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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.

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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 inflammation 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, which 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 NAFLD 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 >50% using I² statistics, or p < 0.10 using the χ² 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
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 confirmed 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) [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
| Author & Country | Study design, Setting | Study duration | Database/Source | Cohort size | Population characteristics | Mean age ± SD (range), yrs | BMI ± SD (range), kg/m² | 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 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 | Top 5 co-morbidity, % | 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 Overall: 51 (43–62) | Non-NAFLD: NAFLD: 27.9 (25.6–30.5) | Overall: Obesity: 28.4 Hypertension: 23.2 T2DM: 15.5 Dyslipidemia: 5.8 Cardiac disease: 4.5 | Top 5 co-morbidity, % | Defined either by imaging or HSI index above 36 | COVID-19 diagnosed by polymerase chain reaction | Disease severity, ICU admission, Transaminis, Mortality | HS was associated with increased disease severity and transaminis 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 Overall: 49 (38–71) | Non-NAFLD: NAFLD: 27.9 (28.3–30.5) | Overall: Obesity: 28.4 Hypertension: 23.2 T2DM: 15.5 Dyslipidemia: 5.8 Cardiac disease: 4.5 | Top 5 co-morbidity, % | Imaging of the liver (US or CT) or known diagnosis of NAFLD | SARS-CoV-2 was using a RT-PCR method | ICU admission and 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 Overall: 51 (42–62) | Chronic Liver Disease: 64.8 ± 15.0 No Chronic Liver Disease: 63.0 ± 16.9 | Overall: Obesity: 28.4 Hypertension: 56.8 Diabetes: 30.4 Hyperlipidaemia: 46.6 | Top 5 co-morbidity, % | 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 and 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 |
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| Study | Design | Start Date | End Date | Setting | Patients | MAFLD | Non-MAFLD | Results |
|-------|--------|------------|----------|---------|----------|-------|-----------|---------|
| Zheng (24) | Retrospective cohort study | 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 patients | MAFLD: 66 patients | Overall: 26.5 ± 3.9 | Overall Dyslipidemia: 68.2% | Patients screened for fatty liver by CT and diagnosed as MAFLD. | Laboratory confirmed COVID-19 | COVID-19 severity | Non-NAFLD: Obesity: 61.2% Hypertension: 31.2% T2DM: 24.2% | Positive SARS-CoV-2 infection | COVID-19 severity, ICU admission, and Mortality | NAFLD/NASH is a significant risk factor for hospitalization for COVID-19 |
| Bramante (25) | Case-control study | March 1, 2020 to Aug 25, 2020 | 10 designated hospitals in 10 cities of Jiangsu Province, China | Overall: 6700 patients | MAFLD: 373 | Overall: 46 (IQR: 28 to 66) | Adult patients with a positive SARS-CoV-2 | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | Non-NAFLD: Obesity: 29.8 ± 69.7 NAFLD: 57.3 ± 8.2 | NAFLD: Obesity: 81.8% Hypertension: 70.8% T2DM: 47.4% | Overall: 45 (16.1%) 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 |
| Huang (26) | Case-control study | January 18, 2020 to February 29, 2020 | 2 designated hospitals in China | Overall: 202 patients | MAFLD: 76 | Overall: 44.5 (34.8–54.1) | Patients with confirmed COVID-19 | Non-NAFLD: Obesity: 23.1 (21.7–24.8) NAFLD: 27.1 (25.3–29.7) | Non-NAFLD: Obesity: 29.8 ± 69.7 NAFLD: 57.3 ± 8.2 | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | Overall: 46 (IQR: 28 to 66) | Adult patients with a positive SARS-CoV-2 | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | 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) | Case-control study | January 20, 2020 to February 17, 2020 | 2 designated hospitals in China | Overall: 202 patients | MAFLD: 76 | Overall: 44.5 (34.8–54.1) | Patients with confirmed COVID-19 | Non-NAFLD: Obesity: 23.1 (21.7–24.8) NAFLD: 27.1 (25.3–29.7) | Non-NAFLD: Obesity: 29.8 ± 69.7 NAFLD: 57.3 ± 8.2 | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | Overall: 46 (IQR: 28 to 66) | Adult patients with a positive SARS-CoV-2 | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | 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 |
| Mahamid (34) | Case-control study | March 15, 2020 to April 30, 2020 | Sharee Zedek Medical Center (SZMC), Jerusalem, Israel | Overall: 71 patients | MAFLD: 22 | Overall: 26.5 ± 3.9 | Overall Dyslipidemia: 68.2% | Patients screened for fatty liver by CT and diagnosed as MAFLD. | Laboratory confirmed COVID-19 | COVID-19 severity | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | Positive SARS-CoV-2 infection | COVID-19 severity, ICU admission, and Mortality | NAFLD/NASH is a significant risk factor for hospitalization for COVID-19 |
| Targher (27) | Retrospective cohort study | January to February 2020 | Four sites in Zhejiang Province, China | Overall: 310 | MAFLD: 94 | Overall: 26.5 ± 3.9 | Overall Dyslipidemia: 68.2% | Patients screened for fatty liver by CT and diagnosed as MAFLD. | Laboratory confirmed COVID-19 | COVID-19 severity | Non-NAFLD: Obesity: 42.5% Hypertension: 43.5% T2DM: 24.1% | Positive SARS-CoV-2 infection | COVID-19 severity, ICU admission, and Mortality | NAFLD/NASH is a significant risk factor for hospitalization for COVID-19 |

(continued on next page)
| Author, Year | Study design, Setting | Study duration | Database/Source | Cohort size | Population characteristics | Mean age ± SD (range), yrs | BMI ± SD (range), kg/m² | Top 5 co-morbidity, % | Assessment of NAFLD/MAFLD | Assessment of COVID-19 | Outcome reported | Study conclusion |
|--------------|-------------------------|----------------|----------------|-------------|---------------------------|---------------------------|--------------------------|------------------------|---------------------------|-------------------------|----------------|----------------|
| Kim (28) 2020 China | Multicenter Observational cohort study US | March 1, 2020 to April 30, 2020 | Multicenter, US | Overall: 867 NAFLD: 456 | Adult COVID-19 patients with CLD | Overall: \(56.9 ± 14.5\) | Overall: \(26.1 ± 2.8\) | NR | Overall: Hypertension: 56.8 Diabetes: 42.9 Obesity: 42.1 Hyperlipidemia: 38.6 CVD: 17.3 | Laboratory confirmed COVID-19 | MAFLD was diagnosed based on the recent consensus criteria | The study established a synergistic effect of MAFLD for severe COVID-19 in patients aged less than 60 years. |
| 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 | MAFLD was diagnosed based on the recent consensus criteria 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: Dyslipidemia: 81.8 Obesity: 67.3 Hypertension: 27.3 T2DM: 20 | 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 | MAFLD was diagnosed based on the recent consensus criteria for severe COVID-19 in patients aged less than 60 years. |
| 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 | 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: \(23.7 ± 3.2\) | MAFLD: Hypertension: 16.9 Dyslipidemia: 53.8 | 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 | MAFLD was diagnosed as a positive result by high-throughput sequencing or RT-PCR for 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; HIS: 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; NHS: RT-PCR: reverse transcription polymerase chain reaction; SARS: Severe acute respiratory syndrome.
Table 2
Outcome of interest in the included studies.

| Author, study ID, Year, & Country | Mortality | ICU admission | Disease severity | Adjusted for |
|----------------------------------|-----------|---------------|------------------|-------------|
| Lopez-Mendez Mexico 2020         | NAFLD uOR: 5.29 p = 0.007 | Liver fibrosis by FIB4 uOR: 1.74 p = 0.023 | Beta: WHO ordinal scale | NA |
| Chen USA 2020                   | 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 | 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. |
| Torgher USA 2020                | Overall, N = Non-NAFLD: 61 NAFD: 18 | ICU admission: FIB4 uOR: 1.74 p = 0.08 | Beta: WHO ordinal scale | NA |
| Hashemi USA 2020                | Rate of mortality, NAFDL vs others: 1.64% vs 13.2% p = 0.54 | Rate of ICU admission, NAFDL vs others: 50.9% vs 35.2% p = 0.0095 | Beta: WHO ordinal scale | NA |
| Zheng China 2020                | 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 Italy 2020             | aOR: 0.99 (0.54, 1.77) 0.94 | aOR: 1.70 (1.20–2.40), p < 0.01 aOR: 2.04 (1.55–2.96), p < 0.01 | Adjusted: 0.45 (0.03, 0.86) p = 0.04 | Age, sex, obesity, ethnicity, NAFLD/NASH, alcohol abuse, Elixhauser morbidity index, and home medications (amiodarone, methotrexate, oral steroids, or calcium channel blockers). |
| Huang China 2020                | NR | NR | NR | NR |
| Ji China 2020                   | 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) | Age, sex, smoking, type 2 diabetes, hypertension, and dyslipidemia |
| Mahamid Israel 2020             | COVID-19 and MAFLD mortality: 1.18 (0.59 – 1.97) p = 0.804 | 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: 4.68 (2.31–9.49) p = 0.001 AOR | Adjusting for sex, obesity, and diabetes. |
| Margher China 2020              | COVID-19 and NAFD vs others: 0.46% vs 31.4%, p = 0.001 | Adjusted: 0.45 (0.03, 0.86) p = 0.04 | Age, sex, smoking, type 2 diabetes, hypertension, and dyslipidemia |
| Kim China 2020                  | COVID-19 and NAFD mortality: 1.18 (0.59 – 1.97) p = 0.804 | COVID-19 and NAFD 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: 4.68 (2.31–9.49) p = 0.001 AOR | Adjusting for age, smoking, obesity, diabetes mellitus, and hypertension. |
| Zhou China 2020                 | 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 | Adjusted: 0.45 (0.03, 0.86) p = 0.04 | Age, sex, smoking, obesity, diabetes mellitus, and hypertension. |
| Zhou China 2020                 | 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: 0.45 (0.03, 0.86) p = 0.04 | Age, sex, smoking, obesity, diabetes mellitus, and hypertension. |
| Gao China 2020                  | 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 | Adjusted: 0.45 (0.03, 0.86) p = 0.04 | Age, sex, smoking, obesity, diabetes mellitus, and hypertension. |

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; NAFD: Non-alcoholic fatty liver disease; NASH: non-alcoholic fatty liver disease; uOR: unadjusted odds ratio; WHO: world health organization.
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] to 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 (I² > 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
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 aspartate transaminase (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 NAFLD patients with neutrophil-to-lymphocyte ratio (NLR) ≤ 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. Targarhi 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 define 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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