

Outcome of Patients with Metabolic-Associated Fatty Liver Disease Who Are Infected with SARS-CoV-2: A Meta-Analysis

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ABSTRACT

Background: Metabolic-associated fatty liver disease (MAFLD) is excess fat accumulation in the liver due to metabolic syndrome. Coronavirus disease 2019 (COVID-19) is an infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 not only attacks the respiratory system but also involves systemic and extra-pulmonary organ disorders, including liver disorders. This review evaluates the severity of COVID-19, mortality, and length of hospital stays of patients with MAFLD who were infected with SARS-CoV-2. **Methods:** Literature searches were conducted through various online databases. The risk of bias assessment was conducted by two researchers using the Newcastle Ottawa Scale tool for NRSI studies, and any discrepancies were resolved by another team member. The meta-analysis was performed using Revman 5.4.1 and results were presented in forest plot by calculating the pooled odds ratio or mean difference between the MAFLD and non-MAFLD groups from the evaluated studies with a 95% CI. **Results:** The results of the meta-analysis using a fixed-effect model from seven studies showed that COVID-19 patients with MAFLD were associated with a higher mortality compared to those without MAFLD (OR 1.41, 95% CI 1.19-1.69, $p=0.01$, I^2 48). However, there were no differences in COVID-19 severity (OR 3.12, 95% CI 0.89-11.03, $p=0.08$, I^2 92) and length of hospital stay (MD 1.27, 95% CI 0.03-2.52, $p=0.04$, I^2 80) between the two groups. **Conclusion:** MAFLD patients infected with SARS-CoV-2 were associated with higher mortality than non-MAFLD patients, but they were not associated with greater severity of COVID-19 nor a longer duration of hospitalization.

Keywords: COVID-19, MAFLD, outcome, severity, mortality, length of hospital stays.

INTRODUCTION

Metabolic-associated fatty liver disease (MAFLD) is a condition where excess fat accumulates in the liver due to metabolic syndrome.¹ Patients with MAFLD can be asymptomatic but may have an increased risk of complications, i.e., liver fibrosis, liver cancer, as well as extrahepatic complications such as cardiovascular complications and chronic kidney disease.² Moreover, patients with MAFLD generally have comorbid metabolic disorders, such as obesity, dyslipidemia, diabetes mellitus, and hypertension, which are known also to increase the risk of severe COVID-19.³

Coronavirus disease 2019 (COVID-19) is an infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).⁴ This disease was first discovered in the city of Wuhan, China in late 2019 and rapidly spread until it was declared a pandemic by the World Health Organization (WHO) in February 2020.⁴ SARS-CoV-2 does not only attack the respiratory system but also involves systemic and extra-pulmonary organ disorders, including liver disorders.³ COVID-19-related liver damage is a liver injury that occurs during the disease and treatment of COVID-19, with or without pre-existing liver disease.³ The hepatobiliary system can be an important target and predictor of the adverse impact of COVID-19 in patients with pre-existing liver disease.³ Several previous studies have been conducted to search the phenotype of populations at risk of experiencing severe and critical COVID-19, including patients with MAFLD, to provide appropriate and intensive management.

METHODS

This is a systematic review and meta-analysis following the guidelines from the 2009 PRISMA statement. The research protocol has been registered in PROSPERO with registration number CRD42022358932. A literature search was conducted through various online databases including PUBMED, Cochrane Library, ProQuest, ScienceDirect, and EBSCOhost using keywords "COVID-19",

"SARS-CoV-2", "Wuhan virus", "NAFLD", "MAFLD", "non-alcoholic fatty liver disease", "metabolic fatty liver disease", "outcome", "mortality", "severity", and "hospitalization". The studies included in this research are NRSIs (Non-Randomized Studies of Interventions) that include adult patients with MAFLD infected with SARS-CoV-2, assessing outcomes of length of hospital stay, severity, and mortality.

The literature search was conducted by two members of the research team, and any disputes were resolved by other members of the research team. Observational studies assessing outcomes (severity, mortality, and length of hospitalization) of adult patients with MAFLD infected with SARS-CoV-2 were included in the systematic review. Furthermore, only cohort studies were included in the meta-analysis. The data extraction of this study included basic study characteristics (name of the researcher, year, country, study design, characteristics of the study population, sample size), outcomes, and bias factors. Outcomes collected from the study were COVID-19 severity, length of hospital stays, and mortality. The risk of bias assessment was conducted by two researchers using the Newcastle Ottawa Scale tool for NRSI studies, and any discrepancies were resolved by another team member. Studies with NOS scores >7 were classified as good-quality studies and studies with NOS scores 6-7 were classified as fair-quality studies. Studies with NOS scores <6 were classified as poor-quality studies and will not be included in the analysis. The meta-analysis was performed using the Revman 5.4.1 software. The systematic review results were presented in the form of a narrative review. The meta-analysis results were presented in the form of a forest plot by calculating the pooled odds ratio or mean difference between the fatty liver and non-fatty liver groups from the evaluated studies with a 95% CI.

RESULTS

The literature search through electronic databases and manual searching yielded 2,560 articles. After eliminating duplicates, 594 studies were retained (**Figure 1**). The number of studies screened based on the title and abstract was 1,966

studies and 17 studies were found relevant to the research topic and the full text was assessed using the eligibility criteria. A total of four studies were excluded due to the following reasons: one study is a literature review; one study included a population with other liver etiologies, namely chronic hepatitis B and hepatitis C; and two

studies reported outcomes that did not meet the research question. As a result, 13 studies that met the eligibility criteria were included in the systematic review (**Table 1**) and 8 cohort studies were further included in a meta-analysis. Based on the risk of bias analysis (**Table 2** and **Table 3**), all the studies have good quality.

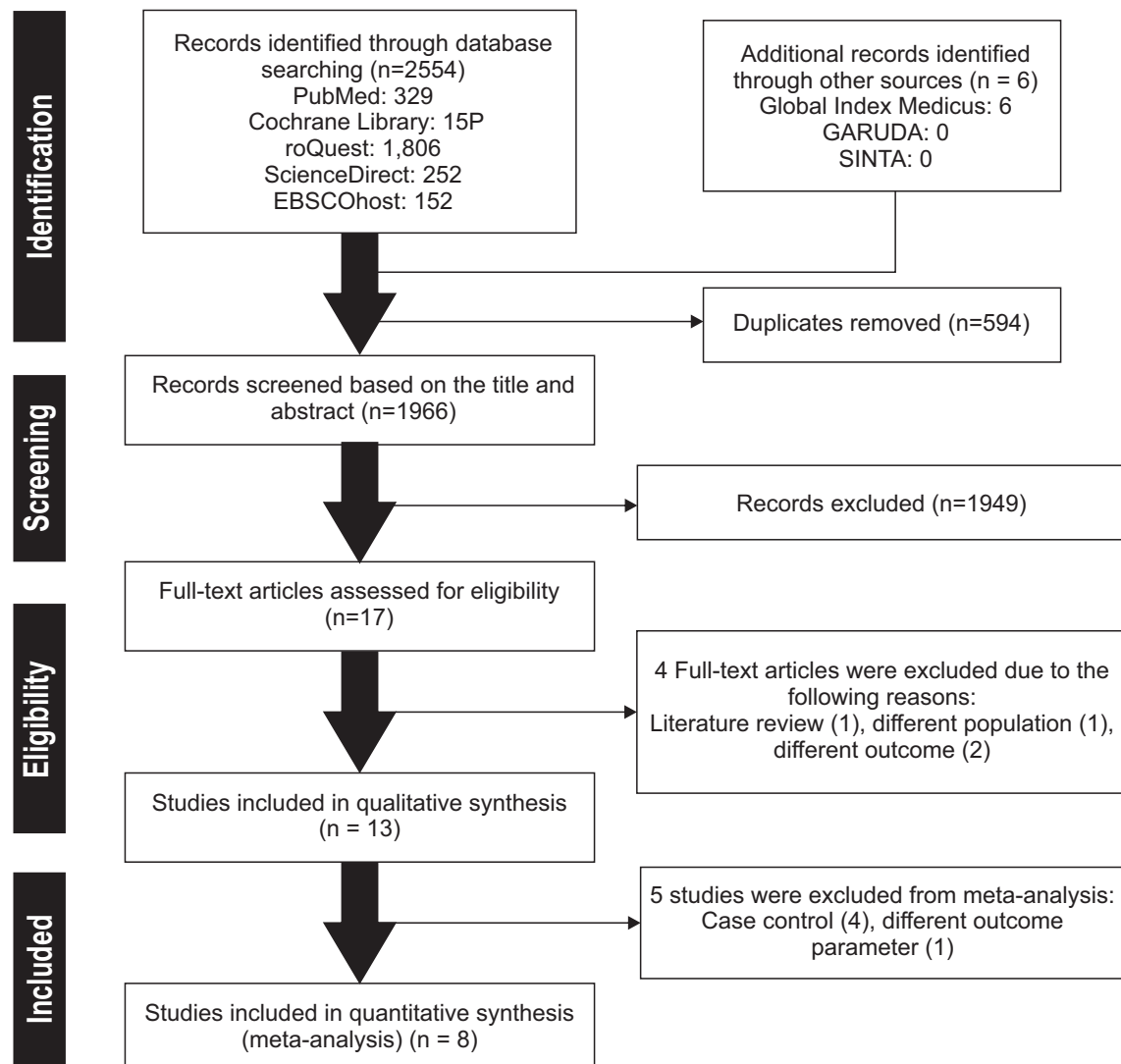


Figure 1. PRISMA Chart

Table 1. Study Characteristics

Author, Year, Study design (Country)	MAFLD diagnosis criteria	Patient Admission Period	Number of Subjects Case: Control:	Age (Year) Case: Control:	Outcome Measured	Additional outcome	Bias/ confounding
Bramante et al 2020, Retrospective cohort (USA)	Patients with ICD codes NAFLD and NASH, or patients with BMI ≥ 30 kg/m ² and elevated SGPT enzymes on three different occasion	March-August 2020	6700 Case: 373 Control: 6327	Median Case: 46	Hospitalization MAFLD was associated with increased risk for hospital admission due to COVID-19 (OR 1,43;95%CI 1,09–1,88, $p<0,01$).	-	Possibility for selection bias, in which there is the possibility of MAFLD patients without an increase in SGPT on three different occasion.
Forlano et al 2020, Retrospective cohort (Great Britain)	Patient with ultrasoundography or CT showing sign of fatty liver	February-April 2020	193 Case: 61 Control: 132	Median Case: 60 (53–75) Control: 70,5 (53–79)	Length of hospital stay There was no significant difference in length of stay between the MAFLD and non-MAFLD group (7 vs 6,5; $p=0,72$) In-hospital mortality There was no significant difference in-hospital mortality rates between the MAFLD and non-MAFLD group (29% vs 31%, $p=0,4$)	Time from symptom onset to hospital admission Patients with MAFLD tended to have a shorter interval from symptom onset to hospital admission than the non-MAFLD (5 vs 7, $p=0,035$)	The sample size was relatively small and the study design was retrospective.
Gao et al 2020, Case control (China)	CT imaging show evidence of hepatic steatosis, with the presence of one of the following diagnostic criteria: BMI ≥ 23 kg/m ² , presence of type 2 DM, or evidence of metabolic dysregulation	January-February 2020	130 Case: 65 Control: 65	Mean $\pm$ SD Case: 46 $\pm$ 13 Control: 47 $\pm$ 13	COVID-19 severity MAFLD was associated with a four times higher risk for severe COVID-19 (OR 4,22; 95%CI 1,45–12,22)	-	N/A
Ji et al 2020, Retrospective cohort (China)	Hepatic steatosis index > 36 and/ or evidence of ultrasound imaging	January-February 2020	202 Case: 76 Control: 126	Median (IQR) Case: 44,5 (34,8–54,1)	COVID-19 severity MAFLD patients has a higher risk of COVID-19 disease progression (44,7% vs. 6,6%; $p<0,0001$)	Viral shedding time MAFLD patients has longer viral shedding time (17,5 $\pm$ 5,2 days vs. 12,1 $\pm$ 4,4 days; $p<0,0001$)	N/A
Madan et al 2022 Case control (India)	Liver attenuation index (LAI) ≤ 5 in the upper abdomen	January-October 2021	446 Case: 289 Control: 157	Mean $\pm$ SD Case: 56,4 $\pm$ 14,3 Control: 58,3 $\pm$ 17,1	Length of stay There was no significant difference in length of stay between patient with MAFLD and without MAFLD (10,1 $\pm$ 7,14 vs 10,7 $\pm$ 8,13; $p=0,430$) Mortality There was no significant difference in mortality rates between patient with MAFLD and without MAFLD (13,2% vs. 13,8%; $p=0,866$)	Need for mechanical ventilation There was no significant differences regarding need for mechanical ventilation between patient with MAFLD and without MAFLD (9,3% vs. 8,9%; $p=0,385$) Length of ICU stay There was no difference in length of ICU stay between patient with MAFLD and without MAFLD (8,3 $\pm$ 6,8 vs. 7,1 $\pm$ 5,7; $p=0,208$)	Retrospective study design, no information regarding alcohol consumption and hepatitis B and C markers was obtained.
Mahamid et al 2020 Case control (Israel)	Evidence of hepatic steatosis, in the presence of any of the following diagnostic criteria: BMI ≥ 23 kg/m ² , presence of type 2 DM, or evidence of metabolic dysregulation	March-April 2020	71 Case: 22 Control: 49	Mean $\pm$ SD Case: 53,7 $\pm$ 19,9 Control: 56,2 $\pm$ 20,0	COVID-19 severity MAFLD was associated with an increase risk for severe COVID-19 (OR 3,57; CI95% 1,22-14,48; $p=0,0031$)	-	The study design was retrospective and case control which prone to selection bias. Hepatitis was assessed through history taking (self-reported) can also give rise to recall bias.

Table 1. Study Characteristics

Author, Year, Study design (Country)	MAFLD diagnosis criteria	Patient Admission Period	Number of Subjects Case: Control:	Age (Year) Case: Control:	Outcome Measured	Additional outcome	Bias/ confounding
Moctezuma-Velázquez et al 2022 Retrospective cohort (Mexico)	Non-alcoholic fatty liver was defined as a Dallas steatosis index ≥ 0 Metabolic fatty liver is defined by the presence of steatosis findings on CT with one of the following conditions: (1) BMI > 25 kg/m ² ; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 150 mg/dL; hypertension; prediabetes.	February-April 2020	470 Case: 359 Control: 111	Median (IQR) Case: 51 (42-61) Control: 52 (42-66)	Mortality MAFLD was associated with an increase mortality rate (OR 2,13; 95%CI 1,05-4,34; p=0,04)	ICU requirement MAFLD was associated with a higher ICU admission rate than the non-PHM group (OR 1,71; IK95% 0,95-3,06; p=0,07) Need for mechanical ventilation MAFLD was associated with an increased risk for mechanical ventilation (OR 2,50; IK95% 1,20-5,21; p=0,01)	The prevalence of NAFLD is higher than in previous studies, which is related to the Dallas steatosis index diagnostic criteria used in the study, potentially resulting in overdiagnosis.
Nath et al. 2022 Prospective (India)	Findings of fatty liver on CT scan without a history of excessive alcohol consumption based on medical records (defined as mean alcohol consumption ≥ 30 grams/day in men and ≥ 20 grams/day in women)	April-December 2021	3983 Case: 814 Control: 3169	Mean $\pm$ SD Case: 47,1 $\pm$ 14,3 Control: 45,2 $\pm$ 16,1	Length of stay There was no significant difference in length of stay between patient with MAFLD and without MAFLD (10,6 $\pm$ 7,2 vs. 10,6 $\pm$ 6,6; p=0,447) Mortality There was no significant difference in mortality rates between patient with MAFLD and without MAFLD (6,7% vs. 5,9%; p=0,381)	-	Subgroup analysis was done based on demographic and clinical parameters to minimize bias.
Vrsaljko et al. 2022 Prospective (Croatia)	Findings of liver steatosis, with no history of significant alcohol consumption and no etiology of liver steatosis or other causes of chronic liver disease	March-June 2023	216 Case: 120 Control: 96	Median (IQR) Case: 59 (49,3-64,8) Control: 63 (55-71)	Length of stay MAFLD was associated with longer hospital stays compared to non-MAFLD (10 vs. 9; p=0,0018) Mortality There was no significant difference in mortality rates between the patient with MALFD and without MALFD (6,7% vs. 3,1%; p=0,3529)	Need for non-invasive ventilation MAFLD was associated with an increase need for HFNC or non-invasive ventilation compared to patient without MALFD (21,7% vs. 10,4%; p=0,0289)	-
Wang et al. 2020 Retrospective (China)	Evidence of fatty liver from abdominal ultrasound without a history of excessive alcohol consumption (defined as an average alcohol consumption of ≥ 30 grams/day in men and ≥ 20 grams/day in women)	March 2020	218 Case: 86 Control: 132	Median (IQR) Case: 46 (19-76) Control: 45 (21-84)	Length of stay There was no significant difference in length of hospital stay between patients with MAFLD and without MAFLD (15 vs. 16; p=0,407) Mortality There was no significant difference in mortality rate between the patients with MAFLD and without MAFLD (0% vs. 1.5%; p=0,251) COVID-19 severity There was no significant difference in the COVID-19 severity between patients with MAFLD and without MAFLD (22.1% vs. 16.7%; p=0,316)	Viral shedding time There was no significant difference in the duration of viral shedding time between patients with MAFLD and without MAFLD (17 vs. 18; p=0,165)	Subgroup analyses were performed based on demographic and clinical parameters to minimize bias.

Table 1. Study Characteristics

Author, Year, Study design (Country)	MAFLD diagnosis criteria	Patient Admission Period	Number of Subjects Case: Control:	Age (Year) Case: Control:	Outcome Measured	Additional outcome	Bias/ confounding
Yoo et al. 2021 Prospective (South Korea)	HSI index ≥ 36.2 Fatty liver index (FLI) ≥ 60 History of MAFLD based on previous medical records (claim-based)	January-July 2020	74,244 Case: 26,041 (HSI) 19,945 (FLI) 8,927 (claim-based)	20–39: 34.4% 40–59: 36.6% ≥ 60 : 29.0%	COVID-19 severity MAFLD was associated with higher COVID-19 disease progression than the non-MAFLD. aOR, 1.41; 95% CI, 1.08–1.83 for HSI-NAFLD aOR, 1.35; 95% CI, 1.05–1.71 for FLI-NAFLD aOR, 1.39; 95% CI, 1.01–1.92 for claim-based NAFLD Mortality MAFLD was not associated with higher COVID-19 mortality rates than the non-MAFLD. aOR, 1.30; 95% CI, 0.55–3.09 for HSI-NAFLD aOR, 1.35; 95% CI, 1.05–1.71 for FLI-NAFLD aOR, 1.39; 95% CI, 1.01–1.92 for claim-based NAFLD	Risk of SARS-CoV-2 infection Patients with MAFLD was more susceptible to SARS-CoV-2 infection compared to patients without MAFLD. aOR, 1.11; 95% CI, 1.01–1.28 for HSI-NAFLD aOR, 1.14; 95% CI, 1.02–1.27 for FLI-NAFLD aOR, 1.23; 95% CI, 1.05–1.46 for claim-based NAFLD	Propensity score matching analysis was conducted to minimize bias and confounding.
Younossi et al. ⁴² 2021 Retrospective (United States of America)	Evidence of fatty liver on radiological imaging (MRI, CT, or ultrasonography) in the absence of other chronic liver disease or a history of excessive alcohol consumption.	March-December 2020	3299 Case: 553 Control: 2736	Mean $\pm$ SD Case: 54.7 $\pm$ 15.8 Control: 54.0 $\pm$ 20.7	Length of stay MAFLD was associated with longer duration of hospitalization compared to the non-MAFLD (9.60 vs. 7.27; $p < 0.0001$) Mortality There was no significant difference in mortality rate between MAFLD and non-MAFLD (10.8% vs. 8.7% $p = 0.11$)	ICU admission rate MAFLD was associated with a higher rate of ICU admission (35.4% vs. 26.5%; $p < 0.0001$), higher need for mechanical ventilation (13.7% vs. 8.1%; $p < 0.0001$), and higher incidence of acute liver disease (3.9% vs. 1.6%; $p = 0.0006$) compared to the non-MAFLD.	N/A
Zhou et al. ¹⁵ 2020 Case Control (China)	Histological or radiological findings of fatty liver accompanied by at least one of the following criteria: (1) BMI > 23 kg/m ² ; (2) diabetes mellitus; (3) two or more of the following risk factors: triglycerides ≥ 1.7 mmol/L; hypertension; prediabetes; waist circumference 90/80 cm in Asian men/women; HDL cholesterol < 1 mmol/L (men) or < 1.3 mmol/L (women).	N/A	110 Case: 55 Control: 55	Mean $\pm$ SD Case: 43.4 $\pm$ 10.8 Control: 40.9 $\pm$ 11.9	Length of stay There was no significant difference in the length of hospitalization between the patients with MAFLD and without MAFLD (21 vs. 18; $p = 0.09$) COVID-19 severity MAFLD was associated with an increase in COVID-19 disease progression than non-MAFLD (OR 3.65; 95% CI 1.31–10.16; $p = 0.01$).	N/A	No matching was performed based on primary outcomes. There was still possibility of selection bias.

The studies included in this meta-analysis were conducted in eight different countries (United States of America^{5,6}, Great Britain⁷, China⁸⁻¹¹, India^{12,13}, Israel¹⁴, Mexico¹⁵, Croatia¹⁶, South Korea¹⁷), with a total of 90,282 subjects involved (28,916 MAFLD patients and 61,366 non-MAFLD patients). All studies included both male and female subjects. The age included in these studies was quite varied, most studies reported subjects with a mean age decade of 40 and 50, however, there are a small number of studies reporting a mean age above 60 years old.

The MAFLD diagnostic criteria used in each study is based on findings of fatty liver on histological or radiological examination combined with biochemical and clinical parameters. A total of four studies used several

scoring modalities, such as the hepatic steatosis index (HSI), liver attenuation index, and fatty liver index (FLI). Patient admission periods varied between 1 month to 10 months.

The outcome of studies is quite diverse. Hospitalization outcomes were reported in one study⁵, length of hospital stay was reported by seven studies^{6,7,9,11-13,16}, mortality was reported by seven studies^{6,7,9,12,13,15-17}, and COVID-19 severity outcomes were reported by six studies^{8-11,14,17}. Other outcomes were also reported by several studies, i.e., time from symptom onset to hospital admission (1 study)⁷, virus clearance time (2 studies)^{9,10}, need for ventilator (2 studies)^{12,15}, need for non-invasive ventilation (1 study)¹⁶, length of ICU stay (1 study)¹², and risk of SARS-CoV-2 infection (1 study)¹⁷. Several studies

Table 2. Risk of bias assessment based on Newcastle Ottawa Scale for case control studies.

Study (Year)	Selection				Comparability		Exposure	
	Case definition adequate	Representative-ness of the sample	Selection of controls	Definition of controls	Comparability of cases and controls	Assessment of outcome	Same method of ascertainment for cases and controls	Non-response rate
Gao (2021)	*	-	-	*	*	*	*	*
Madan (2022)	*	*	*	*	-	*	*	*
Mahamid (2020)	*	-	-	*	*	*	*	*
Zhou (2020)	*	*	-	*	*	*	*	*

Table 3. Risk of bias assessment based on Newcastle Ottawa Scale for cohort studies.

Study (Year)	Selection			Comparability		Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Follow-up was long enough for outcomes to occur	Adequacy of follow-up of cohorts
Bramante (2020)	*	*	*	*	*	*	*	*
Forlano (2019)	*	*	*	*	*	*	*	*
Ji (2020)	*	*	*	*	-	*	*	*
Moctezuma-Velázquez (2022)	*	*	*	*	-	*	*	*
Nath (2022)	*	*	*	*	*	*	*	*
Vrsaljko (2022)	*	*	*	*	-	*	*	*
Wang (2020)	*	*	*	*	**	*	*	*
Yoo (2021)	*	*	*	*	**	*	*	*
Younossi (2021)	*	*	*	*	-	*	*	*

reported differences in mortality outcomes in the form of percentages, while only one study reported them in the form of ORs. All studies examining the outcome of length of stay reported differences in median form. A total of four studies reported the outcomes of differences in severity in the form of ORs, while the other studies reported them in the form of percentages. Case-control studies were excluded from the meta-analysis and further meta-analysis was performed on eight cohort studies, in which seven studies assessed mortality outcome^{6,7,9,13,15-17}, three studies assessed COVID-19 severity outcome^{9,10,17}, and five studies assessed in-hospital length of stays^{6,7,9,13,16}.

The results of the meta-analysis using a fixed effect model from seven studies with a total of 44,752 subjects showed that COVID-19 patients with MAFLD were associated with higher mortality compared to those without MAFLD, with a pooled OR of 1.47 (95% CI 1.22 - 1.77, $p < 0.0001$, I^2 48%) (**Figure 2**). Two studies^{6,15} reported that MAFLD was associated with a higher COVID-19 mortality rate compared to the non-MAFLD group, while five other studies^{7,9,13,16,17} reported that there were no significant differences in mortality rates between the MAFLD and the non-MAFLD patients.

However, this meta-analysis found that the significantly different mortality between the MAFLD and non-MAFLD groups was not in line with the results of the severity of COVID-19 which were not significantly different between the two groups. This indicates that the increased mortality could be caused by conditions other than SARS-CoV-2 infection directly itself. The results of the meta-analysis of three cohort studies using a random-effect model showed that the MAFLD group was not associated with a higher degree of severity of COVID-19 compared to the non-MAFLD group, with an OR of 3.12 (95% CI 0.89-11.80, $p = 0.08$) with significant heterogeneity ($p < 0.00001$ and I^2 92%) (**Figure 3**). Subgroup analysis was performed on the age and gender, and the result showed that there was a significant age difference ($p < 0.00001$),

but not in gender ($p = 0.33$) (**Figure 4**). The varying diagnostic criteria for MAFLD used between studies may be one of the causes of significant heterogeneity in this meta-analysis. A liver biopsy was not performed and used as a diagnostic tool in the existing studies. Ultrasound, CT scan, and biomarkers were used and have different sensitivities and specificities in diagnosing MAFLD, which may contribute to the heterogeneity of the meta-analysis.

The severity outcome in all the relevant studies was investigated before COVID-19 vaccination was initiated, and thus, vaccination status did not affect the severity of COVID-19 in either the MAFLD or non-MAFLD groups. Previous studies also showed that the COVID-19 severity caused by each SARS-CoV-2 variant varies with a hospitalization risk of 1.51% (95% CI = 0.00–6.15%) for the Omicron variant, 4.02% (95% CI = 1.04–6.99%) for the Alpha variant, 6.56% (95% CI = 1.50–11.61%) for the Delta variant, and 19.96% (95% CI = 16.16–23.75%) for the Beta variant.¹⁸ Due to the unavailability of SARS-CoV-2 variants data, it could not be analyzed whether SARS-CoV-2 variants were one of the factors influencing the meta-analysis results and heterogeneity in this study. In addition, the studies with severity outcomes involved subjects with obesity levels of less than 50%, and hence, subgroup analysis to assess whether obesity affects heterogeneity was not performed.

An analysis was also conducted on the difference in length of hospital stay of COVID-19 patients with MAFLD compared to patients without MAFLD, involving a total of five studies (9,442 subjects). The result showed no difference in the length of hospital stay between the two groups with a mean difference of 1.27 (95% CI 0.13-2.66) with a p -value of 0.08 and significant heterogeneity (I^2 81%) (**Figure 5**). Subgroup analysis based on obesity, age, and vaccination era showed that the length of stay between the MAFLD compared to non-MAFLD was not statistically significantly different between different subgroup ($P = 0.65$, $P = 0.33$, and $P = 0.31$, respectively). (**Figure 6**).

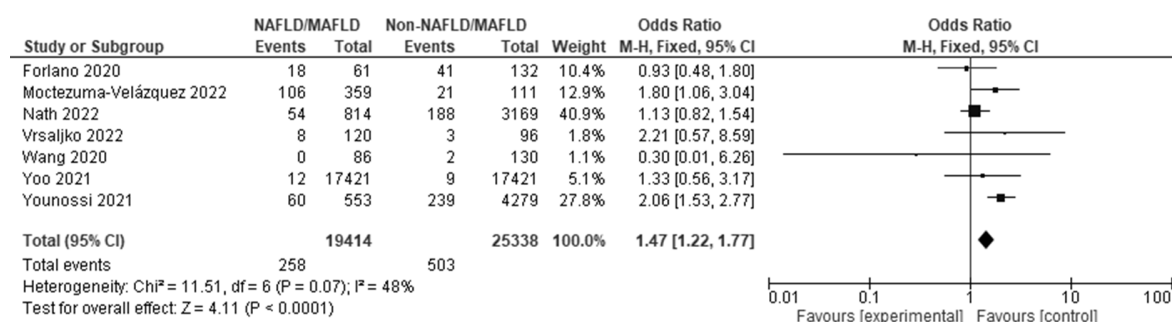


Figure 2. Forest Plot on Comparison of the Mortality between the MAFLD and Non-MAFLD patients with COVID-19

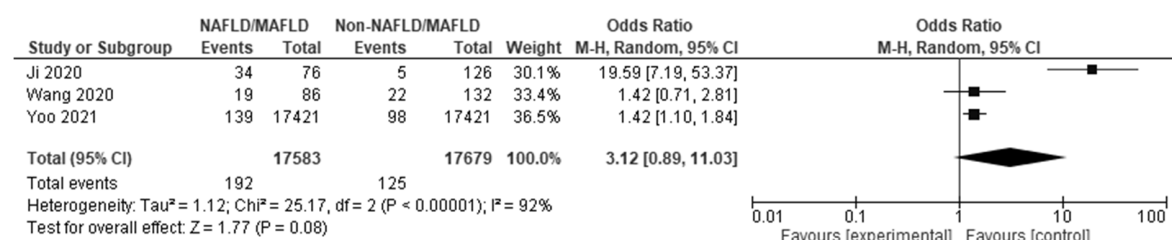


Figure 3. Forest Plot on Comparison of the Severity of COVID-19 between the MAFLD and Non-MAFLD patients

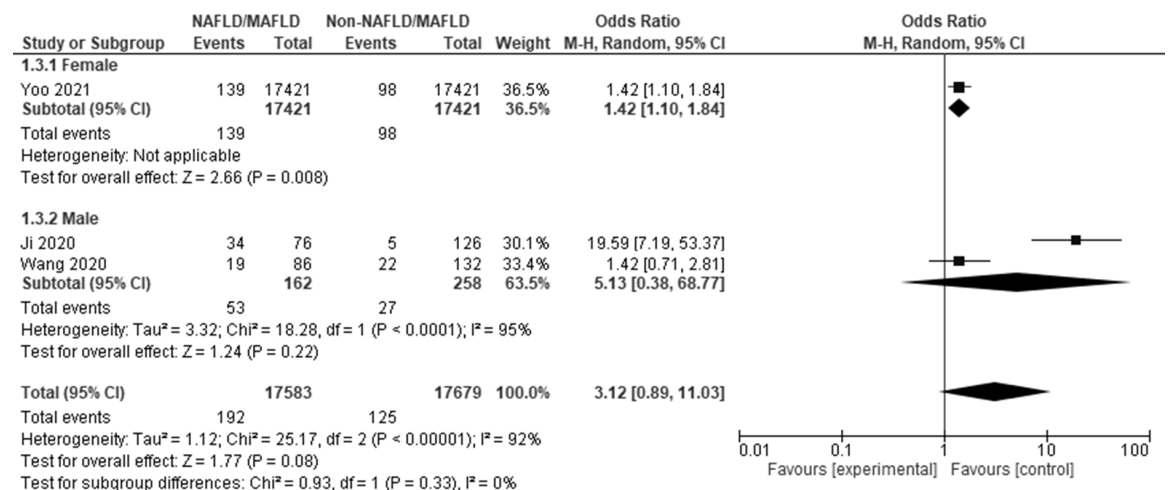
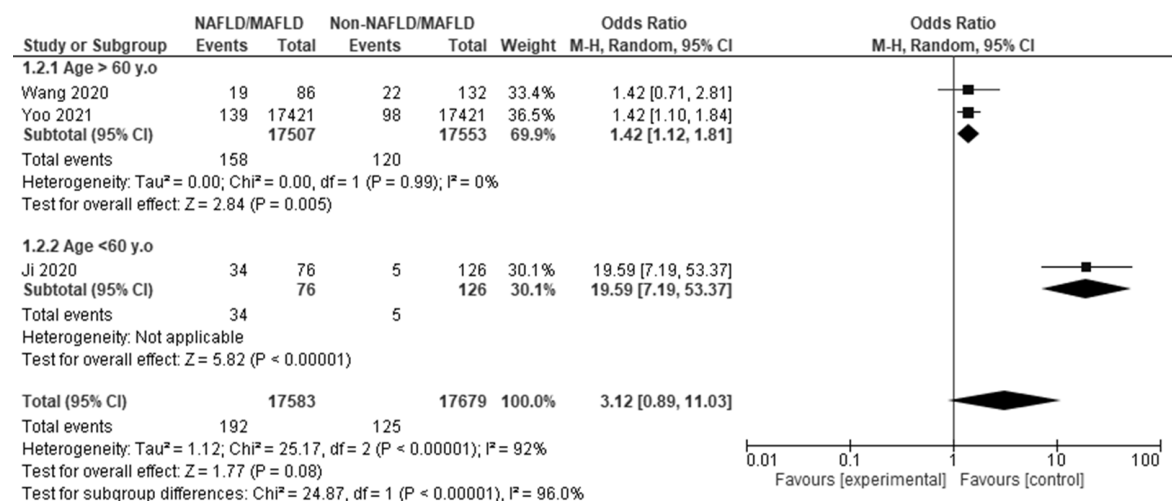


Figure 4. Subgroup Analysis on Comparison of the Severity of COVID-19 between the MAFLD and Non-MAFLD patients

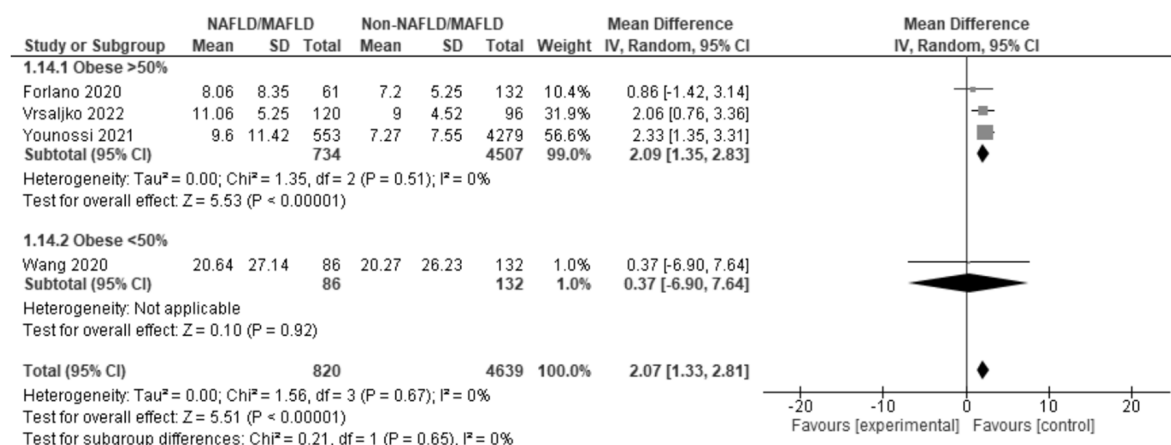
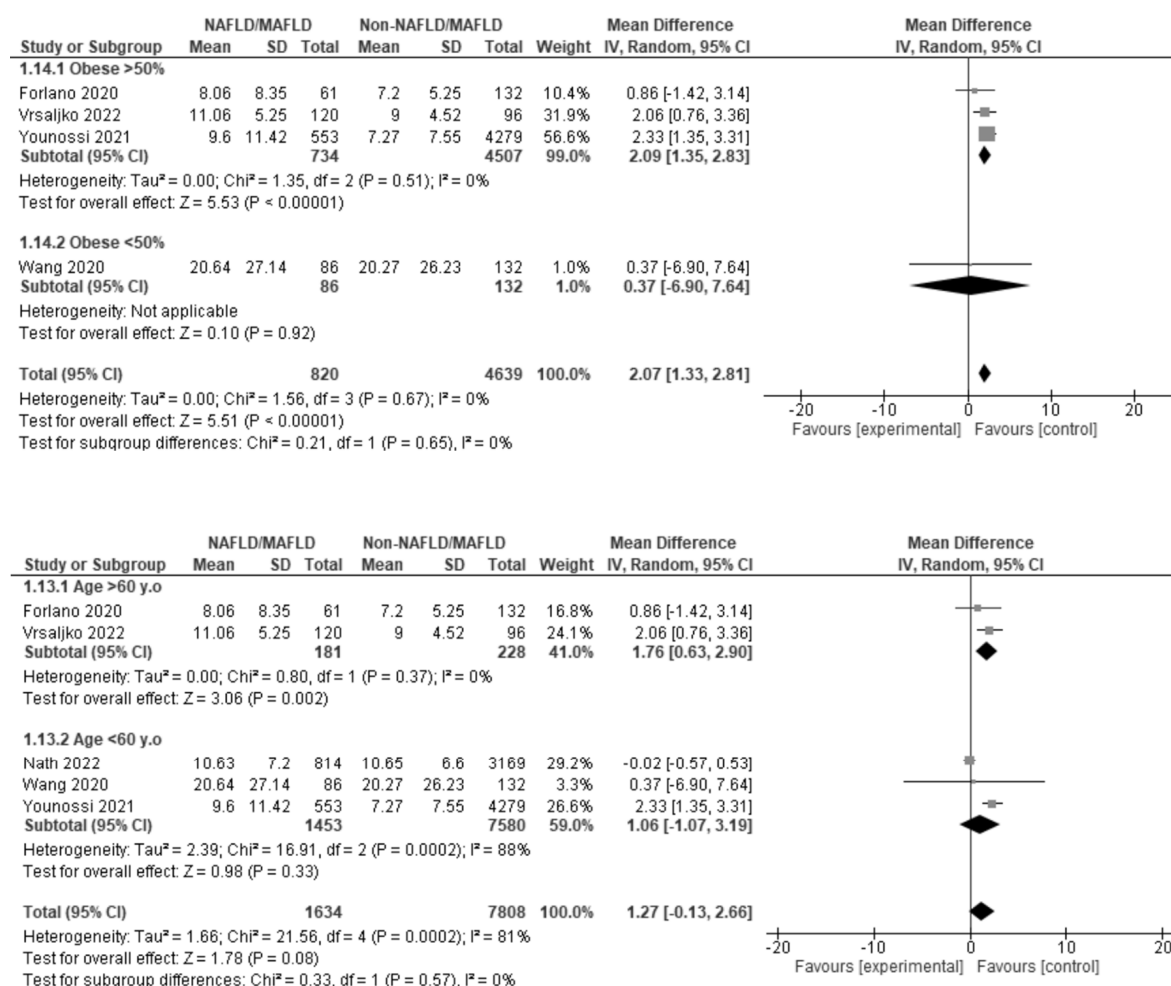


Figure 5. Forest Plot on Comparison of the Length of Stay between the MAFLD and Non-MAFLD patients with COVID-19



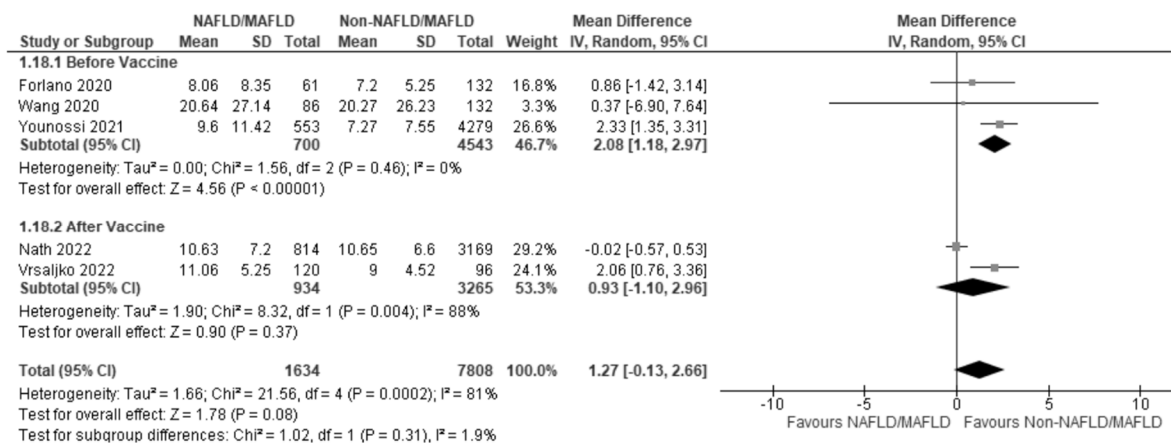


Figure 6. Subgroup analysis Comparing Length of Stay between the MAFLD and Non-MAFLD patients with COVID-19.

DISCUSSION

Meta-analysis of the outcome of MAFLD patients who were infected with SARS-CoV-2 found that patients with MAFLD were associated with a higher rate of mortality compared to patients without MAFLD, but no difference in COVID-19 severity and in-hospital length of stay. This contradictory result may indicate that the increased mortality rate could be caused by conditions other than the SARS-CoV-2 infection directly itself. Also of note, there was significant heterogeneity in meta-analysis and only three cohort studies were included in COVID-19 severity outcome. Several clinical and methodological differences between studies may be the cause of significant heterogeneity. Subgroup analysis on COVID-19 severity was performed and the result showed that there were significant differences between the different degrees of severity of COVID-19 between studies with the proportion of age above 60 years and under 60 years. One predictor for severe COVID-19 is age, in which patients over 59 years old are known to have a higher risk of severe COVID-19 and require ICU admission.¹⁹ However, a case-control study by Zhou et al. showed that MAFLD patients aged less than 60 years old who were infected with SARS-CoV-2 COVID-19 were associated with a fourfold increased risk of severe COVID-19 (OR 4.07; 95% CI 1.20–13.79; $p=0.02$).¹¹ This meta-analysis included three cohort studies with different proportions of the population aged

over 60 years, where Ji et al.¹⁰ included 15.3% elderly subjects, while Wang et al.⁹ and Yoo et al.¹⁷ included 26% and 29% elderly subjects, respectively. Meta-analysis in the study subgroup with a larger population aged 60 years, showed that MAFLD patients had a higher risk of severe COVID-19 compared to non MAFLD with an OR of 1.42 and heterogeneity was not significant (95% CI 1.12–1.81, $p=0.005$, $I^2=0\%$). However, the number of studies on this outcome is less than ten and the distribution of the number of studies is not evenly distributed in the two subgroups, so this subgroup analysis may not be valid in detecting subgroup differences.

One of WHO's strategies to reduce the burden of COVID-19 is to rapidly develop COVID-19 vaccination.²⁰ COVID-19 vaccination began to be developed on July 22nd, 2020 and the first dose was administered in December 2020.²¹ All studies with COVID-19 severity outcome in this meta-analysis included subjects before the initiation of COVID-19 vaccination administration, and therefore, vaccination status does not affect the severity of COVID-19 in the MAFLD and non-MAFLD in this meta-analysis.

A study conducted by Younossi et al. found that MAFLD patients infected with SARS-CoV-2 who died had more comorbidities with more severe respiratory distress at the time of admission when compared with MAFLD patients who survived.⁶ In multiple regression analysis, independent predictors of mortality in patients with MAFLD and COVID-19 included older

age, morbid obesity, Elixhauser comorbidity index score ≥ 11 , oxygen saturation $< 90\%$, and higher FIB-4 score.⁶ Approximately 25% of COVID-19 patients who died were also found to have acute liver disorders characterized by significant elevation of transaminases, the liver enzymes.⁶ Post-mortem liver biopsy of MAFLD patients infected with SARS-CoV-2 showed microvascular steatosis and excessive activation of T cells, indicating that liver damage in COVID-19 was caused by an immune cell-mediated mechanism, not due to the impact of direct cell damage by the SARS-CoV-2 virus.¹⁰ Impaired immunity also caused longer viral clearance time, and thus, increased the COVID-19 disease progression in MAFLD patients compared to non-MAFLD patients.¹⁰

This systematic review has several weaknesses, one of which is that the design of all studies included in this systematic review is observational, so the possibility of selection bias may still occur. In addition, publication bias analysis cannot be performed because the number of included studies in each evaluated outcome is less than 10. Varying MAFLD diagnostic criteria between studies may be one of the causes of significant heterogeneity in this meta-analysis. Ultrasound examination, CT scan, and biomarkers have different sensitivity and specificity in diagnosing MAFLD. A liver biopsy was not used to confirm the diagnosis in existing studies. MAFLD stages are classified based on the degree of necroinflammation by examining liver histology, which was not performed in these existing studies. Liver necro-inflammation in MAFLD is linked to increased production of acute-phase proteins and inflammatory cytokines and, therefore may affect immune response to infection such as COVID-19.²² The unavailability of a degree of MAFLD necro-inflammation by liver biopsy in the existing study is one of the shortcomings of this meta-analysis and further analysis between degree of MAFLD with severity of COVID-19 may clarify the association.

CONCLUSION

Patients with MAFLD who were infected with SARS-CoV-2 were associated with higher

mortality rates, but not a higher degree of severity of COVID-19, and no difference in the length of hospital stays compared to those without MAFLD.

CONFLICT OF INTEREST

There are no conflicts of interest involved in developing this systematic review and meta-analysis.

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