD/MAFLD are states of chronic inflammation. When occurring together, these may worsen disease status causing increased hospitalization rates. Contrarily, some studies have reported no increase in disease severity or need for hospitalization in NAFLD patients with COVID compared to controls. This could be due to the small study population and the retrospective nature of the study results[39,54]. Since our meta-analysis may be one of the largest to date, the results provided are expected to be closer to the true value. Our meta-analysis found that patients with NAFLD/MAFLD had a statistically significant longer hospital length of stay compared to those without. An unadjusted assessment of eight studies found that patients with pre-existing NAFLD, on average, spent an additional 2 d in the hospital compared to COVID-19 patients without NAFLD. Patients with NAFLD have ongoing inflammation processes which compound the disease process of COVID-19, thus leading to a more severe course of illness. This could explain the higher hospitalization rates and longer duration of hospital stay. Previous studies have reported similar results with longer hospital stays for NAFLD patients afflicted with COVID-19[32,60,61]. On the contrary, some studies reported no difference in the duration of hospital stay in those with or without NAFLD[54,62].

Our meta-analysis of four studies revealed that NAFLD patients had a greater need for supplemental oxygen as compared to controls. NAFLD patients may have a more severe disease course and therefore, require supplemental oxygen during their hospital stay. One previous study reported that NAFLD patients had a more frequent need for oxygen support[53].

CLD due to NAFLD has seen a rising trend over the years. Over 83 million Americans suffered from NAFLD with a prevalence rate of 26% according to data from 2015. This value is said to rise by 21% to over 100 million patients by the year 2030[63]. The growing epidemics of obesity and diabetes mellitus II have played a major role in increasing the prevalence of NAFLD worldwide, including the progression of NAFLD to non-alcoholic steatohepatitis (NASH), cirrhosis, and even hepatocellular malignancy[63,64]. NAFLD is found in more than 50% of individuals suffering from obesity or type 2 diabetes mellitus. In their study, Estes et al[61] reported the median age of NAFLD patients to be around 50 years. They also found that more males suffered from NAFLD as compared to females. These results are similar to our study. The absence of an established screening method and global health policies focusing on NAFLD, and primary care interventions lead to a substantial increase in patients with NAFLD going undetected[57]. It also means that it's up to the clinician's preference and choice of the screening tool to measure NAFLD, thus creating a selection bias amongst various studies. This discrepancy could be observed in the studies included in our meta-analysis as multiple screening modalities were used in different clinical settings, including HSI, FIB-4 scoring, CT scan of the liver, liver function tests, and liver biopsy amongst others.

The presence of NAFLD confers additional susceptibility to COVID-19 infection in individuals exposed to SARS-CoV-2[65]. Pre-existing NAFLD at the time of COVID-19 diagnosis can be an indicator of increased severity of infection and utilization of health care services. As mentioned earlier, more than half of the individuals suffering from type 2 diabetes mellitus (2nd most common comorbidity in COVID-19) have comorbid NAFLD to a certain degree[62]. Similarly, NAFLD is associated with multiple risk factors

like cardiovascular diseases, obesity, and coexisting chronic lung disease which independently influences COVID-19 susceptibility and severity[63,66-70]. The impact of NAFLD on disease severity is seen through a blunted immune response to SARS-CoV-2 infection in COVID-19, leading to an increased risk of severe disease[32,15,49,71]. A retrospective observational study observed that ongoing inflammation in NAFLD puts patients with active COVID-19 infection at an increased risk of thromboembolism and associated mortality[53]. Various SARS-CoV-2 entry factors like angiotensin-converting enzyme (ACE), ADAM17, dipeptidyl peptidase 4, and TMPRSS2 and NAFLD-related genes such as ACE, dipeptidyl peptidase 4, interleukin (IL)-10, tumor necrosis factor (TNF), and AKT1 as well as cytokine-mediated signaling, PI3K-Akt, AMPK, and mechanistic target of rapamycin signaling pathways have been identified which sheds light on the propensity for increased severity of illness in SARS-CoV-2 infected NAFLD patients[72]. The spike protein of coronavirus has a high affinity for the receptor of ACE, which is found in the lung and the hepatobiliary cells. Furthermore, COVID-19 infection upregulates the expression of ACE receptors[73]. This leads to the hyperactivation of an immune cascade that damages the hepatocytes[74,75]. Chronic low-grade inflammatory state in individuals with NAFLD/MS creates a hypoxic environment for adipocytes leading to their dysfunction. This promotes the increased release of pro-inflammatory cytokines IL-6, IL-8, C reactive protein, and TNF-α, and the recruitment of macrophages, B-cells, and T-cells. This effect is compounded by the systemic hyperactivation of the inflammatory cascade in active COVID-19 infection, which aggravates the ongoing inflammation of the hepatocytes, leading to decompensation of NAFLD and extensive hepatocyte damage[76]. Additionally, patients with NAFLD have insulin resistance, which further serves as a conducive ground for widespread inflammation[77,78].

Bramante *et al*[75] conducted a retrospective study that showed that with each additional year of having NAFLD/NASH the risk of hospitalization for COVID-19 increased. An assessment of the association between liver fibrosis scores and the clinical outcomes in patients with COVID-19 reported that a one-point score increase in FIB-4

was significantly associated with increased death, but not hospitalization. The authors also found that for every unit elevation in aspartate aminotransferase/alanine aminotransferase ratio, the risk of death increased by 178%[80]. Patients with higher FIB-4 > 2.67 scores had a higher risk of developing COVID-19[81]. Therefore, primary prevention is essential to control NAFLD during its development. Bramante *et al*[75] also showed that patients on prior treatments for NAFLD such as metformin and glucagon-like-peptide 1 receptor agonists had a reduced risk of hospitalization with the most significantly decreased risk from recent bariatric surgery. This highlights the importance of obesity as a cofactor to worse outcomes in COVID-19 patients and weight loss as the most significant contributing factor to improved outcomes in NAFLD[62]. Several studies found a higher incidence of obesity and NAFLD in patients hospitalized for COVID, which can also worsen disease severity[55,61,79]. This association may be confounded by the presence of obesity, which is an independent risk factor for COVID-19 severity. Previous studies reported odds ratios after adjusting for obesity and found statistically significant results in the association between NAFLD and COVID-19[81,82]. However, in a regression analysis, Li *et al*[79] observed that NAFLD independently does not affect the prognosis of severe COVID-19. Any association between NAFLD and COVID-19 is likely attributed to the confounding effect of obesity, measured in terms of body mass index, waist circumference, and hip circumference. Further studies with a larger sample size are needed to explain the varied results observed in these studies. Roca-Fernández *et al*[63] reported that higher liver fat percentages or evidence of liver fibro-inflammation, and features of NAFLD, increased the likelihood of symptomatic COVID-19. Interestingly, they found that obese patients with higher liver fat had a higher probability of having symptomatic COVID-19 compared to obese patients with normal liver fat. This is in favor of NAFLD being an independent risk factor for COVID-19 irrespective of obesity.

Strengths and limitations

We followed rigorous methodology, adhered to PRISMA guidelines, and registered our study in PROSPERO. Most of the studies were retrospective case-control and cohort studies which can be associated with the risk of bias, particularly in the absence of adjusting for confounders. NAFLD/MAFLD patients underlying medical conditions and co-morbidities that are components of MS can interfere with the outcomes studied. We excluded studies on NAFLD/MAFLD patients with other underlying causes for liver diseases including alcoholic liver disease. We understand there may be additional etiology for liver disease in patients that is underdiagnosed and may impact our study findings. The retrospective nature of most of the studies in our analysis does not imply a causal relationship between NAFLD/MAFLD and measured outcomes. We included studies that measured NAFLD/MAFLD using non-invasive procedures such as imaging and biomarker/lab diagnosis. Since they are not the gold standard for diagnosis, there may be misclassification of patients with and without NAFLD/MAFLD. The method of diagnosis of NAFLD/MAFLD varied across studies so, there may be some misdiagnoses that can influence the results of the study. However, we included studies that compared absent or mild NAFLD/MAFLD to moderate or severe NAFLD/MAFLD to maintain homogeneity. We considered NAFLD/MAFLD patients in the same group, however, there may be important differences between these two groups that may alter the outcomes. We observed the per-study protocol in our meta-analysis. We detected significant differences in our study population for the various outcomes measured. However, there was statistical heterogeneity in our results that should be taken into consideration. We also excluded studies in a language other than English due to difficulty with translation and interpretation of results. This can introduce bias in our study results. The studies included in our meta-analysis were from 12 different countries with more studies from China and the United States, but we consider the results to be generalizable globally. However, since the studies were from different countries the level of care at each health institution may be different, which can lead to different levels of disease severity, disease progression, and death. Our study aims for hypothesis generation and further

research in NAFLD/MAFLD patients to better understand the disease pathophysiology and patient risk profiles.

CONCLUSION

Our meta-analysis suggests that NAFLD/MAFLD patients appear to have higher rates of hospital admissions and longer in-hospital stays without any increase in mortality compared to non-NAFLD/MAFLD patients. Further research is needed to explore if fatty liver disease may be a risk factor that can lead to severe COVID-19 infection.

Implications for clinical practice

NAFLD/MAFLD are chronic pandemics rapidly on the rise. There is a lack of awareness and education among healthcare professionals and patients about its health impact, morbidity, and economic impact as they progress. There is a lack of systems/protocols in place to enforce the diagnosis of NAFLD globally and as a part of regular screening in primary care clinics, diabetic clinics, and routine health care visits. Propagation of information on NAFLD and involvement of international organizations, scientific societies, and the pharmaceutical industry to improve public health policies related to NAFLD. Patient education on NAFLD/MAFLD as a co-morbid risk factor for infectious diseases such as COVID-19 like other known risk factors such as hypertension, obesity, and diabetes, and measures to diagnose and treat NAFLD actively are needed.

Implication for research

Futures research on longitudinal prospective studies with larger numbers on NAFLD/MAFLD as a risk factor for COVID-19. Future studies should focus on genetics, immunology, and molecular epidemiology to better understand the mechanisms for poor outcomes in the NAFLD population.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) and its hepatic manifestation metabolic-associated fatty liver disease (MAFLD) have a rising prevalence worldwide. It is a co-morbidity like obesity, hypertension, and chronic kidney disease. NAFLD/MAFLD like obesity is considered chronic inflammatory states according to recent literature. Therefore, patients with NAFLD/MAFLD are hypothesized to have worse outcomes with coronavirus disease 2019 (COVID-19).

Research motivation

Existing literature shows conflicting information on the association of NAFLD/MAFLD in COVID-19 patients. Some studies show worse outcomes with NAFLD/MAFLD and COVID-19 infection. Some studies state it is not a risk factor for severe COVID-19. Understanding the pathophysiology and pathogenesis between fatty liver disease and COVID-19 is necessary for prevention, and management of NAFLD/MAFLD patients. Insight into this relationship will help further research and better preventative and nutritional management of these patients. It is imperative to explore the relationship of NAFLD/MAFLD with COVID-19 to improve patient care and treatment protocols for better outcomes.

Research objectives

In this meta-analysis, we investigated the association between NAFLD/MAFLD with the mortality and severity of COVID-19 infection.

Research methods

A systematic review of literature across five databases was done from January 2019 to June 2022. Observational studies were included. Studies that evaluated NAFLD/MAFLD using lab assessment/biomarker assessment, non-invasive imaging, or liver biopsy were included. We registered our study protocol in Prospero and followed the "PRISMA" guidelines (Figure 1). Meta-analysis was conducted on studies

with outcomes for hospitalization, hospital length of stay, supplemental oxygen utilization, and mortality of COVID-19 infection outcomes using Rev Man version 5.3. To evaluate the validity of our studies the NIH quality assessment tool was used. The stability of the results was assessed using sensitivity analysis.

Research results

A total of 43388 patients from thirty-two studies were included in the final analysis. There were 8538 (20%) with NAFLD/MAFLD. A total of 42475 patients from twenty-nine studies were included in the mortality analysis. There was an odds ratio of 1.36, a *P*-value of 0.07 for mortality with COVID-19. A total of 5043 patients from eight studies were included in the hospital length of stay analysis. NAFLD patients spent a mean hospital stay of an additional about 2 d when compared to non-NAFLD. For hospitalization rates, the odds ratio is 3.25 and a *P*-value of 0.0002. For supplemental oxygen utilization, the odds ratio was 2.04 with a *P*-value of 0.01. Our meta-analysis was able to show that there is an association between NAFLD/MAFLD and COVID-19. Our study aims to increase awareness that NAFLD/MAFLD may be a potential risk factor for severe outcomes in infections. More research is needed to better explain the relationship and the pathophysiology behind it.

Research conclusions

This systematic review and meta-analysis of observational studies suggests that NAFLD/MAFLD patients had higher odds of developing severe forms of COVID-19 in comparison to non-NAFLD patients. Further research to understand the causality and strength of this relationship is needed.

Research perspectives

This review was not able to clarify why the association between NAFLD/MAFLD and COVID-19 was seen. Large size prospective studies with balanced confounding factors are necessary. Since the global burden of NAFLD/MAFLD is rapidly rising,

understanding genetics and immunological mechanism will help advance treatment and prevention strategies.

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