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Non-alcoholic fatty liver disease and clinical outcomes in patients with COVID-19: A comprehensive systematic review and meta-analysis

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) patients represent a vulnerable population that may be susceptible to more severe COVID-19. Moreover, not only the underlying NAFLD may influence the progression of COVID-19, but the COVID-19 may affect the clinical course of NAFLD as well. However, comprehensive evidence on clinical outcomes in patients with NAFLD is not well characterized.
Objectives: To systematically review and meta-analysis the evidence on clinical outcomes in NAFLD patients with COVID-19.
Methods: MEDLINE, EMBASE, and Cochrane Central were searched from inception through November 2020. Epidemiological studies assessing the clinical outcomes in COVID-19 patients with NAFLD were included. Newcastle-Ottawa Scale (NOS) was used to assess study quality. Generic inverse variance method using RevMan was used to determine the pooled estimates using the random-effects model.
Results: Fourteen studies consisting of 1851 NAFLD patients, were included. Significant heterogeneity was observed among the studies, and studies were of moderate to high quality [mean, (range):8 (6, 8)]. For NAFLD patients, the adjusted odds ratio (aOR) for the severe COVID-19 was 2.60 (95%CI:2.24–3.02; $p < 0.001$) (studies,n:8), aOR for admission to ICU due to COVID-19 was 1.66 (95%CI:1.26–2.20; $p < 0.001$) (studies,n:2), and aOR for mortality for was 1.01 (95%CI:0.65–1.58; $p = 0.96$) (studies,n:2).
Conclusions: An increased risk of severe COVID-19 infection and admission to ICU due to COVID-19 with no difference in mortality was observed between NAFLD and non-NAFLD patients. Future studies should include the mortality outcome to conclusively elucidate the impact of NAFLD in patients with COVID-19.

1. Introduction

Since March 2020, the world is facing the COVID-19 global pandemic caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. At the time this systematic review was conducted, there were more than 44.6 million confirmed cases, and more than 1.2 million deaths have been attributed to COVID-19 globally [2]. Epidemiological studies have reported a high prevalence of co-morbid conditions such as obesity, diabetes, cardiovascular disease, hypertension, and chronic obstructive pulmonary disease in patients with COVID-19 [3]. Additionally, studies have shown that around 1–11% of patients with SARS-CoV-2 infection suffer from co-morbid chronic liver disease (CLD), with non-alcoholic fatty liver disease (NAFLD) being the most frequent type of CLD; hence understanding relations between the COVID-19 and liver disease is essential for clinical management [4–6].

NAFLD or metabolic (dysfunction) associated fatty liver disease (MAFLD) is a common clinico-histopathologic condition defined by excessive accumulation of fat in the hepatic parenchyma with lack of secondary causes of hepatic fat accumulation, such as hepatitis B or C infection, significant alcohol consumption, long-term use of steatogenic drugs, or monogenic hereditary disorders [7]. Based on understandings gained from the last two decades and considering

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that NAFLD is primarily a metabolic disorder, a new name for NAFLD — that is, metabolic associated fatty liver disease (MAFLD) has been proposed [8]. Its manifestation range from simple hepatic steatosis involving fat accumulation in hepatocytes without concomitant inflammation or fibrosis to non-alcoholic steatohepatitis (NASH) with or without associated fibrosis [9]. NAFLD affects nearly 25% of the population globally and has the potential to cause significant liver damage in a large number of patients [6]. Patients with NAFLD usually suffer from co-morbid conditions such as obesity, kidney diseases, and metabolic risk factors such as diabetes, hypertension, and dyslipidemia. As a result, NAFLD patients represent a vulnerable population at an increased risk of progression to severe COVID-19 [10,11]. Both obesity and NAFLD have been associated with elevated pro-inflammatory cytokines such as TNF-α [12]. Moreover, SARS-CoV-2's use of the angiotensin-converting enzyme 2 (ACE2) receptor for cellular entry and increased expression of ACE2 on hepatocytes of patients with NAFLD may pose an increased risk in NAFLD patients [13], although this has not yet been convincingly demonstrated.

Rapidly emerging clinical data from observational studies (SECURE-Cirrhosis Registry [14] and COVID-HEP registry [15]) and clinical trials have indicated that not only the underlying liver disease (such as NAFLD) may influence the progression of COVID-19, but SARS-CoV-2 infection may affect the clinical course of NAFLD as well. Yet, the clinical features of COVID-19 patients with NAFLD are not clear. A previous meta-analysis has explored the association of the COVID-19 with CLD; however, none have explicitly focused on NAFLD and COVID-19 [16,17]. Furthermore, results from a preliminary genetic analysis have generated contradictory hypotheses and found that genetic predisposition to hepatic fat accumulation and MAFLD does not increase the susceptibility towards severe COVID-19 [18]. Thus, a systematic literature review was performed to identify all the published studies, and a meta-analysis was conducted to determine the association between NAFLD with clinical outcomes in patients with COVID-19.

2. Methods

2.1. Study search and selection

A literature search was performed in three bibliographic databases—EMBASE, MEDLINE (using the Ovid interface), and the Cochrane Central Register of Controlled Trials—from inception till November 2020. A search strategy was designed using a combination of keywords to retrieve articles that reported the association between NAFLD and COVID-19 (refer supplement for detailed search strategy). In addition, bibliographies of relevant primary studies and systematic reviews were also searched. We restricted the literature search to English language only. The articles retrieved were screened based on their title and abstracts for their eligibility. Articles included based on title and abstract were further assessed for inclusion based on full-text. Two researchers (AS and SH) independently assessed all the articles and evaluated their eligibility for inclusion using the Covidence™ software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Studies were included if they met the following inclusion criteria: (i) epidemiological studies such as case-control studies, cohort studies, retrospective studies, prospective studies (ii) Laboratory confirmed COVID-19 diagnosis (iii) reported association between mortality, severity/progression, or intensive care unit (ICU) admission among COVID-19 patients with NAFLD, and (iv) provided suitable data to estimate the risk of severe COVID-19 infection, admission to ICU, and mortality. Articles reporting interventional trials, reviews, case reports, genetic studies, animal studies, editorial, commentary, and study protocol were excluded. The following data were extracted from each publication: 1) Study details: author name, year, trial registration, database, follow-up duration, 2) Population characteristics: age, body mass index (BMI), co-morbidities, NAFLD and COVID-19 assessment and 3) Outcome: effect estimates such as risk ratio (RR), odds ratio (OR), the hazard ratio (HR) or absolute number in NAFLD and non-NAFLD group, and study conclusion. Any conflicts at the screening and data extraction phase were resolved by consensus.

2.2. Quality assessment

The Newcastle-Ottawa Scale (NOS) was used for the quality assessment of included studies. The NOS has three parameters, namely, selection, comparability, and outcome/exposure, that are applied to evaluate the quality of a study. As per the scale, studies were classified as either high, medium, or low quality depending on the score achieved in the selection, comparability, and exposure (case-control studies) or outcome (cohort studies) domain of the scale [19]. Two reviewers (AS and SH) independently performed the quality assessment of the included studies, and any discrepancies were resolved through discussion.

2.3. Statistical analysis

Meta-analysis was performed using Review Manager version 5.4.1 using the generic inverse variance method [20]. Wherever reported, we used the available effect estimate of OR, RR, and HR; if not available, the absolute numbers were used to calculate the unadjusted OR. Pooled OR with 95% confidence intervals (CIs) were computed to assess the pooled estimates of the odds of mortality, severity, and ICU admission of COVID-19 patients with NAFLD compared to patients without NAFLD. Pooled analysis was also performed using both the adjusted (adjusted for confounding factors) as well as unadjusted data. Heterogeneity between studies was determined with a cutoff value of $\geq$50% using I^2 statistics, or $p < 0.10$ using the χ^2 test for Cochran Q statistics. Based on the heterogeneity assessment, a random effect model or fixed effect model was chosen to pool the effect estimates [21]. A restricted-maximum likelihood random-effects meta-regression was performed for continuous (age, BMI) and categorical moderators (assessment of COVID-19: RT-PCR or lab confirmed) to assess the effect of these variables on COVID-19 severity using ProMeta Version 3.0 ([Computer software]. Cesena, Italy: Internovi). A funnel plot was plotted to estimate the publication bias. Sensitivity analysis was performed using the leave-one-out method, where each study was sequentially omitted from the pooled effect estimates.

3. Results

Our literature search found a total of 107 unique citations, from which 14 studies involving 19149 overall participants, including 1851 NAFLD patients, were found eligible for inclusion in the qualitative and quantitative analysis (Fig. 1). Eleven of the included articles reported cohort studies [11,22–31], while three were case-control or cross-sectional analysis [32–34]. The majority of the studies were from Asia (seven, in China) [11,24,26,27,29–31], while four were from the USA [22,23,25,28], and one from the UK [33], Mexico [32], and Israel [34] each. The studies were conducted in the time frame between December 2019 to September 2020. All the included studies primarily used data collected from the hospital electronic medical/health records (EMR/EHR) databases or patient data (Table 1).

Five studies confirmed the NAFLD as per imaging based on

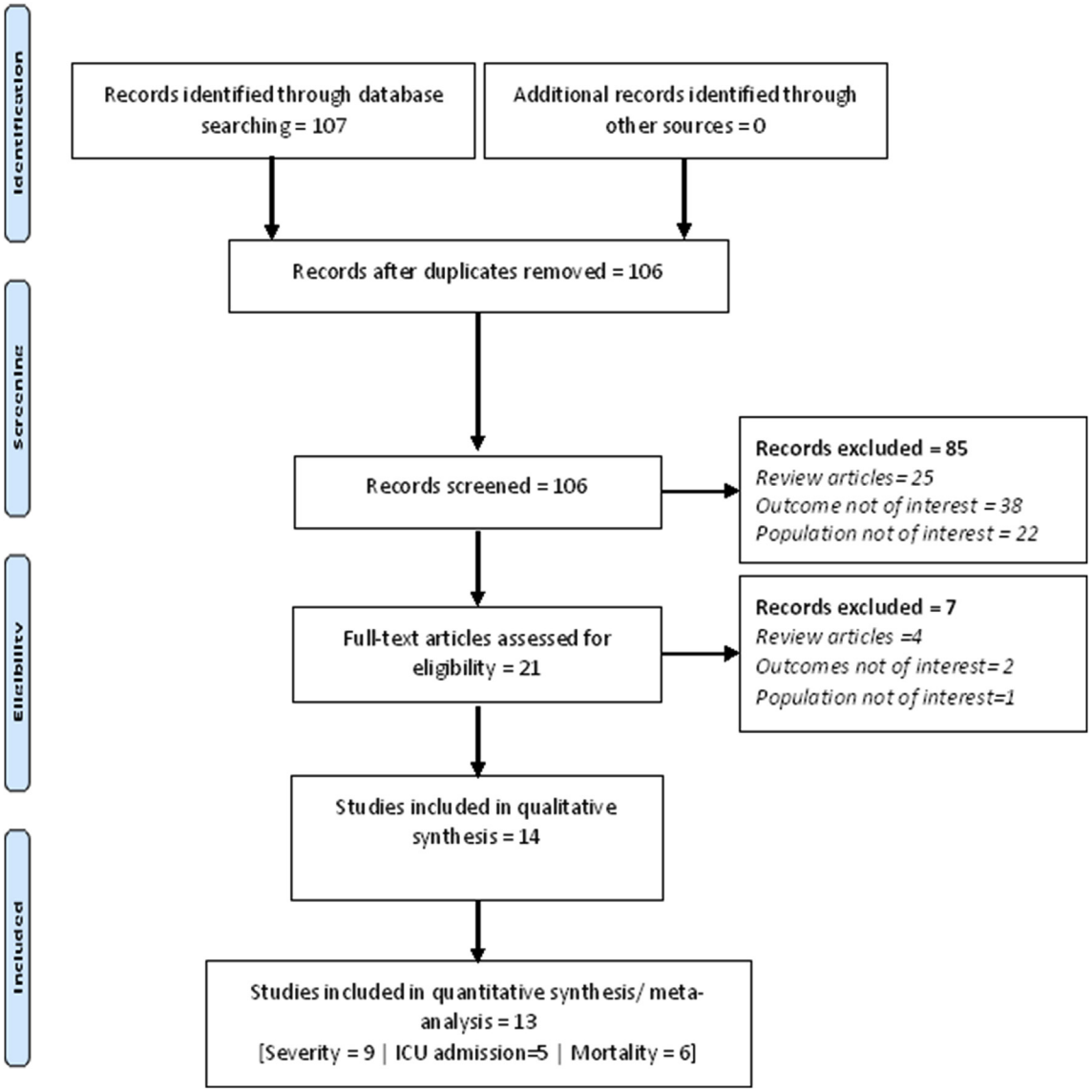

Fig. 1. PRISMA flow diagram showing study selection.
Footnote: Outcome not of interest, risk of COVID-19 severity, risk of ICU admission, or mortality not reported; Population not of interest, Non-NAFLD population.

ultrasound or computerized tomography (CT) [23,24,27,30,33], four studies as per the hepatic steatosis index (HIS) [11,22,26,32], three used consensus definition of MAFLD [29,31,34] and two as per International Classification of Diseases (ICD) [25,28] code. Obesity, hypertension, type 2 diabetes mellitus (T2DM), and dyslipidemia were the major co-morbidities reported across the included studies with a higher prevalence in the NAFLD cohort [22–26,28–33]. Other co-morbidities included cardiovascular diseases (CVD), lung disease, and metabolic dysregulation [23,26,28,31–33]. The diagnosis of COVID-19 infection was conformed based on reverse transcription-polymerase chain reaction (RT-PCR) in eight studies [11,22,23,29,31–34]; five studies used lab-confirmed status of COVID-19 infection [24–28], while one study did not provide clear information on the assessment of COVID-19 infection [30] (Table 1).

3.1. Clinical outcomes

3.1.1. COVID-19 severity

Overall, nine studies reported the outcomes related to COVID-19 severity in NAFLD patients [11,24,25,27–31,34], and data from eight studies were pooled in the meta-analysis (Table 2) [11,25,27–31,34]. The pooled unadjusted OR (uOR) for severe COVID-19 in patients with NAFLD vs. those without NAFLD, based on data from seven included studies, was 2.36 (95% CI: 1.09–5.11, $p = 0.03$) [25,27–31,34] (Supplement Fig. 1). The adjusted OR (aOR) for severe COVID-19 in patients with NAFLD vs. those without NAFLD, based on data from eight included studies, was 2.60 (95% CI: 2.24–3.02, $p < 0.001$) (Fig. 2) [11,25,27–31,34]. Furthermore, Zheng et al. (not included in the meta-analysis) showed that the presence of obesity noticeably increased the risk of severe COVID-19 compared to non-obese NAFLD patients (aOR: 6.32; 95%CI: 1.16–34.54, $p = 0.033$) [24]. All of the studies reporting disease severity outcomes performed multivariable analysis and reported the aOR adjusted for the covariates such as age, sex, race, BMI, recent healthcare exposure (hospitalization or nursing facility residence < 90 days before COVID-19 diagnosis), and co-morbidities (hypertension, diabetes, obesity, smoking, cardiovascular disease HCC, COPD, dyslipidemia, and alcohol consumption). Sensitivity analysis using the leave-one-out method indicated that the pooled estimate was reliable and was not dependent on any

Table 1
Characteristics of the included studies.

Author, Year & Country	Study design, Setting	Study duration	Database/Source	Cohort size	Population characteristics	Mean age ± SD (range), yrs	BMI ± SD (range), kg/m^2	Top 5 co-morbidity, %	Assessment of NAFLD/MAFLD	Assessment of COVID-19	Outcome reported	Study conclusion
Lopez-Mendez (32) 2020 Mexico	Retrospective, cross sectional study	March 14th - June 5th, 2020	EMR of patients admitted to Medica Sur Clinic & Foundation	Overall: 155 patients HS: 66	Adult patients COVID-19 patients	**Overall**: 51 (42–62)	**Non-NAFLD**: **NAFLD**: 27.9 (25.8–30.5)	**Overall**: Obesity: 28.4 Hypertension: 23.2 T2DM: 15.5 Dyslipidemia: 5.8 Cardiac disease: 4.5	Determined by HSI value above 36	Positive RT-PCR SARS-CoV-2 test in nasopharyngeal swab	ICU admission and Mortality	Prevalence of HS and significant liver fibrosis was high in COVID-19 patients but was not associated with clinical outcomes.
Chen (22) 2020 USA	Retrospective single-center cohort study	March 10th - September 3rd, 2020	Medical records of hospitalized adult patients at Michigan Medicine	Overall: 342 patients HS: 178	Hospitalized adult patients COVID-19 patients	**Non-NAFLD**: 66.5 (54.0 −79.2) **NAFLD**: 58.5 (49–67)	**Non-NAFLD**: 26.6 (24.8 −29.2) **NAFLD**: 34.7 (30.3–40.7)	**Non-NAFLD**: Hypertension: 67.7 Diabetes: 37.8 Dyslipidemia: 47.6 **NAFLD**: Hypertension: 70.6 Diabetes: 48.3 Dyslipidemia: 46.6	Defined either by imaging or HSI index above 36	COVID-19 diagnosed by polymerase chain reaction	Disease severity, ICU admission, Transaminitis, Mortality	HS was associated with increased disease severity and transaminitis in COVID-19.
Forlano (33) 2020 UK	Retrospective study	February 25th - April 5th, 2020	Medical records of Imperial College Healthcare NHS Trust	Overall: 193 patients NAFLD: 61	Adult patients admitted and diagnosed with COVID-19	**Non-NAFLD**: 70.5 (53–79) **NAFLD**: 60 (53–75)	**Non-NAFLD**: 27.1 (23.3 −30.9) **NAFLD**: 30.6 (27–33.8)	**Non-NAFLD**: Hypertension: 50 T2DM: 35 Dyslipidemia: 24 IHD: 13 Lung disease: 11 **NAFLD**: Hypertension: 42 T2DM: 47 Dyslipidemia: 23 IHD: 19 Lung disease: 18	Imaging of the liver (US or CT) or known diagnosis of NAFLD	SARS-CoV-2 was using a RT-PCR method	ICU admission, Mortality	NAFLD was not associated with worse outcomes in hospitalized COVID-19 patients. Within NAFLD group, mortality was associated with gender and pronounced inflammatory response.
Hashemi (23) 2020 USA	Retrospective cohort study	March 11th - April 2nd, 2020	EHR from nine hospitals (two large tertiary centres and seven community hospitals) in a single healthcare system in Massachusetts, USA.	Overall: 363 patients NAFLD: 55	Adult patients hospitalized with a positive SARS-CoV-2 infection	**Chronic Liver Disease**: 64.8 ± 15.0 **No Chronic Liver Disease**: 63.0 ± 16.9	**Chronic Liver Disease**: 32.0 ± 6.8 **No Chronic Liver Disease:** 29.9 ± 6.6	**Chronic Liver Disease**: Hypertension: 65.2 Diabetes: 40.6 Hyperlipidaemia: 46.4 CAD: 14.5 Congestive heart disease: 10.1 **No Chronic Liver Disease:** Hypertension: 56.8 Diabetes: 30.4 Hyperlipidaemia: 46.6 CAD: 14.3 Congestive heart disease: 10.9	NAFLD defined by the presence of diffuse HS on any prior imaging studies or liver histology in the absence of secondary causes of hepatic fat accumulation including significant alcohol use, long-term use of steatogenic medications or hereditary disorders.	Positive SARS-CoV-2 infection via PCR nasopharyngeal swab or tracheal aspirate	ICU admission, Mortality	NAFLD patients were more likely to be admitted to the ICU and require mechanical ventilation, only those with cirrhosis, which were mostly secondary to non-NAFLD CLD, had an increased risk of mortality
	Cohort study											

Zheng (24) 2020 China		January 17th - February 11th, 2020	Patients from 3 hospitals in Wenzhou (Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, and Ruian People's Hospital)	Overall: 214 MAFLD: 66 patients	COVID-19 patients aged 18–75 years	**Age category, n (%)** 18–44 yrs: 39 (59.1%) 45–64 yrs: 22 (33.3%) ≥65 yrs: 5 (7.6%)	**Overall** 26.5 ± 3.9	**Overall** Dyslipidemia:68.2 Hypertension:28.8 T2DM: 24.2	Patients screened for fatty liver by CT and diagnosed as MAFLD.	Laboratory confirmed COVID-19	COVID-19 severity	Risk of obesity to COVID-19 severity is greater in those with, than those without MAFLD
Bramante (25) 2020 US	Retrospective cohort study	March 1, 2020 to Aug 25, 2020	NR	Overall: 6700 patients NAFLD: 373	Adult patients with a positive SARS-CoV-2	46 (IQR: 28 to 66)	**Non-NAFLD**: 29.8 ± 69.7 **NAFLD**: 35.3 ± 8.2	**Non-NAFLD**: Obesity: 61.2 Hypertension: 33.2 T2DM: 15.2 **NAFLD**: Obesity: 81.8 Hypertension: 70.8 T2DM: 47.4	Patients with NAFLD/ NASH were defined as those with ICD codes for NAFLD or NASH or a BMI≥30kg/m2 and an elevated alanine aminotransferase (ALT) on 3 separate dates	Positive SARS-CoV-2 infection	COVID-19 severity, ICU admission, and Mortality	NAFLD/NASH is a significant risk factor for hospitalization for COVID-19
Huang (26) 2020 China	Retrospective cohort study	January 18, 2020 to February 29, 2020	10 designated hospitals in 10 cities of Jiangsu Province, China	Overall: 280 patients NAFLD: 86	Patients with a positive SARS-CoV-2 in throat swab samples by RT-PCR	**Non-NAFLD**: 42.5 (31.8 −57.3) **NAFLD**: 43.5 (32.8–53.3)	**Non-NAFLD**: 23.1 (21 −24.8) **NAFLD**: 27.1 (25.3–29.7)	**Overall** Hypertension: 45 (16.1%) Diabetes: 21 (7.5%) Chronic lung disease: 10 (3.6%)	NAFLD was defined using the published hepatic steatosis index (HSI) in the absence of other causes of CLD	Positive SARS-CoV-2 infection	Development of liver injury identified by increased ALT levels	Patients with NAFLD are more likely to develop liver injury when infected by COVID-19
Ji (11) 2020 China	Retrospective cohort study	January 20, 2020 to February 17, 2020	2 designated hospitals in China	Overall: 202 NAFLD: 76	Patients with confirmed COVID-19	Overall: 44.5 (34.8–54.1)	Overall: 24.0 ± 2.8	NR	NAFLD was identified as hepatic steatosis index (HSI = 8 × [ALT/ AST] + BMI [+ 2 if type 2 diabetes yes, + 2 if female]) >36 points and/or by abdominal ultrasound examination	Positive SARS-CoV-2 infection in the throat swab by RT-PCR	Risk of disease progression	Patients with NAFLD had a higher risk of disease progression
Mahamid (34) 2020 Israel	Case-control study	March 15, 2020 to April 30, 2020	Sharee Zedek Medical Center (SZMC), Jerusalem, Israel	Overall: 71 patients NAFLD: 22	Patients with confirmed COVID-19	**Overall (n = 71)**: 51.0 ± 21.7; **Non-NAFLD (n = 49):** 56.2 ± 20.0; **NAFLD (n = 22):** 53.7 ± 19.9	**Overall (n = 71)**: 25 ± 3.2; **Non-NAFLD (n = 49):** 26.1 ± 4.1; **NAFLD (n = 22):** 29.2 ± 4.3	NR	NAFLD was diagnosed according to the new definition for metabolic associated fatty liver disease: an international expert consensus statement from 2020 and computed tomography imaging	Positive SARS-CoV-2 infection by RT-PCR assay of oropharyngeal and nasal swab specimens	Relationship between NAFLD and COVID-19 severity	Patients with NAFLD were at a high risk for severe COVID-19 irrespective of sex
Targher (27) 2020 China	Retrospective	January to February 2020	Four sites in Zhejiang Province, China	Overall: 310; NAFLD: 94	Patients with laboratory confirmed COVID-19	**MAFLD with low FIB-4 (≤ 1.3):** 41.2 ± 14.2; **MAFLD with intermediate FIB-4 (1.3 −2.67):** 54.2 ± 10.8; **MAFLD with**	**MAFLD with low FIB-4 (≤ 1.3):** 26.5 ± 4.7; **MAFLD with intermediate FIB-4 (1.3 −2.67):** 26.6 ± 3.2; **MAFLD with**	NR	MAFLD was diagnosed based on screening of hepatic steatosis by computed tomography	Laboratory confirmed COVID-19	Risk of severe illness due to COVID-19	NAFLD fibrosis score associated with greater COVID-19 severity

(*continued on next page*)

Table 1 (*continued*)

Author, Year & Country	Study design, Setting	Study duration	Database/Source	Cohort size	Population characteristics	Mean age ± SD (range), yrs	BMI ± SD (range), kg/m^2	Top 5 co-morbidity, %	Assessment of NAFLD/MAFLD	Assessment of COVID-19	Outcome reported	Study conclusion
						high FIB-4 (> 2.67): 59.9 ± 9.1	**high FIB-4 (> 2.67):** 26.1 ± 2.8					
Kim (28) 2020 NCT04439084 US	Multicenter Observational cohort study	March 1, 2020 to April 30, 2020	Multicenter, US	Overall:867 NAFLD: 456	Adult COVID-19 patients with CLD	Overall: 56.9 ± 14.5	NR	**Overall:** Hypertension: 56.8 Diabetes: 42.9 Obesity: 42.1 Hyperlipidemia: 38.6 CVD: 17.3	Presence of pre-existing NAFLD according to ICD-10 codes confirmed by manual chart review	Laboratory confirmed COVID-19	Risk of severe COVID-19 and mortality	ALD, decompensated cirrhosis, and HCC and not NAFLD were the risk factors that predicted higher overall mortality in COVID-19 patients
Zhou (29) 2020 China	Retrospective cohort study	January 17th - February 11th, 2020	Patients from 3 hospitals in Wenzhou (Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, Ningbo No.2 Hospital, and Ruian People's Hospital)	Overall: 327 patients; MAFLD: 93	COVID-19 patients aged 18—75 years	NR	NR	**Younger patients (< 60 yrs):** Hypertension: 17.3 Diabetes: 11.2 **Older patients (< 60 yrs):** Hypertension: 43.2 Diabetes: 24.3	MAFLD was diagnosed based on the recent consensus criteria	COVID-19 was diagnosed by high-throughput sequencing or RT-PCR assays of oropharyngeal swab specimens	COVID-19 severity	The study established a synergistic effect of MAFLD for severe COVID-19 in patients aged less than 60 years.
Zhou†(30) 2020 China	Cohort study	NR	Patients from 3 major teaching hospitals: First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, and Ruian People's Hospital	Overall: 110 MAFLD: 55	COVID-19 patients less than 60 years old	Overall: 42.1 ± 11.4 MAFLD: 43.4 ± 10.8 Non-MAFLD: 40.9 ± 11.9	Overall: 25.6 ± 2.9 MAFLD: 26.1 ± 3.1 Non-MAFLD: 25.0 ± 2.7	**MAFLD** Dyslipidaemia: 81.8 Obesity: 67.3 Hypertension: 27.3 T2DM: 20	MAFLD was diagnosed based presence of steatosis by histology or imaging	NR	COVID-19 severity	Study reported a positive association between MAFLD and COVID-19 severity
Gao(31) 2020 China	Cohort study	January 17th -February 11th, 2020	EMR of 4 hospitals in China (First Affiliated Hospital of Wenzhou Medical University, Wenzhou Central Hospital, Ningbo No. 2 Hospital, and Ruian People's Hospital)	Overall: 130 MAFLD: 65	Nondiabetic COVID-19 patients aged between 18 and 75 years	Overall: 46 ± 13 MAFLD: 46 ± 13 Non-MAFLD: 47 ± 13	Overall: 25.0 ± 3.8 MAFLD: 26.2 ± 3.9 Non-MAFLD: 23.7 ± 3.2	**Non-MAFLD**: Hypertension: 16.9 Dyslipidemia: 53.8 Overweight: 61.5 Metabolic dysregulation: 63.1 **MAFLD**: Hypertension: 21.5 Dyslipidemia: 75.4 Overweight: 84.6 Metabolic dysregulation:: 84.6	Diagnosed as MAFLD according to the recent set of consensus diagnostic criteria	COVID-19 was diagnosed as a positive result by high-throughput sequencing or RT-PCR	COVID-19 severity	Increased likelihood of severe COVID-19 in diabetic patients with MAFLD

ALD: Alcoholic liver disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CAD: coronary artery disease; CLD: chronic liver disease; CVD: cardiovascular diseases; EHR: Electronic medical records; EMR: Electronic medical records; FIB: Fibrosis; HCC: hepatocellular carcinoma; HSI: hepatic steatosis index; ICD: International Classification of Diseases; ICU: intensive care unit; IHD: Ischaemic heart disease; IQR: interquartile range; MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; NASH: non-alcoholic fatty liver disease; NHS: RT-PCR: reverse transcription polymerase chain reaction; SARS: Severe acute respiratory syndrome.

HIS: Hepatic Steatosis Index.

Table 2
Outcome of interest in the included studies.

Author, study ID, Year, & Country	Mortality	ICU admission	Disease severity	Adjusted for
Lopez-Mendez (32) 2020 Mexico	NAFLD uOR: 5.29 (1.46–19.23) p = 0.007	Liver fibrosis by FIB4 uOR:1.74 (1.13–2.68) p = 0.023	NR	NA
Chen (22) 2020 USA	uOR: 0.61 (0.35, 1.06) p = 0.08 aOR: 0.94 (0.49, 1.78) p = 0.84	uOR: 1.25 (0.82, 1.91) p = 0.31 aOR: 1.60 (1.00, 2.57) p = 0.05	Beta: WHO ordinal scale Unadjusted: 0.21 (−0.19, 0.61) p = 0.30 Adjusted: 0.45 (0.03, 0.86) p = 0.04	Age, sex, race, recent healthcare exposure (hospitalization or nursing facility residence < 90 days before COVID-19 diagnosis), hypertension, and dyslipidemia.
Forlano (33) 2020 UK	**Overall, N** NAFLD: 61 Non-NAFLD: 132 **Death** NAFLD: 18 Non-NAFLD: 41	**Overall, N** NAFLD: 61 Non-NAFLD: 132 **ICU admission** NAFLD: 11 Non-NAFLD: 27	NR	NA
Hashemi (23) 2020 USA	**Rate of mortality, NAFDL vs others:** 16.4% vs 13.2% p = 0.54	**Rate of ICU admission, NAFDL vs others:** 50.9% vs 35.2% p = 0.0095	NR	NA
Zheng (24) 2020 China	NR	NR	**Obesity and COVID-19 severity in MAFLD** uOR: 5.77 (1.19–27.91) p = 0.029 aOR: 6.32 (1.16–34.54) p = 0.033	Age, sex, smoking, type 2 diabetes, hypertension, and dyslipidemia
Bramante (25) 2020 US	aOR: 0.99 (0.54 −1.77) 0.94	aOR: 1.70 (1.20 −2.40), p < 0.01	**As per admission:** uOR: 4.70 (3.81–5.92), p < 0.01 aOR: 2.04 (1.55–2.96), p < 0.01	Age, sex, obesity, ethnicity, NAFLD/NASH, alcohol abuse, Elixhauser co-morbidity index, and home medications (amiodarone, methotrexate, oral steroids, or calcium channel blockers).
Huang (26) 2020 China	NR	NR	NR	NR
Ji (11) 2020 China	NR	NR	aOR: 6.4 (1.5–31.2) Patients with NAFLD had a higher risk of disease progression (6.6% [5/126] vs. 44.7% [34/76] p < 0.0001)	NR
Mahamid (34) 2020 Israel	NR	NR	**COVID-19 and NAFLD severity:** Severe COVID-19 in NAFLD patients compared to non-NAFLD: 8/22 (36.3%) vs. 5/49 (10.2%). uOR: 3.57 (1.22–14.48), p = 0.003 aOR Men: 3.29 (3.28–3.58), p = 0.001 Women: 3.25 (3.09–3.47), p = 0.002	Age, smoking, BMI, and metabolic syndrome components
Targher (27) 2020 China	NR	NR	uOR **MAFLD low FIB-4**: 1.21 (0.46–3.14), p = 0.701 **MAFLD intermediate/high FIB-4**: 4.68 (2.31–9.49) p < 0.001 aOR **MAFLD low FIB-4**: 0.82 (0.30–2.24), p = 0.696 **MAFLD intermediate/high FIB-4**: 2.95 (1.37–6.34) p < 0.005	Adjusting for sex, obesity, and diabetes.
Kim (28) 2020 NCT04439084 US	**COVID-19 and NAFLD mortality:** aHR: 1.08 (0.59 −1.97) p = 0.804	NR	uHR: 0.55 (0.39–0.80), p = 0.001 aHR: 0.68 (0.41–1.13), p = 0.137	Age, sex, race/ethnicity, etiology of CLD, cirrhosis, hepatic decompensation, HCC, diabetes, hypertension, cardiovascular disease, chronic obstructive, pulmonary disease (COPD), smoking status, and alcohol consumption.
Zhou (29) 2020 China	NR	NR	**Younger patients (60 yrs as cut-off):** uOR: 3.97 (1.89 −8.35), p = <0.001 aOR: 2.67 (1.13–6.34), p = 0.03 **Older patients (60 yrs as cut-off):** uOR: 0.72 (0.24 −2.15), p = 0.55 aOR: 0.61 (0.18–2.03), p = 0.42	Adjusted for age, sex, smoking, overweight, diabetes mellitus, and hypertension.
Zhou (30) 2020 China	NR	NR	uOR: 3.65 (1.31–10.16) p = 0.01 aOR: 4.07 (1.20–13.79) p = 0.02	Age, sex, smoking, obesity, diabetes mellitus, and hypertension.
Gao(31) 2020 China	NR	NR	uOR: 4.22 (1.45–12.22) aOR: 4.07 (1.10–15.09)	Age, sex, smoking status, obesity, hypertension, and dyslipidemia.

aOR: adjusted odds ratio; ALT: alanine aminotransferase; BMI: body mass index; CLD: chronic liver disease; COPD: chronic obstructive pulmonary disease; HCC: hepatocellular carcinoma; ICU: intensive care unit; MAFLD.
Metabolic associated fatty liver disease; NAFDL: Non-alcoholic fatty liver disease; NASH: non-alcoholic fatty liver disease; uOR: unadjusted odds ratio; WHO; world health organization.

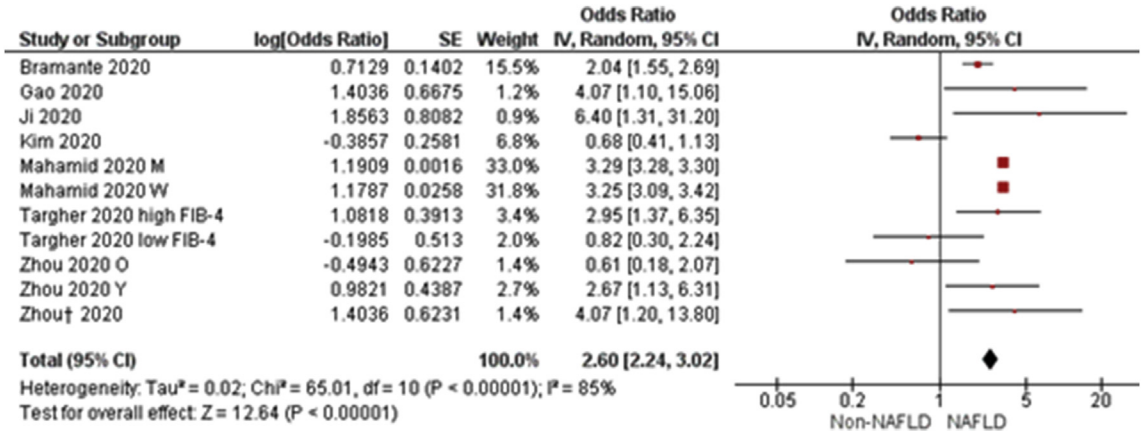

Fig. 2. Pooled adjusted risk of COVID severity in NAFLD.
Footnote: Zhou 2020 O: effect estimate for older COVID-19 patients (>60 years); Zhou 2020 Y: effect estimate for younger COVID-19 patients (<60 years); Targher 2020 study provide effect estimate for two group of NAFLD patients denoted as high FIB-4 and low FIB-4; Zhou† 2020; Zhou et al. Liver International. 2020; 40:2160–2163.

single study (Supplement Fig. 2). The statistical significance and direction of pooled aOR remained unchanged, with Mahamid et al. study having the highest impact on the pooled aOR (aOR ranged from 1.98 [95% CI: 1.23–3.21] - 3.09 [95% CI: 2.84–3.38]) [34]. The meta-regression analysis showed that the risk of COVID-19 severity in NAFLD patients was not affected by age ($p = 0.65$) or BMI ($p = 0.29$); however, the impact of the reported method of assessment of COVID-19 was significant ($p = 0.014$) (Supplement Fig. 3 and 4).

3.1.2. COVID-19 ICU admission

Five studies report the outcome related to ICU admission in NAFLD patients with COVID-19 infection (Table 2) [22,23,25,32,33]. The pooled uOR for ICU admission in patients with NAFLD vs. those without NAFLD, based on data from four studies, was 1.46 (95% CI: 1.08–1.96, $p = 0.01$) (Supplement Fig. 5) [22,23,32,33]. Two of the studies performed multivariable analysis and reported the aOR of ICU admission adjusted for age, sex, race, recent healthcare exposure (hospitalization or nursing facility residence<90 days before COVID-19 diagnosis), hypertension, dyslipidemia, obesity, alcohol abuse, Elixhauser co-morbidity index, and home medications (amiodarone, methotrexate, oral steroids, or calcium channel blockers) [22,25]. The pooled aOR for ICU admission in patients with NAFLD vs. those without NAFLD, based on data from two studies, was 1.66 (95% CI: 1.26–2.20, $p < 0.001$) (Fig. 3) [22,25].

3.1.3. COVID-19 mortality

Six studies reported the mortality in NAFLD patients with COVID-19 infection (Table 2) [22,23,25,28,32,33]. The pooled uOR for mortality in patients with NAFLD vs. those without NAFLD, based on data from five studies, was 1.09 (95% CI: 0.66–1.81, $p = 0.04$) (Supplement Fig. 6) [22,23,25,32,33]. The aOR for mortality in patients with NAFLD vs. those without NAFLD, based on data from two studies, was 1.01 (95% CI: 0.65–1.58, $p = 0.96$) (Fig. 4) [22,28]. The studies reported aOR adjusted for age, sex, race, recent healthcare exposure (hospitalization or nursing facility residence < 90 days before COVID-19 diagnosis), hypertension, dyslipidemia, etiology of CLD, cirrhosis, hepatic decompensation, HCC, diabetes, cardiovascular disease, COPD, smoking status, and alcohol consumption.

3.1.4. Study quality and bias

Based on NOS for non-randomized studies, the methodological quality of the majority of the included studies were of moderate to high quality with a mean score of 8 (range: 6–8). However, the inherent bias of observational studies design should be factored while interpreting the result. There was a significant heterogeneity (I^2>85%) among the studies reporting COVID-19 severity outcome [11,25,27–31,34]. The funnel plot of meta-analysis of studies reporting the COVID-19 severity in NAFLD patients was relatively symmetric (Supplement Fig. 7), suggesting the absence of publication bias [11,25,27–31,34].

4. Discussion

This comprehensive systematic review and meta-analysis assessing the clinical outcome in NAFLD patients with COVID-19 infection indicated a high risk of severe COVID-19 disease and increased risk of ICU admissions; however, no difference was observed in mortality between COVID-19 patients with or without underlying NAFLD.

The SARS-CoV-2 is genetically related to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) that are known to impair liver function through direct (translocation of the virus from gut to liver) or indirect mechanism (inflammation, ischemia, others) [35]. Co-morbid conditions such as obesity and

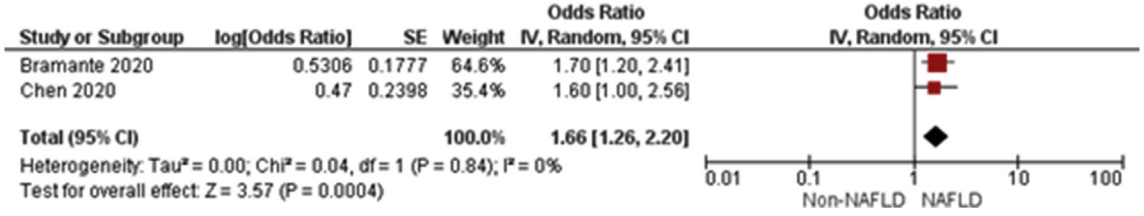

Fig. 3. Pooled adjusted risk of admission to ICU in NAFLD.

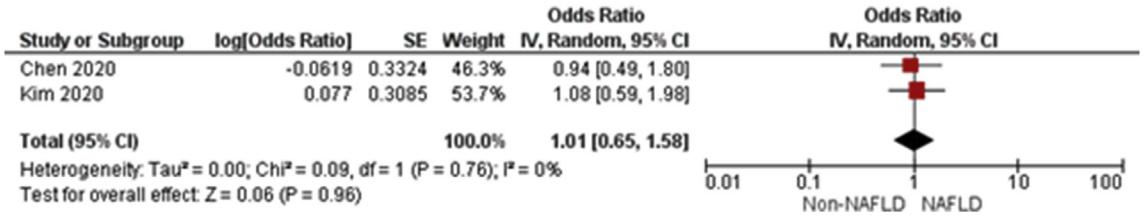

Fig. 4. Pooled adjusted risk of mortality in NAFLD.

dysmetabolism are shown to be associated with severe COVID-19 by exacerbating the infection, which eventually leads to the cytokine storm [36]. Studies have also found NAFLD in COVID-19 patients to be associated with elevated alanine aminotransferase (ALT) and aminotransferase (AST), which may lead to unfavorable clinical outcomes in this population [22,26,37]. This leads to valid concerns about the possibility that NAFLD may have an adverse role in inflammation and systemic complications of COVID-19.

Our meta-analysis revealed a higher risk of COVID-19 severity in NAFLD patients, even after adjusting for various possible confounding factors. Our finding was in alignment with the previously published studies. A multicenter cohort study from China reported five times higher odds of severe COVID-19 in MAFLD patients with neutrophil-to-lymphocyte ratio (NLR) $\leq$ 2.8 and seventeen times higher odds for those with MAFLD and NLR > 2.8, even after adjustment for various confounding factors (age, sex, pre-existing diabetes, obesity, and hypertension) [38]. In another study, the presence of obesity in NAFLD patients was associated with a six-fold increased risk of severe COVID-19 illness after adjusting for other major co-morbidities [24]. Likewise, a pooled-analysis that included fewer studies and only focused on COVID-19 severity, without assessing the association with ICU admission and mortality, reported NAFLD as a predictor of severe COVID-19 (OR 2.35; 95% CI: 1.902–2.923, p < 0.001). This previous pooled-analysis did not include all the data from Mahamid et al. Targher et al., and Zhou et al. despite detailed and relevant information and included selective data in the pooled analysis from these studies [27,30,34]. In our analysis, age and BMI did not affect the risk of COVID-19 severity in NAFLD patients; a previous meta-analysis assessing the impact of CVD on COVID-19 severity and mortality observed similar findings [39]. Nevertheless, it should be considered that the meta-regression in the current scenario has certain limitations in explaining the association due to fewer studies available, thus highlighting the need for more studies with larger cohorts [39].

COVID-19 patients with co-morbid conditions are at higher risk of ICU admission. Our study findings revealed higher ICU admission risk due to COVID-19 in patients with NAFLD. Ghoneim et al. reported a higher incidence of COVID-19 in patients with metabolic syndrome, and NASH had the strongest association with COVID-19 [aOR 4.93 (4.06–6.00)] [40]. Similar findings were reported by a well-conducted retrospective study that found higher odds (OR range: 1.74 to 2.95) of ICU admission in COVID-19 patients with higher NAFLD Fibrosis Score and Fibrosis-4 index [27,32]. We do not find any impact of COVID-19 on the mortality outcome in patients with NAFLD. The possible reason for having no impact on the mortality rate could be due to the mild effect on the liver due to the COVID-19 cytokine storm [41].

Our results are concurrent with the recent findings. We analyzed the evidence with adjusted and unadjusted effect sizes separately and used the absolute data, if reported, to calculate the uOR. This meta-analysis has a few constraints that need to be considered while interpreting findings—first, there was lack of a robust and consistent definition of NAFLD and respective disease severity across the selected studies, which can be considered as one of the recommendations for the future primary studies in this domain. Second, the study population had several co-morbidities such as, obesity, diabetes, and hypertension. Previous studies have shown these to be associated with poorer COVID-19 related prognosis. While it is challenging to dissect the contribution of co-morbidity to the outcomes, we pooled both unadjusted and the adjusted effect estimates separately to mitigate this to the extent possible. Furthermore, studies reporting aOR adjusted for major confounding covariates such as age, sex, race, and co-morbidities, there was some variation in the covariate adjusted in various studies. Third, there was the restricted scope for a robust sub-group analysis due to a fewer number of included studies. Lastly, there is a scope for uniform criteria to definition severe COVID-19 in the included studies. Having outlined the restrictions, based upon the results of this systematic review, we recommend future studies to report criteria for COVID-19 severity assessment and to include the mortality outcome.

5. Conclusions

This systematic review and meta-analyses found an increased risk of severe COVID-19 and admission to ICU due to COVID-19 in patients with underlying NAFLD; however, no difference in mortality was observed between NAFLD and non-NAFLD patients. Future studies should include the mortality outcome to conclusively elucidate the impact of NAFLD in patients with COVID-19 infection.

Declaration of competing interest

All authors declare the absence of any competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2021.03.019.

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Contributors

AS and SH designed the study. AS and SH independently screened the study and performed data extraction. AS and SH performed the quality check for study screening and data extraction. AS and SH analyzed the data. AS, SH, and BA drafted the manuscript. All authors participated in data interpretation and all authors were involved in the preparation of the manuscript. All authors critically reviewed and edited the manuscript and approved the final version.

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