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SYSTEMATIC REVIEWS

Impact of non-alcoholic fatty liver disease on coronavirus disease 2019: A systematic review

Abdul Moeed, Muhammad Omar Larik, Muhammad Ahmed Ali Fahim, Hafsah Alim Ur Rahman, Lubna Najmi, Mah I Kan Changez, Muhammad Moiz Javed, Md Al Hasibuzzaman

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Abstract

BACKGROUND

Many studies have revealed a link between non-alcoholic fatty liver disease (NAFLD) and coronavirus disease 2019 (COVID-19), making understanding the relationship between these two conditions an absolute requirement.

AIM

To provide a qualitative synthesis on the currently present data evaluating COVID-19 and NAFLD.

METHODS

This systematic review was conducted in accordance with the guidelines provided by preferred reporting items for systematic reviews and meta-analyses and the questionnaire utilized the population, intervention, comparison, and outcome

framework. The search strategy was run on three separate databases, PubMed/MEDLINE, Scopus, and Cochrane Central, which were systematically searched from inception until March 2024 to select all relevant studies. In addition, ClinicalTrials.gov, Medrxiv.org, and Google Scholar were searched to identify grey literature.

RESULTS

After retrieval of 11 studies, a total of 39282 patients data were pooled. Mortality was found in 11.5% and 9.4% of people in NAFLD and non-NAFLD groups. In all, 23.2% of NAFLD patients and 22% of non-NAFLD admissions diagnosed with COVID-19 were admitted to the intensive care unit, with days of stay varying. Ventilatory support ranged from 5% to 40.5% in the NAFLD cohort and from 3.1% to 20% in the non-NAFLD cohort. The incidence of acute liver injury showed significance. Clinical improvement on days 7 and 14 between the two classifications was significant. Hospitalization stay ranged from 9.6 days to 18.8 days and 7.3 days to 16.4 days in the aforementioned cohorts respectively, with 73.3% and 76.3% of patients being discharged. Readmission rates varied.

CONCLUSION

Clinical outcomes except mortality consistently showed a worsening trend in patients with NAFLD and concomitant COVID-19. Further research in conducting prospective longitudinal studies is essential for a more powerful conclusion.

Key Words: Non-alcoholic fatty liver disease; Coronavirus disease 2019; Mechanical ventilation; Intensive care unit; Acute liver injury

Core Tip: Non-alcoholic fatty liver disease (NAFLD) and coronavirus disease 2019 (COVID-19) have both shown increasing rates over the years, with the liver being the second most affected organ in COVID-19 after the lungs. Several studies have suggested that COVID-19 patients with concomitant NAFLD have a higher risk for severe disease. Therefore, this systematic review provides a comprehensive overview of improvements, complications, mortality, and intensive care unit- and hospital-related outcomes in COVID-19 patients with and without NAFLD.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The World Health Organization declared it a global pandemic in March 2020. COVID-19 has had a significant impact worldwide, with an estimated mortality burden of 14.9 million between 2020 and 2021[1]. COVID-19 has profoundly impacted populations across the globe[2].

Numerous studies have indicated that a notable proportion of COVID-19 patients admitted to hospitals have underlying conditions such as hypertension, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD), which may increase the risk of mortality from the virus[3]. Non-alcoholic fatty liver disease (NAFLD) is a multifaceted disorder characterized by the pathological accumulation of fat in hepatocytes, occurring in the absence of significant alcohol consumption, is closely associated with T2DM and CVD[4,5]. The diagnosis of NAFLD typically involves a comprehensive evaluation, including imaging modalities such as ultrasound, computed tomography (CT), or magnetic resonance imaging, alongside liver biopsies for histological confirmation[6]. The escalating global burden of obesity has substantially fueled the increasing prevalence and incidence rates of NAFLD. Presently, NAFLD stands as one of the most common chronic liver diseases globally, affecting approximately 30% of the world's population. Recent medical research has placed considerable emphasis on investigating the association between NAFLD/metabolic-associated fatty liver disease (MAFLD) and COVID-19. A growing body of evidence indicates that individuals with NAFLD face an elevated risk of experiencing severe manifestations of COVID-19, resulting in poorer clinical prognosis[7].

NAFLD and COVID-19 are regarded as "colliding pandemics" characterized by their escalating incidence rates[8]. Pan *et al*[9] reported a combined NAFLD prevalence of 0.31 (95% confidence interval [CI]: 0.28–0.35) among COVID-19 patients. Similarly, Hayat *et al*[10], in a meta-analysis of 16 studies, found a combined COVID-19 prevalence of 0.29 (95%CI: 0.19-0.40; $P < 0.001$) among NAFLD patients. Beyond respiratory manifestations, COVID-19 significantly impacts the liver, with the liver being the second most commonly affected organ, following the lungs. Several studies have highlighted a potential link between NAFLD and the severity of COVID-19, indicating that individuals with NAFLD may experience more severe outcomes from COVID-19 infection. Understanding the interplay between these two conditions is crucial for effective management and mitigation strategies, particularly in individuals with underlying liver disorders like

NAFLD[11].

This systematic review expands the discussion by examining the effects of NAFLD on COVID-19 patients, addressing a significant gap in existing literature. By incorporating a larger number of studies and patients, it enhances statistical power and provides detailed analyses of outcomes such as mortality, intensive care unit (ICU) admissions, ventilatory support, and hospital-related metrics. It identifies specific mechanisms of disease interaction, including immune system interactions, inflammation pathways, and metabolic dysfunctions, and offers clinical recommendations for tailored treatment protocols and effective resource allocation. Additionally, it provides public health insights and suggests future research directions, including biomarker development and long-term outcome studies. This comprehensive approach not only benefits COVID-19 patients with NAFLD but also enhances healthcare system preparedness and contributes significantly to the development of a comprehensive treatment protocol for this patient population.

Pathogenesis

NAFLD has a complex multifactorial pathology involving metabolic dysfunction, genetic predisposition and environmental influences. It usually starts in the background of insulin resistance and a disbalance in lipid metabolism[12]. Increased lipolysis in adipose tissue is the hallmark of NAFLD. Alongside insulin resistance, increased dietary fats and adipocyte dysfunction contribute to the pathogenesis of NAFLD. Overtime accumulation of triglycerides in hepatocytes induces lipotoxicity and oxidative stress, leading to cellular damage and inflammation in the liver.

As previously mentioned, inflammation is a key regulator in the eventual progression of NAFLD to non-alcoholic steatohepatitis (NASH) and fibrosis. Therefore, systemic inflammatory response syndrome (SIRS) may exacerbate NAFLD in the context of severe bacteremia or COVID-19. A large proportion of patients with COVID-19 have shown moderate elevations in liver enzymes, which directly correlate with the severity of the illness. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptors and enters the tissues[13]. Although the gallbladder and biliary tract express ACE2 abundantly, levels are comparatively lower in healthy hepatic tissues. Under the influence of ongoing inflammation and fibrotic conditions, hepatocytes have demonstrated increased ACE2 affinity of SARS-CoV-2 S protein in the presence of trypsin[14,15], found abundantly in hepatic tissues, among other cleavage sites unique to SARS-CoV-2 [16] responsible for its infectivity and transmissibility. This increased affinity leads to exacerbation of inflammatory processes in already diagnosed NAFLD patients, increasing the number of COVID-related complications. On a more cellular level, Kupffer cell hyperactivity and increased steatosis have been demonstrated in histopathological studies[17, 18]. However, there has been a high prevalence of non-specific findings such as vascular thrombosis, sinus congestion and hepatic steatosis alongside Kupffer cell hyperplasia[14].

Often, COVID-19 results in SIRS and activation of inflammatory cytokines, including interleukin 2 (IL-2), IL-6, IL-7, granulocyte-colony stimulating factor, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1 alpha, and tumor necrotic factor alpha (TNF-α) with IL-6[18,19]. Significant contributors to the progression and inflammation in NAFLD patients are IL-6 and TNF-α[20]. IL-6 has been found to cause biliary stasis as well. Moreover, MCP-1 is elevated in a moderate number of COVID-19 patients and exacerbates hepatosteatosis. Activation of nuclear factor kappa B and IL-1 causes Kupffer cell activation and shifts the homeostasis towards the pro-inflammatory M1 subtype of Kupffer cells[20,21]. Hypoxia in severe COVID-19 causes secondary hepatic damage. It leads to oxidative stress *via* reperfusion injury, accelerating inflammation and damage.

Although direct viral cytotoxic effects of SARS-CoV-2 on hepatocytes seem unlikely[22,23], cholangiocyte damage is more possible due to the expression of ACE2 receptors, as mentioned above. Raised aminotransferases during hospitalization of COVID-19 patients (16%-93%) have been shown in clinical studies[24]. More specifically, gamma-glutamyl transferase levels have been found in about 24% of the patients, demonstrating viral insult to the gallbladder and biliary tract[25]. An *ex vivo* study also showed viral insult to cholangiocytes, resulting in apoptosis induction and subsequent biliary stasis[22]. Elevated bile acids have been related to the severity of NAFLD and NASH.

MATERIALS AND METHODS

Data sources and search strategy

The following systematic review was performed with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines taken into account and a PRISMA checklist is supplied[26]. The research questionnaire was created utilizing the patient, intervention, control, and outcome framework[27] and a search strategy comprising of the Boolean operators "AND" and "OR" along with various Medical subject headings terms was ran on three separate databases: PubMed/MEDLINE, Scopus, and Cochrane Central. Then these databases were systematically searched from inception until March 2024 without any restrictions or filters applied, and all relevant randomized controlled trials and observational studies were selected. Search strategy terms included 'NAFLD,' 'non-alcoholic fatty liver disease,' 'non-alcoholic fatty liver disease,' 'MAFLD,' 'metabolic-dysfunction associated fatty liver disease,' 'nonalcoholic steatohepatitis,' 'COVID-19,' 'COVID19,' 'COVID 19,' 'coronavirus', 'coronaviruses,' 'SARS-CoV-2,' and 'SARSCoV-2.' As this study sees publicly available data, no approval or registration was required. A detailed overview of the search strategy used is given in Supplementary Table 1. Moreover, Google Scholar, ClinicalTrials.gov, and Medrxiv.org were searched to identify grey literature.

Study selection

After completing the literature search, all retrieved articles were exported to the endnote reference library (version X7.5; Clarivate Analytics, Philadelphia, PA, United States), where duplicates were removed. Screening of the remaining articles

based on title and abstract was performed by two independent authors (Muhammad Omar Larik and Muhammad Ahmed Ali Fahim), after which full texts were evaluated for relevance. Disagreements were resolved with a discussion with a third author (Hafsah Alim Ur Rahman).

Inclusion criteria for our analysis: (1) Original articles; (2) Studies presented in the English language; (3) Patients above 18 years of age; (4) Patients with confirmed concomitant COVID-19 and NAFLD; and (5) Studies reporting one or more primary or secondary outcomes. Studies were excluded on the basis of the following: (1) Conference abstracts, reviews, letters, and case reports; (2) Studies with inadequate or incomplete data; (3) Duplicated studies; (4) Articles irrelevant to the research purpose; (5) Non-human studies; (6) Diagnosed alcohol dependence or abuse/history of significant alcohol consumption (> 30 g/day in men and > 20 g/day in women); (7) Patients with active hematological diseases, malignant tumors, or who are immunocompromised; and (8) Palliative management cases.

Study outcomes

We defined our primary outcomes of interest as mortality, ICU outcomes (including admission and length of stay), need for ventilatory support, respiratory or hepatic complications, and improvement. Our secondary outcomes of interest were defined as hospitalization outcomes (length, readmission, and discharge).

Data extraction

The study baseline patient and COVID-19 symptom characteristics were extracted onto an excel sheet and verified by two independent authors (Muhammad Omar Larik and Muhammad Ahmed Ali Fahim). Any disagreements were resolved with the help of a third author (Hafsah Alim Ur Rahman). Extracted data included first author name, year of publication, study design, study location, sample size, study outcomes, COVID-19 symptoms, number of patients in each group, general patient characteristics (age and sex), comorbidities (T2DM, hypertension), body mass index (BMI), primary and secondary endpoints.

Study quality assessment

The Newcastle-Ottawa scale assessment for prospective and retrospective cohort studies[28] was utilized by two independent authors (Muhammad Ahmed Ali Fahim and Hafsah Alim Ur Rahman) to assess the quality of each cohort study reported in this systematic review. The studies were analyzed according to the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at the start of the study, comparability of cohorts based on the design or analysis, assessment of outcome, was follow-up long enough for outcomes to occur and adequacy of follow up of cohorts. All inconsistencies were resolved with discussion and agreement. Cohort studies receiving a score of 8 or 9 points were regarded as having a low risk of bias, with studies receiving a score of 6 or 7 points being judged as having a moderate risk of bias. Moreover, studies with a score of 5 points were deemed to have a high risk of bias. All studies were included in the final systematic review regardless of the score.

RESULTS

After retrieval of a total of 1977 studies from the aforementioned resources, 11 studies[29-39] (9 retrospective and 2 prospective cohort studies) were specified and included in the systematic review. The PRISMA flow chart, as shown in Figure 1, shows a more detailed explanation of the process. The primary and secondary outcomes for a sum total of 39282 patients were extracted and pooled, with 17516 and 21766 patients accounted for in the NAFLD and non-NAFLD groups with concomitant COVID-19, respectively.

Table 1 identifies the combined study and baseline patient characteristics of the included studies, respectively. In summary, mean ages for both cohorts were comparable with 54.5 years and 56 years being the sum average age for the NAFLD and non-NAFLD cohorts respectively with Zoncapè *et al*[39] presenting the oldest and Huang *et al*[30] the youngest patients for both cohorts. Additionally, male percentages were also comparable being 53.1% for the NAFLD and 53.3% for non-NAFLD groups although the study published by Nath *et al*[35] reported a 82.6% and 72.9% male population in their distribution. The parameter of BMI was reported by select studies with four studies reporting a mean obese (> 30 kg/m^2) and three studies reporting an overweight BMI (25-30 kg/m^2) in the NAFLD cohort compared to four studies presenting an overweight and two studies submitting a healthy (18 to < 25 kg/m^2) BMI in the non-NAFLD cohort. T2DM incidence varied ranging between 0% to 51% of patients in the NAFLD grouping in contrast to 3.8% to 48.1% in the non NAFLD classification. Table 2 outlines the baseline COVID-19 symptoms that patients presented with, as highlighted by 5 of the 11 studies. Table 3 outlines our primary and secondary outcomes.

Comparison of clinical outcomes

Mortality: The outcome of mortality was assessed in 10 of 11 studies, with loss of life being reported in 11.5% of patients of the combined NAFLD cohort compared to 9.40% in the non-NAFLD cohort of COVID-19-infected patients. This however only reached statistical significance in the study of Moctezuma-Velázquez *et al*[34]. Additionally, it must be noted that of these 10 studies, Wang *et al*[37] revealed no patient mortality in its NAFLD cohort with Huang *et al*[30] being the only study that assessed but did not find any patient mortality in either cohort. From the remaining studies that revealed patient mortality the outcome ranged between 6.7%-51.9% in the NAFLD group with both Vrsaljko *et al*[36] and Nath *et al*[35] reporting the lowest percentages of any study at 6.7% of patients. Contrary to this, the highest percentage mortality in the NAFLD classification was seen in Vázquez-Medina *et al*[33] in addition to it being the only study

Table 1 Baseline and study characteristics

Ref.	Publication year	Study design	Country	Patients		Age in years		Male		BMI in kg/m²		Hypertension		Diabetes mellitus	
				NAFLD	Non-NAFLD	NAFLD	Non-NAFLD	NAFLD	Non-NAFLD	NAFLD	Non-NAFLD	NAFLD	Non-NAFLD	NAFLD	Non-NAFLD
Milic *et al*[29]	2022	Retrospective observational	Italy	130	105	60.5± 5.2	63 ± 6.4	95 (73.1)	67 (63.8)	30.8 ± 1.5	26.8 ± 1.5	43 (33.1)	27 (25.7)	26 (20.0)	7 (6.7)
Huang *et al*[30]	2020	Retrospective observational	China	86	194	43.3 ± 5.9	43.5 ± 7.4	50 (58.1)	96 (49.5)	27.3 ± 1.3	23.0 ± 1.1	18 (20.9)	27 (13.9)	10 (11.6)	11 (5.7)
Younossi *et al*[32]	2022	Retrospective observational	United States	553	2736	54.7 ± 15.8	54.0 ± 20.7	280 (50.6)	1340 (49.0)	32.6 ± 8.2	29.5 ± 6.8	346 (62.9)	1138 (41.6)	282 (51.0)	0 (0)
Vázquez-Medin *et al*[33]	2022	Retrospective observational	Mexico	79	60	54.6 ± 14.0	56.0 ± 17.5	62 (78.5)	42 (70.0)	N/d	N/d	3 (3.8)	9 (15.0)	0 (0)	8 (13.3)
Moctezuma-Velázquez *et al*[34]	2022	Retrospective observational	Mexico	359	111	51.3 ± 5.5	53.0 ± 6.9	231 (64.0)	67 (60.0)	31.2 ± 1.9	25.5 ± 1.1	122 (34.0)	25 (22.0)	111 (31.0)	15 (14.0)
Nath *et al*[35]	2022	Prospective observational	India	814	3169	47.1 ± 14.3	45.2 ± 16.1	673 (82.6)	2311 (72.9)	N/d	N/d	N/d	N/d	72 (43.3)	149 (43.5)
Vrsaljko *et al*[36]	2022	Retrospective observational	Croatia	120	96	58.0 ± 4.5	63.0 ± 4.6	78 (65.0)	59 (61.5)	31.5 ± 1.7	27.3 ± 1.9	47 (39.2)	45 (46.9)	20 (16.7)	10 (10.4)
Wang *et al*[37]	2021	Prospective observational	China	86	132	46.8 ± 16.5	48.8 ± 18.2	52 (60.5)	58 (43.9)	26.4 ± 5.3	21.2 ± 5.1	20 (23.3)	12 (9.1)	9 (10.5)	5 (3.8)
Madan *et al*[38]	2022	Retrospective observational	India	289	157	56.4 ± 14.3	58.3 ± 17.1	195 (67.5)	93 (59.2)	26.6 ± 5.2	N/d	N/d	N/d	129 (44.6)	68 (43.3)
Zoncapè *et al*[39]	2023	Retrospective observational	Italy	333	339	68.5 ± 14.0	73.7 ± 15.1	235 (70.6)	172 (55.3)	N/d	N/d	229 (68.8)	183 (54.0)	148 (44.4)	60 (17.7)
Brozat *et al*[31]	2024	Retrospective observational	United States	14667	14667	57.8 ± 15.1	57.3 ± 14.7	7356 (50.2)	7070 (48.2)	N/d	N/d	9761 (66.6)	9527 (65.0)	7051 (48.1)	7051 (48.1)

Data are *n* (%) or mean ± standard deviation. BMI: Body mass index; NAFLD: Non-alcoholic fatty liver disease; N/d: Not defined.

reporting > 50% of patient death in a cohort. Regarding the non-NAFLD group, mortality ranged between 1.5% reported by Wang *et al*[37] and 38.3% for Vázquez-Medina *et al*[33]. Although COVID-19 mortality seemed consistently greater in the NAFLD cohort, this observation failed to achieve any statistically significant differences ($P > 0.05$), and thus mortality is comparable among both NAFLD and non-NAFLD counterparts.

ICU-related outcomes: When evaluating prognosis, ICU data were pooled together. Admission data was extracted from five studies with 3697 (23.2%) NAFLD patient admissions and 3927 (22%) non-NAFLD admissions diagnosed with COVID-19. Statistical significance varied as higher NAFLD ICU admissions achieved significance in Moctezuma-Velázquez *et al*[34], contrary to a higher non-NAFLD cohort reaching significance in Younossi *et al*[32] as the two groups

Table 2 Baseline coronavirus disease 2019 symptoms

Ref.	NAFLD	Non-NAFLD	*P* value
Milic *et al*[29]	Respiratory cluster: 67 (51.5)	Respiratory cluster: 58 (55.2)	0.66
	Neurocognitive cluster: 38 (29.2)	Neurocognitive cluster: 44 (41.9)	0.06
	Musculoskeletal cluster: 32 (24.6)	Musculoskeletal cluster: 30 (28.6)	0.59
	Psychological cluster: 30 (23.1)	Psychological cluster: 39 (37.1)	0.03[a]
	Sensory cluster: 20 (15.4)	Sensory cluster: 21 (20.0)	0.45
	Dermatological cluster: 32 (24.6)	Dermatological cluster: 27 (25.7)	0.97
Huang *et al*[30]	Fever: 55 (64.0)	Fever: 132 (68.0)	0.503
	Cough: 47 (54.7)	Cough: 109 (56.2)	0.812
	Fatigue: 16 (18.6)	Fatigue: 42 (21.6)	0.562
	Sore throat: 10 (11.6)	Sore throat: 22 (11.3)	0.944
	Muscle ache: 7 (8.1)	Muscle ache: 21 (10.8)	0.49
	Shortness of breath: 7 (8.1)	Shortness of breath: 16 (8.2)	0.976
	Headache: 3 (3.5)	Headache: 16 (8.2)	0.144
	No pneumonia: 6 (7.0)	No pneumonia: 19 (9.8)	
	Unilateral pneumonia: 11 (12.8)	Unilateral pneumonia: 26 (13.4)	
	Bilateral pneumonia: 69 (80.2)	Bilateral pneumonia: 149 (76.8)	
Younossi *et al*[32]	Cough: 318 (57.9)	Cough: 1273 (47.7)	< 0.0001[b]
	Fever: 319 (58.1)	Fever: 1283 (48.0)	< 0.0001[b]
	Shortness of breath: 361 (65.8)	Shortness of breath: 1519 (56.9)	0.0001[b]
	Altered mental status: 22 (4.0)	Altered mental status: 203 (7.6)	0.0026[b]
	Sore throat: 22 (4.0)	Sore throat: 64 (2.4)	0.033[a]
	Headache: 74 (13.5)	Headache: 240 (9.0)	0.0012[b]
	Fatigue: 144 (26.2)	Fatigue: 588 (22.0)	0.0318[a]
Vázquez-Medina *et al*[33]	Cough: 49 (62)	Cough: 39 (65.0)	0.3
	Fever: 59 (74.68)	Fever: 39 (65.0)	0.4
	Shortness of breath: 53 (67.09)	Shortness of breath: 41 (68.3)	0.7
	Headache: 14 (17.72)	Headache: 13 (21.7)	0.7
Wang *et al*[37]	Cough: 75 (87.2)	Cough: 104 (78.8)	0.113
	Fever: 66 (76.7)	Fever: 97 (73.5)	0.588
	Fatigue: 39 (45.3)	Fatigue: 61 (46.2)	0.901

Data are *n* (%).
[a]$P < 0.05$;
[b]$P < 0.01$. NAFLD: Non-alcoholic fatty liver disease.

were compared. Huang *et al*[30] had the lowest percentages of patients in both cohorts admitted to the ICU with 5.8% and 6.7% of patients in NAFLD and non-NAFLD facing admission respectively. Moctezuma-Velázquez *et al*[34] reported nearly half (49%) of their NAFLD patient population being admitted compared to Madan *et al*[38] which saw 39.5%, the highest percentage amongst the non-NAFLD cohorts. Conflicting evidence was present regarding ICU-related outcomes between NAFLD and non-NAFLD patients infected with COVID-19. ICU admissions were more prevalent among the NAFLD patients in some study populations, but occasionally more prevalent in other non-NAFLD populations. A similar trend was identified in terms of statistical significance, where certain studies observed significantly greater ICU admissions in NAFLD patients ($P < 0.05$), whereas other studies failed to reach statistically significant differences among both groups.

Table 3 Primary and secondary outcomes

Ref.	NAFLD	Non-NAFLD	*P* value and 95%CI
Milic *et al*[29]	Duration of hospital stay, mean ± SD: 12.1 ± 10.3	Duration of hospital stay, mean ± SD: 11.5 ± 10.2	0.61
	Patients on ventilatory support: 24 (18.5)	Patients on ventilatory support: 21 (20.0)	0.9
Huang *et al*[30]	Respiratory failure: 10 (11.6)	Respiratory failure: 12 (6.2)	0.118
	ARDS: 2 (2.3)	ARDS: 2 (1.0)	0.4
	Hepatic failure: 0 (0)	Hepatic failure: 0 (0)	
	Hospital discharge: 63 (73.3)	Hospital discharge: 148 (76.3)	0.587
	Severe illness: 12 (14.0)	Severe illness: 16 (8.2)	0.142
	ICU admission: 5 (5.8)	ICU admission: 13 (6.7)	0.78
	Mortality: 0 (0)	Mortality: 0 (0)	
Younossi *et al*[32]	Acute liver injury: 21 (3.9)	Acute liver injury: 38 (1.6)	0.0006[b]
	Duration of hospital stay, mean ± SD: 9.6 ± 11.4	Duration of hospital stay, mean ± SD: 7.3 ± 7.6	< 0.0001[b]
	ICU admission: 196 (35.4)	ICU admission: 726 (26.5)	< 0.0001[b]
	Patients on ventilatory support: 76 (13.7)	Patients on ventilatory support: 221 (8.1)	< 0.0001[b]
	Mortality: 60 (10.8)	Mortality: 239 (8.7)	0.11
	Readmission: 25 (4.5)	Readmission: 95 (4.5)	
Vázquez-Medina *et al*[33]	Duration of hospital stay, mean ± SD: 11 ± 9.16	Duration of hospital stay, mean ± SD: 11.2 ± 7.8	0.9[1]
	Mortality: 41 (51.9)	Mortality: 23 (38.3)	0.07[1]
	Patients on ventilatory support: 32 (40.5)	Patients on ventilatory support: 12 (20.0)	0.002[1,b]
Moctezuma-Velázquez *et al*[34]	ICU admission: 175 (49.0)	ICU admission: 31 (28.0)	< 0.001[b]
	Patients on ventilatory support: 117 (32.0)	Patients on ventilatory support: 11 (10.0)	< 0.001[b]
	Mortality: 106 (30.0)	Mortality: 21 (19.0)	0.03[a]
Nath *et al*[35]	Duration of hospital stay, mean ± SD: 10.6 ± 7.2	Duration of hospital stay, mean ± SD: 10.7 ± 6.6	0.447
	Mortality: 55 (6.7)	Mortality: 188 (5.9)	0.381
Vrsaljko *et al*[36]	Clinical improvement of day 7: 27 (22.5)	Clinical improvement of day 7: 39 (40.6)	0.0048[b]
	Clinical improvement of day 14: 86 (71.7)	Clinical improvement of day 14: 85 (88.5)	0.0024[b]
	Duration of hospital stay, day median (IQR): 10 (8-15)	Duration of hospital stay, day median (IQR): 9 (6-12)	0.0018[b]
	Patients on ventilatory support: 6 (5)	Patients on ventilatory support: 3 (3.1)	
	Mortality: 8 (6.7)	Mortality: 3 (3.1)	0.3529
Wang *et al*[37]	Severe events: 19 (22.1)	Severe events: 22 (16.7)	0.316
	Duration of hospital stay in days, median (IQR): 15 (5-41)	Duration of hospital stay in days, median (IQR): 16 (5-40)	0.407
	Mortality: 0 (0)	Mortality: 2 (1.5)	0.251
Madan *et al*[38]	Duration of ICU stay, mean ± SD: 8.3 ± 6.9	Duration of ICU stay, mean ± SD: 7.1 ± 5.7	0.208
	Duration of hospital stay, mean ± SD: 10.1 ± 7.1	Duration of hospital stay, mean ± SD: 10.7 ± 8.1	0.43
	Patients on ventilatory support: 27 (9.3)	Patients on ventilatory support: 14 (8.9)	0.385
	ICU admission: 94 (32.5)	ICU admission: 62 (39.5)	0.752
	Mortality: 38 (13.2)	Mortality: 21 (13.8)	0.866
Zoncapè *et al*[39]	Duration of hospital stay, mean ± SD: 18.8 ±	Duration of hospital stay, mean ± SD: 16.4 ±	0.087

	15.5	11.9	
	Mortality: 25 (7.5)	Mortality: 28 (8.3)	0.393
Brozat *et al*[31]	Duration of hospital stay: 9.82	Duration of hospital stay: 8.80	95%CI: 0.78-1.26
	Duration of ICU stay: 2.32	Duration of ICU stay: 2.02	95%CI: 0.14-0.47
	ICU admission: 3227 (22.0)	ICU admission: 3095 (21.1)	95%CI: 0.95-1.08
	Patients on ventilatory support: 2816 (19.2)	Patients on ventilatory support: 2567 (17.5)	95%CI: 1.01-1.14
	Hospital readmission in 30 days: 1247 (8.5)	Hospital readmission in 30 days: 1115 (7.6)	95%CI: 0.86-1.03
	Hospital readmission in 90 days: 1701 (11.6)	Hospital readmission in 90 days: 1569 (10.7)	
	Mortality: 1672 (11.4)	Mortality: 1511 (10.3)	95%CI: 0.91-1.06

Data are *n* (%).
[a]$P < 0.05$.
[b]$P < 0.01$.
[1]Vázquez-Medina *et al* compares NAFLD, MAFLD and control. ARDS: Acute respiratory distress syndrome; CI: Confidence interval; ICU: Intensive care unit; IQR: Interquartile range; NAFLD: Non-alcoholic fatty liver disease; MAFLD: Metabolic-associated fatty liver disease.

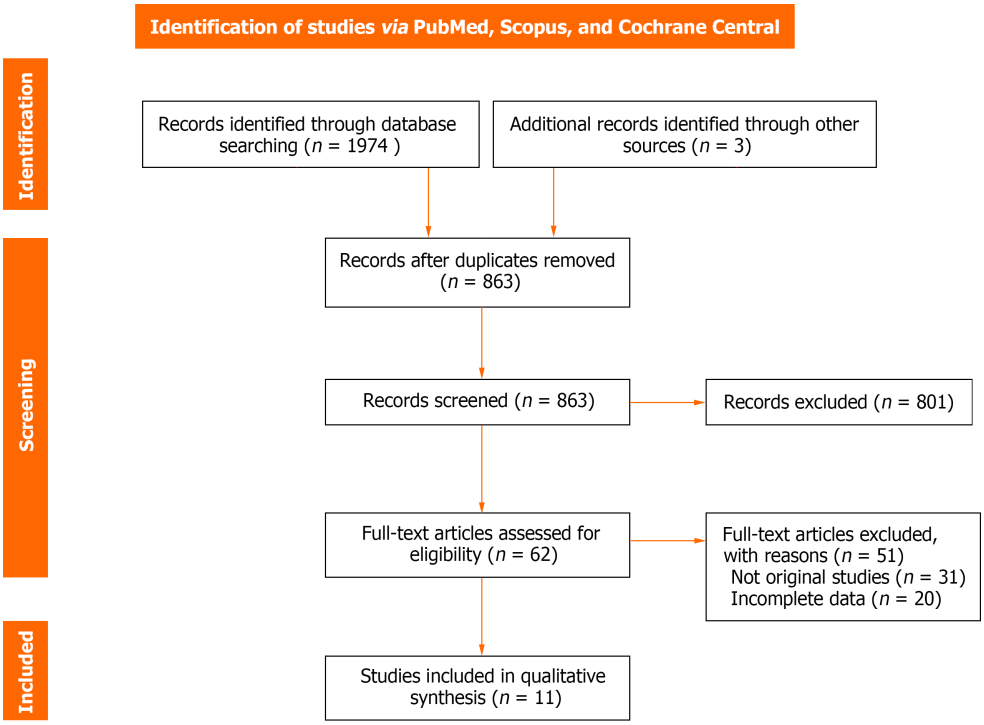

Figure 1 Preferred reporting items for systematic review and meta-analyses flowchart.

Furthermore, Madan *et al*[38] reported the duration of ICU stay, with a mean of 8.3 days and 7.1 days in the NAFLD and non-NAFLD cohort, respectively, with no statistically significant differences observed. Meanwhile, Brozat *et al*[31] had patients reporting 2.32 days and 2.02 days in NAFLD and non-NAFLD cohorts, a statistically significant difference between the two groups.

Ventilatory support: One of our outcomes of interest was the complication of NAFLD and non-NALFD patients infected with COVID-19 needing ventilatory support. 3098 and 2849 patients reported the outcome in the two cohorts, respectively, across seven studies. The range of percentage populations receiving ventilatory support varied from 5%-40.5% in the NAFLD cohort and 3.1%-20% in the non-NAFLD cohort, Vrsaljko *et al*[36] being the study reporting the lowest percentage-wise ventilatory needs per group. Yet Vázquez-Medina *et al*[33] reported over 40% of its NAFLD patient population facing the outcome. Moreover, both Vázquez-Medina *et al*[33] and Milic *et al*[29] had ventilatory support of the non-NAFLD class being 20%. The results varied as a higher number of patients in the NAFLD cohort receiving mechanical ventilation was statistically significant in the studies of Vázquez-Medina *et al*[33], Moctezuma-Velázquez *et al*[34] and Brozat *et al*[31] compared with non-NAFLD, with the opposite being significant in the report of Younossi *et al*[32]. Additionally, Wang *et al*[37] reported "severe events" as a combined outcome of several events, including respiratory ventilation, with 22.1% and 16.7% of patients in the two cohorts reporting the outcome. This,

however, attained no statistical significance.

In summary, patients with pre-existing NAFLD were more likely to require ventilatory support in comparison to their non-NAFLD counterparts. However, in terms of statistical analysis, half of the studies reached statistical significance in identifying the greater rate of ventilatory support requirement ($P < 0.05$), whereas the other half could not identify any association with respect to this outcome.

Clinical complications and improvement: Huang *et al*[30], comparing the COVID-19-infected NAFLD and non-NAFLD cohorts, reported the incidence of respiratory failure (11.6% to 6.2% of patients, respectively), the incidence of acute respiratory distress syndrome (2.3% to 1.0% of patients, respectively), and severe illness (14.0% to 8.2% of patients respectively) in their outcomes. None of which attained statistical significance. Hepatic failure was also assessed by Huang *et al*[30], revealing no events in either cohort. Contrary to this, Younossi *et al*[32] did present liver outcomes as an acute liver injury with 3.9% and 1.6% of patients in NAFLD and non-NAFLD groups, respectively, a result that yielded significance. Debatable results were revealed in terms of clinical complications, with NAFLD patients showing tendency for hepatic failure, but no significant associations with respiratory failure and/or severe illness. However, further data are essential to arrive at robust conclusions.

Clinical improvement was assessed in the study presented by Vrsaljko *et al*[36] on days 7 and 14, simplified to discharge from the hospital on the aforementioned days, with 22.5% of NAFLD and 40.6% of non-NAFLD patients being discharged on day 7 and 71.7% and 88.5% of patients of the aforementioned cohorts discharging at day 14 with all results being statistically significant, thus identifying the potential for poorer prognosis and recovery in NAFLD patients in comparison to their non-NAFLD counterparts.

Hospital-related outcomes: The event of hospitalization was reported by all studies except Huang *et al*[30] and Moctezuma-Velázquez *et al*[34]. When comparing measures of central tendencies, NAFLD patients with concomitant COVID-19 stay fell within a range of 9.6-18.8 day, with non-NAFLD patients falling within 7.3-16.4 day. Interestingly, Zoncapè *et al*[39] had the highest stay duration for both cohorts along with Younossi *et al*[32] having the lowest for both as well. Six studies reported a stay > 10 day and three studies reported ≤ 10 days for both cohorts. The study data were not consistent as three studies Vázquez-Medina *et al*[33], Nath *et al*[35], and Wang *et al*[37] reported their NAFLD cohort to have a shorter stay than that of non-NAFLD with none achieving significance. However, a statistically significant longer NAFLD stay was achieved in Younossi *et al*[32], Vrsaljko *et al*[36], and Brozat *et al*[31].

Moreover, Brozat *et al*[31] saw that 8.5% and 7.6% of their NAFLD and non-NAFLD cohorts had readmissions within 30 days along with 11.6% and 10.7% at 90 days. Younossi *et al*[32] also assessed readmission with a lower rate of 4.5% and 3.5% being seen, with no statistically significant differences noted.

Lastly, in the study by Huang *et al*[30], hospital discharge was seen in 73.3% of NAFLD patients and 76.3% of non-NAFLD patients with COVID-19, with no statistically significant differences noted.

Quality assessment

Of 9 retrospective and 2 prospective cohort studies were assessed for bias, with all 11 studies receiving points classifying them as having a low or moderate risk of bias. All studies provided adequate information regarding the representativeness of the exposed cohort, selection of the non-exposed cohort and demonstration that the outcomes of interest were not present at the start of the study. Among the studies, only Vrsaljko *et al*[36] failed to provide information regarding the ascertainment of exposure. All 11 studies received a minimum of 1 point in terms of comparability. Assessment of outcome was deemed inadequate for Milic *et al*[29], Wang *et al*[37], and Zoncapè *et al*[39]. When considering whether the follow-up time was long enough for outcomes to occur, Huang *et al*[30], Younossi *et al*[32], Moctezuma-Velázquez *et al*[34], and Zoncapè *et al*[39] did not receive a point. Lastly, Milic *et al*[29] and Younossi *et al*[32] were not awarded any points in quality assessment for the adequacy of the follow-up of cohorts. The summary of quality assessment is represented in Table 4.

DISCUSSION

In this comprehensive systematic review of 11 studies (n = 39282 patients; NAFLD, n = 17516; non-NAFLD, n = 21766) comprising patient populations from various regions (including the United States, China, India, Mexico, Italy, and Croatia), the influence of NAFLD on various clinical parameters pertaining to COVID-19 was evaluated. Generally, conflicting results were observed among the included studies, with certain studies predominantly suggesting the worsening of COVID-19 outcomes in the NAFLD cohorts, in contrast to other studies that fail to reveal any quantitative or statistically significant differences. Mortality, however, was consistently associated with being independent of NAFLD disease.

Several existing studies have proven the detrimental effects of comorbid NAFLD in the face of concurrent COVID-19 infection. In a systematic review and meta-analysis evaluating the impact of NAFLD on COVID-19 ICU-oriented endpoints, it was noted that the NAFLD cohort had a statistically significant increase in the incidence of ICU admission (odds ratio [OR]: 1.86; P = 0.007), need for mechanical ventilation (OR: 2.05; P = 0.02), and risk of severe disease (OR: 1.59; P = 0.10)[7]. Additionally, another meta-analysis performed by Kurniawan and Hariyanto[40] revealed a statistically significant increase in the risk of severe COVID-19 illness in the NAFLD cohort (OR: 1.67; $P < 0.00001$); however, no tangible differences were revealed in terms of mortality (OR: 1.00; P = 0.98). Thus, these results quantify the worsening of clinical prognosis in COVID-19 infection (except mortality) in patients with existing NAFLD. Due to the innate difficulties

Table 4 Quality assessment of included studies

Study name	Milic *et al* [29]	Huang *et al* [30]	Younossi *et al*[32]	Vázquez-Medina *et al*[33]	Moctezuma-Velázquez *et al*[34]	Nath *et al* [35]	Vrsaljko *et al*[36]	Wang *et al* [37]	Madan *et al* [38]	Zoncapè *et al*[39]	Brozat *et al* [31]
Selection (4)											
Representativeness of the exposed cohort	1	1	1	1	1	1	1	1	1	1	1
Selection of the non-exposed cohort	1	1	1	1	1	1	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1	1	0	1	1	1	1
Demonstration that outcome of interest was not present at start of study	1	1	1	1	1	1	1	1	1	1	1
Comparability (2)											
Comparability of cohorts on the basis of the design or analysis	1	2	2	1	2	2	1	2	2	2	2
Outcome (3)											
Assessment of outcome	0	1	1	1	1	1	1	0	1	0	1
Was followed up long enough for outcomes to occur	1	0	0	1	0	1	1	1	1	0	1
Adequacy of follow-up of cohorts	0	1	0	1	1	1	1	1	1	1	1
Total (9)	6	8	7	8	8	9	7	8	9	7	9

in performing prospective observational studies concerning the current topic of interest, most eligible studies were retrospective. This boasts several advantages, such as immensely enhancing the sample size, but is plagued with the potential for selection bias[41]. Interestingly, our analysis featured two prospective studies authored by Nath *et al*[35] and Wang *et al*[37], which failed to reveal any significant differences in terms of duration of hospital stay (P = 0.45 and P = 0.41, respectively) and mortality (P = 0.38 and P = 0.25, respectively). Therefore, reasonable hesitancy may be associated with interpreting the results of retrospective studies, although the increased patient population may contribute to a valid and reliable conclusion. Nonetheless, a potential mechanism of worsening clinical outcomes and prognosis could be the heightened prevalence of comorbidities among the NAFLD population, traditionally demonstrating a greater incidence of obesity, hypertension, T2DM, CVD, and more[42]. Such conditions have also been linked with poorer clinical outcomes in COVID-19 infection, thus jointly attributing to worsened clinical outcomes and prognosis in concomitant NAFLD and COVID-19 co-infected patients[18,43]. However, mortality has consistently shown an independent association with this trend.

Although no definitive treatment for COVID-19 has been established till date, several studies included in this systematic review have utilized various different treatment strategies for their patients, including: (1) Glucocorticoids; (2) Tocilizumab; (3) Antibiotics; and (4) Lopinavir/ritonavir combination[29,30]. Direct hepatocyte injury *via* SARS-CoV-2 is a possibility, but another often disregarded indirect mechanism may involve the picture of drug-induced liver injury arising after the commencement of treatment. In a retrospective study conducted by Fan *et al*[44], more than one-third of patients demonstrated abnormal hepatic function while hospitalized with COVID-19 infection, with more than half of these patients receiving the lopinavir/ritonavir combination. Reasonably, this may further aggravate hepatic dysfunction in NAFLD patients, thus potentially resulting in worsened clinical status and prognosis.

The hepatic impact of concomitant NAFLD and COVID-19 disease has not been extensively researched. COVID-19 is a respiratory infection, with the primary foci of injury usually encompassing the respiratory system (*e.g.*, lungs). However, recent reports have indicated potential liver dysfunction in a notable number of COVID-19 patients, specifically transaminase elevations over cholestatic abnormalities[45]. Additionally, a systematic review and meta-analysis performed by Chen *et al*[46] revealed a significantly larger degree of hepatic damage in severe COVID-19 manifestations in comparison to mild COVID-19 disease. This can be further exemplified by postmortem findings evaluated after COVID-19 mortality. All patients demonstrated parenchymal congestion, sinusoidal congestion and hemorrhage into the space of Disse, with a few cases associated with hepatocellular necrosis, infiltration, and steatosis[47]. Furthermore, existing literature strongly suggests an increased risk of a longer viral shedding time (up to three-fold greater) in NAFLD patients, posing a sizeable threat to their clinical progression[48]. Ultimately, these findings suggest that with the increasing global prevalence of both NAFLD and COVID-19, severe manifestations of either disease pose a looming threat to the population.

It has been established that NAFLD patients have background low-activity inflammation. This phenomenon is maintained by the activation of stellate cells and cytokine production by Kupffer cells, with IL-1β, TNF-α, interferon-γ, IL-6, and reactive oxygen species serving as characteristic pro-inflammatory markers in the disease, ultimately inducing fibrotic changes[49]. Interestingly, during the acute response of COVID-19 infection, similar inflammatory cytokines and markers are raised, potentially responsible for the worsening of clinical markers in NAFLD patients[50]. The elevated immune response in such patients may chronically persist as sequelae, explaining the slower recovery duration and readmission rates observed among the studies. Thus, low-activity inflammation of NAFLD is assumed to be amplified during the acute-phase response of COVID-19 infection, highlighting the interaction of the two diseases at a molecular level.

Clinical implications and future recommendations

Several clinical implications may be inferred from our systematic review's results and literature search. Despite the independent association of mortality with concomitant NAFLD and COVID-19 illness; the worsened in-hospital outcomes remain significant nonetheless. In light of this, hospitalists are encouraged to provide greater care to patients with liver dysfunction, especially NAFLD or MAFLD. Additionally, the potential for drug-drug interactions or drug toxicities presents a notable challenge in the management of such patients[51]. Thus, clinicians are advised to exercise vigilance with respect to monitoring liver function tests and drug dosages to avoid the risk of developing hepatotoxicity. The commonly used combination of lopinavir/ritonavir should be maximally avoided due to the alarming level of hepatotoxicity observed in COVID-19 patients while providing no significant benefit on the molecular level[52]. This calls for tailored strategies for NAFLD patients infected with COVID-19, in which drug recommendations, guidelines, and dosages need to be further researched and adjusted. The tendency for poorer outcomes also calls for greater vaccination efforts in the respective population, where patients with NAFLD (or any other gastrointestinal-related illness) should receive priority for COVID-19 vaccination and booster shots. Moreover, to curb the potentially worsening clinical parameters of NAFLD patients, it is strongly advised to engage in comprehensive multidisciplinary coordination through a team of pulmonologists and hepatologists to optimize the management and outcomes of such patients[53]. Long-term complications of concomitant NAFLD and COVID-19 have not been clearly identified; thus, regular follow-up with a multidisciplinary team is essential for surveillance and monitoring for new changes or worsening hepatic function in NAFLD patients.

Certain developments are strongly encouraged to arrive at a sustainable conclusion regarding the influence of NAFLD on COVID-19-related endpoints. First, the publication of global longitudinal data is important in evaluating robust trends and patterns in outcomes and identifying hotspots that may be disproportionately impacted. Additionally, future prospective observational or randomized studies are preferred due to their relatively lower risk of biases in light of the current conflicting evidence[41]. Second, the discovery of novel biomarkers with prognostic significance can serve as an indispensable tool for clinicians in creating an optimal and personalized management strategy and predicting disease severity. Thirdly, additional research on the impact of different therapeutic regimens on the outcome of concomitant NAFLD and COVID-19 is essential, as current literature is unable to reveal sufficient research into novel biomarkers. Finally, research into the social determinants (*via* regional, ethnic, and socioeconomic analyses) is necessary to implement timely interventions and appropriate policy-making, as Younossi *et al*[32] revealed an interesting increase in prevalence in Hispanic patients. In contrast, a greater mortality rate was observed in white patients, potentially setting the stage for future studies that provide greater insights into the impact of race or ethnicity on NAFLD outcomes.

Limitations

Our systematic review had several limitations. While the definition of NAFLD was fairly consistent across the 11 studies we analyzed, the techniques used to diagnose it varied. Liver biopsy, considered the gold standard, was not utilized in any study. Other techniques, such as the hepatic steatosis index, Dallas steatosis index, liver attenuation index, ultrasound, and CT scan, were utilized. Ultrasound and CT scans are operator-dependent and can lead to misdiagnosis, potentially impacting the study outcomes. The majority of studies included in our review were retrospective observational studies, which are prone to inaccurate data entry and collection discrepancies. However, the large number of studies included may have mitigated this limitation. We believe that more prospective studies, particularly those observing patients with confirmed NAFLD and those without, who then develop COVID-19, would be ideal for our objectives. Due to the retrospective nature of the studies, there was limited data on each patient's alcohol intake, which could potentially lead to misclassification of some cases of alcohol-related steatosis, such as NAFLD. Furthermore, there was a lack of sufficient post-discharge data, preventing us from assessing the long-term effects of COVID-19 on NAFLD. Consequently, we could not conclude associated post-discharge morbidity and mortality. Lastly, the studies we reviewed were conducted in six countries across 3 continents. While we believe the results can be generalized globally, differences in healthcare systems and practices among countries may affect disease severity, progression, and mortality rates.

CONCLUSION

In conclusion, our systematic review provides valuable insights into the impact of NAFLD on various COVID-19 outcomes, including the duration of hospital stay, rate of ICU admission, duration of ICU stays, risk of developing severe disease, and mortality. Although mortality was generally found to be independently associated with the concomitant diseases of NAFLD and COVID-19, the remaining clinical outcomes consistently illustrated a worsening trend. The mechanism of hepatocyte injury *via* COVID-19 is often multifaceted, ranging from direct injury at the molecular level to

drug-induced hepatic injury during COVID-19 treatment. Further research is essential in conducting wide-ranging prospective longitudinal studies to reach a robust, evidence-based conclusion. Ultimately, as the global prevalence of NAFLD and COVID-19 continues to rise at an alarming rate, targeted intervention is essential in mitigating the risk of adverse clinical outcomes.

FOOTNOTES

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