narra j

Original Article

Non-alcoholic fatty liver disease (NAFLD) and COVID-19 outcomes: A systematic review, meta-analysis, and meta-regression

Andree Kurniawan[1]* and Timotius I. Hariyanto[2]*

[1]Department of Internal Medicine, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia; [2]Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

*Corresponding author: timotius.hariyanto95@gmail.com

Abstract

It is important to identify risk factors for poor outcomes of coronavirus disease 2019 (COVID-19) patients. Currently, the correlation between non-alcoholic fatty liver disease (NAFLD) and COVID-19 outcomes has not been established. This study was conducted to determine the association between NAFLD and in-hospital outcomes of COVID-19 patients. The systematic searches were conducted by using PubMed and the Europe PMC databases and particular keywords were used as of December 10, 2020. Further searches were conducted up to 2022. All articles that include data about COVID-19 and fatty liver disease were collected. Statistical analysis was performed by using Review Manager 5.4 and Comprehensive Meta-Analysis version 3 software. A total of 7,210 COVID-19 patients from 18 studies were included in the final analysis. Meta-analysis revealed that NAFLD increased the risk of developing poor in-hospital outcome (pooled both severe disease and death) in COVID-19 patients (RR 1.42; 95%CI: 1.17–1.73, p<0.001, I^2=84%, random-effect modeling). Subgroup analysis however found that having NAFLD only increased the chance of getting severe COVID-19 (RR 1.67; 95%CI: 1.32–2.13, p<0.001, I^2=86%, random-effect modeling) and not mortality (RR 1.00; 95%CI: 0.68–1.47, p=0.98, I^2=80%, random-effect modeling). Meta-regression suggested that age (p=0.001) and diabetes (p=0.029) were significantly influenced the relationship between NAFLD and in-hospital outcomes of COVID-19 (pooled both severe disease and mortality). The weaker association of NAFLD and in-hospital outcomes of COVID-19 was found for studies with median age ≥45 years old (RR 1.29) when compared to studies with median age <45 years old (RR 2.96). In addition, studies with the prevalence of diabetes ≥25% (RR 1.29) had a weaker association with in-hospital outcomes when compared to studies with diabetes prevalence <25% (RR 1.85). In conclusion, NAFLD increased the risk of chance of getting severe COVID-19 and therefore it should be evaluated closely to reduce the chance of getting severe COVID-19.

Keywords: NAFLD, SARS-CoV-2, chronic liver disease, metabolic disease, hepatology

Introduction

The coronavirus disease 2019 (COVID-19) is a significant health problem for almost every country around the world. The disease has impacted several aspects of human live such as health, society, and economics. Therefore, identification of the risk factor for poor outcomes from this disease is utmost important, enabling the risk stratifications and optimization of the allocations for hospital resources. The manifestation of this disease is diverse from mild respiratory

Received: March 1, 2023 - Accepted: April 16, 2023 - Published online: April 19, 2023

symptoms to serious life-compromising infirmities such as respiratory failure, shock, arrhythmia, sepsis, and multi-organ failure [1, 2]. Up until now, comorbid conditions such as hypertension, diabetes, dyslipidemia, HIV infection, cardiovascular diseases, dementia, and thyroid diseases are correlated with the development of poor outcomes from COVID-19 [3-9]. A previous study [10] found that non-alcoholic fatty liver disease (NAFLD) is associated with higher 30-day all-cause mortality in patients with community-acquired pneumonia (CAP). Nonetheless, the correlation between NAFLD and COVID-19 is yet to be established. The aim of this study was to determine the potential association between NAFLD and in-hospital outcomes of COVID-19 patient through a systematic review and meta-analysis.

Methods

Eligibility criteria

Articles incorporated in this study were selected if complied with the population, intervention, comparison and outcomes (PICO) framework (P: COVID-19 positive patients; I: non-alcoholic fatty liver disease (NAFLD) as patients' comorbidity; C: patients who do not have NAFLD; and O: in-hospital outcomes (severe COVID-19 and mortality). All randomized clinical trial, observational studies (cohort or case-control), and cross-over studies were considered eligible. Any studies besides original research (e.g., review articles, letters, or commentaries); case reports; studies reported other than in the English language; studies focusing on the populations of young age (below 18 years old) and women during their pregnancy were excluded.

Search strategy and study selection

The articles were explored systemically and obtained from PubMed and Europe PMC database. Search terms applied were: ("fatty liver disease" OR "clinical characteristic" OR "risk factor") AND ("coronavirus disease 2019" OR "COVID-19"); restricted from 2019 until December 10, 2020 and written in English. The titles and abstracts were first assessed on all articles obtained through literature searching process. The process was then followed by full text screening to determine the suitability with our eligibility criteria. Additional searchers for potential eligible articles were conducted by analyzing the papers cited by authors of all identified studies. The search strategy was presented in the PRISMA diagram [11].

Data extraction and quality assessment

The extraction process was conducted by two authors and an extraction form was developed to list the essential information on authors, year, study design, number of participants, age, gender, diabetes, NAFLD, dyslipidemia, body mass index (BMI), severe COVID-19, and mortality from COVID-19. The outcome of interest was in-hospital results, which comprised of severe COVID-19 and mortality. The clinical characteristic criteria (at the time of, or after, the admission) for severe COVID-19 followed the WHO criteria; if the patient had any of the followings: (1) respiratory distress (≥30 breaths per min); (2) oxygen saturation ≤93% at rest; (3) proportion of the partial pressure of arterial oxygen (PaO_2) to a fractional concentration of oxygen inspired air (FiO_2) ≤300 mmHg; or (4) critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) or intensive care unit (ICU) admission based on WHO criteria. Mortality was established by the proportion of patients' death caused by COVID-19.

The studies' quality was evaluated independently using the Newcastle–Ottawa Scale (NOS) [12]. Two authors marked scores regarding selection, comparability, and exposure in each study from zero to nine with a good-quality cut off of 7.

Statistical analysis

A meta-analysis was conducted using Review Manager 5.4 (Cochrane Collaboration) and Comprehensive Meta-Analysis version 3 software. To calculate dichotomous variables, Mantel-Haenszel's formula with random-effects models was applied. Heterogeneity assessment implies low, moderate, and high degrees by employing I^2 statistics with the content of <25%, 26-50%, and >50% [13]. The risk ratio (RR) along with its 95% confidence intervals (CIs) was used to assess the association between fatty liver disease and (1) disease severity of COVID-19; (2) mortality of

COVID-19; and (3) poor COVID-19 outcome (both severity and mortality) in the meta-analysis. The results were considered significant when the two-tailed p-value was ≤0.05. Random-effects meta-regression was achieved using a restricted-maximum likelihood toward pre-specified variables including age, diabetes, and dyslipidemia. The qualitative risk of publication bias was assessed with Begg's funnel plot analysis.

Results

Study selection and characteristics

There were 4,574 records were obtained by systematic electronic searches and 3,358 remained after removal 1216 duplicates between databases. After reading the titles or abstracts, a total of 3,310 articles were excluded, leaving 48 full texts for eligibility. Absence of interest (severe COVID-19 and mortality), having no a control/comparison group and written in non-English with a total of 17, 10, and 3 sequentially were excluded. Ultimately, 7,210 COVID-19 patients within 18 studies [14-31] were included in the meta-analysis (**Figure 1**). Within these studies, 17 were retrospective cohorts [14-21, 23-31] and one was a case-control study [22]. The fundamental aspects of the studies are compiled in **Table 1**.

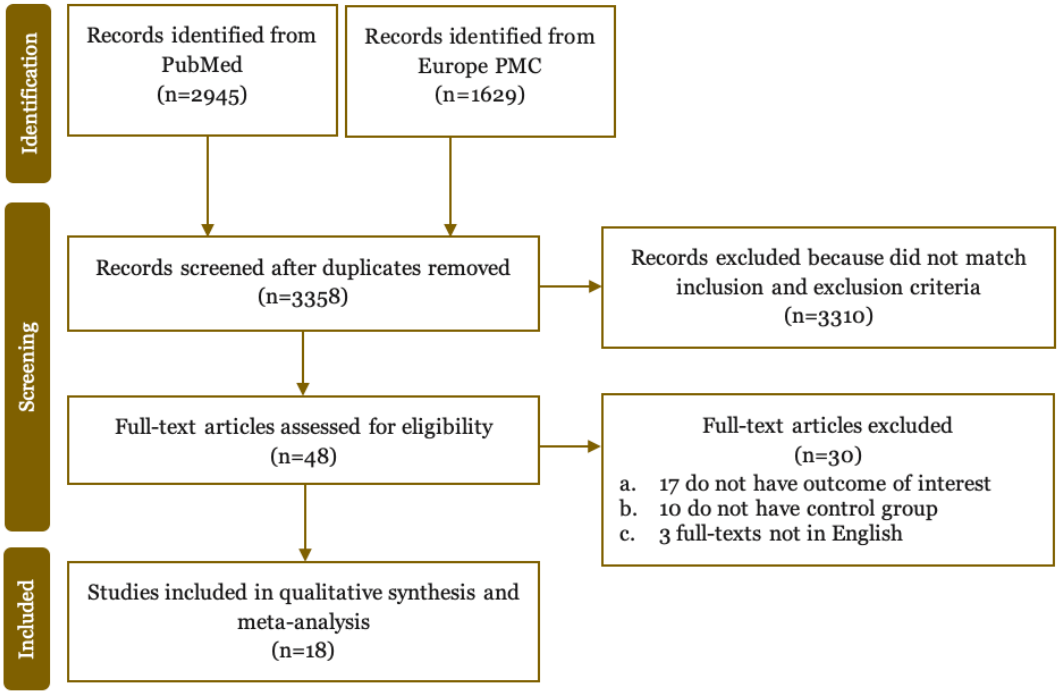

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart of the study

Quality of study assessment

We assess the observational studies' quality by using the Newcastle Ottawa Scales (NOS) for cohort and case-control design (**Table 2**). All studies were classified as 'good' and therefore included in the meta-analysis.

NAFLD and COVID-19 outcomes

The pooled analysis showed a significant association between NAFLD and poor in-hospital outcome of COVID-19 (severe disease and mortality), with high heterogeneity (RR 1.42; 95%CI: 1.17–1.73, p<0.001, I^2=84%, random-effect modeling) (**Figure 2**). On the subgroup analysis, patients with NAFLD had a higher chance of getting severe COVID-19 (RR 1.67; 95%CI: 1.32–2.13, p<0.001, I^2=86%, random-effect model) but not mortality (RR 1.00; 95%CI: 0.68–1.47, p=0.98, I^2=80%, random-effect model).

Table 1. Characteristics of included studies (n=18)

Study (Year 2020)	Sample size	Design	Overall age (median)	Male (%)	Diabetes (%)	NAFLD (%)	Dyslipidemia (%)	BMI (mean)
Cai *et al.* [14]	298	Retrospective cohort	47.5 (62.5 vs 41)	48.6 (67.2 vs 44.1)	6 (13.7 vs 4.1)	4.7 (10.3 vs 3.3)	N/A	23.2 (24.5 vs 22.9)
Chen *et al.* [15]	342	Retrospective cohort	63 (58.5 vs 66.5)	53.5 (50 vs 57.3)	43.3 (48.3 vs 37.8)	52 (56.7 vs 51.2)	47 (46.6 vs 47.6)	30 (34.7 vs 26.6)
Forlano *et al.* [16]	193	Retrospective cohort	64.2 (61 vs 70.5)	62.6 (60 vs 64)	39.3 (47 vs 35)	31.6 (18 vs 20)	23.8 (23 vs 24)	28.4 (30.6 vs 27.1)
Gao *et al.* [17]	130	Retrospective cohort	46 (47 vs 46)	63.1 (67.1 vs 50.3)	N/A	50 (77.2 vs 44.4)	64.6 (75.4 vs 53.8)	25 (26.2 vs 23.7)
Hashemi *et al.* [18]	363	Retrospective cohort	63.4 (64.8 vs 63)	55.4 (53.6 vs 55.8)	32.2 (40.6 vs 30.4)	15.1 (16.4 vs 13.2)	46.5 (46.4 vs 46.6)	30.3 (32 vs 29.9)
Huang *et al.* [20]	280	Retrospective cohort	43 (43.5 vs 42.5)	52.1 (58.1 vs 49.5)	7.5 (11.6 vs 5.7)	30.7 (14 vs 8.2)	N/A	24.2 (27.1 vs 23.1)
Ji *et al.* [20]	202	Retrospective cohort	44.5 (55.1 vs 42.9)	55.9 (69.2 vs 52.8)	N/A	37.6 (87.2 vs 25.8)	N/A	24 (26.6 vs 23.4)
Kim *et al.* [21]	867	Retrospective cohort	56.9 (59.8 vs 52.1)	54.7 (57.6 vs 49.5)	42.9 (48.4 vs 34.2)	52.6 (47.9 vs 61.8)	38.6 (40.8 vs 35.1)	N/A
Mahamid *et al.* [22]	71	Case-control	51 (53.7 vs 56.2)	27.2 (31.8 vs 32.7)	29.5 (36.3 vs 38.8)	30.9 (36.3 vs 10.2)	25.3 (40.1 vs 18.3)	25 (29.2 vs 26.1)
Mushtaq *et al.* [23]	589	Retrospective cohort	45.8 (47.7 vs 44.5)	84.7 (80.8 vs 89.6)	39.8 (50.3 vs 27.7)	54.3 (60.6 vs 39.3)	N/A	28.4 (30.7 vs 25.6)
Rabiee *et al.* [24]	112	Retrospective cohort	61 (63.4 vs 59.7)	54.5 (43.3 vs 33.3)	45.5 (60 vs 27.1)	14.3 (33.3 vs 6.1)	20.5 (30 vs 14.8)	N/A
Sun *et al.* [25]	63	Retrospective cohort	47 (59 vs 47)	58.7 (60 vs 52.8)	7.9 (15.7 vs 4.5)	1.5 (5.2 vs 0)	N/A	24.4 (25.9 vs 24)
Targher *et al.* [26]	310	Retrospective cohort	48.3 (59.9 vs 45.9)	54.8 (57.1 vs 43.5)	12.5 (28.6 vs 7.4)	30.3 (50 vs 50)	N/A	24 (26.1 vs 23)
Wang *et al.* [27]	45	Retrospective cohort	39 (43 vs 38)	51.1 (60 vs 48.6)	9.0 (20 vs 5.7)	6.7 (0 vs 8.6)	N/A	N/A
Wargny *et al.* [28]	2796	Retrospective cohort	69.7 (69.6 vs 69.7)	63.7 (70.2 vs 61.1)	100 (28.6 vs 71.3)	8.3 (8.7 vs 8.1)	46.8 (49 vs 45.9)	28.4 (29.1 vs 28.1)
Wu *et al.* [29]	299	Retrospective cohort	50 (62 vs 43)	45.8 (59.2 vs 41.7)	12.3 (25.4 vs 8.3)	13.3 (16.9 vs 12.3)	5.3 (7 vs 4.8)	N/A
Zhang *et al.* [30]	140	Retrospective cohort	57 (64 vs 51.5)	50.7 (56.9 vs 46.3)	12.1 (13.8 vs 11)	5.7 (6.9 vs 5)	5 (3.4 vs 6.1)	N/A
Zhou *et al.* [31]	110	Retrospective cohort	42.1 (43.4 vs 40.9)	74.5 (81.8 vs 67.3)	11.8 (20 vs 3.6)	50 (73.9 vs 43.6)	61.8 (81.8 vs 41.8)	25.6 (26.1 vs 25)

BMI: body mass index; NA: not available; NAFLD: non-alcoholic fatty liver disease; vs: NAFLD group vs non-NAFLD group

Table 2. Newcastle-Ottawa quality assessment of observational studies (n=18)

First author (2020)	Study design	Selection	Comparability	Outcome	Total score	Result
Cai *et al.* [14]	Retrospective cohort	***	**	***	8	Good
Chen *et al.* [15]	Retrospective cohort	***	**	***	8	Good
Forlano *et al.* [16]	Retrospective cohort	***	**	***	8	Good
Gao *et al.* [17]	Retrospective cohort	***	**	**	7	Good
Hashemi *et al.* [18]	Retrospective cohort	***	**	***	8	Good
Huang *et al.* [20]	Retrospective cohort	***	**	***	8	Good
Ji *et al.* [20]	Retrospective cohort	**	**	***	7	Good
Kim *et al.* [21]	Retrospective cohort	***	**	****	9	Good
Mahamid *et al.* [22]	Case-control	***	**	***	8	Good
Mushtaq *et al.* [23]	Retrospective cohort	**	**	***	7	Good
Rabiee *et al.* [24]	Retrospective cohort	***	**	***	8	Good
Sun *et al.* [25]	Retrospective cohort	**	**	***	7	Good
Targher *et al.* [26]	Retrospective cohort	**	**	***	7	Good
Wang *et al.* [27]	Retrospective cohort	***	**	***	8	Good
Wargny *et al.* [28]	Retrospective cohort	****	**	***	9	Good
Wu *et al.* [29]	Retrospective cohort	****	**	***	9	Good
Zhang *et al.* [30]	Retrospective cohort	***	**	***	8	Good
Zhou *et al.* [31]	Retrospective cohort	***	**	***	8	Good

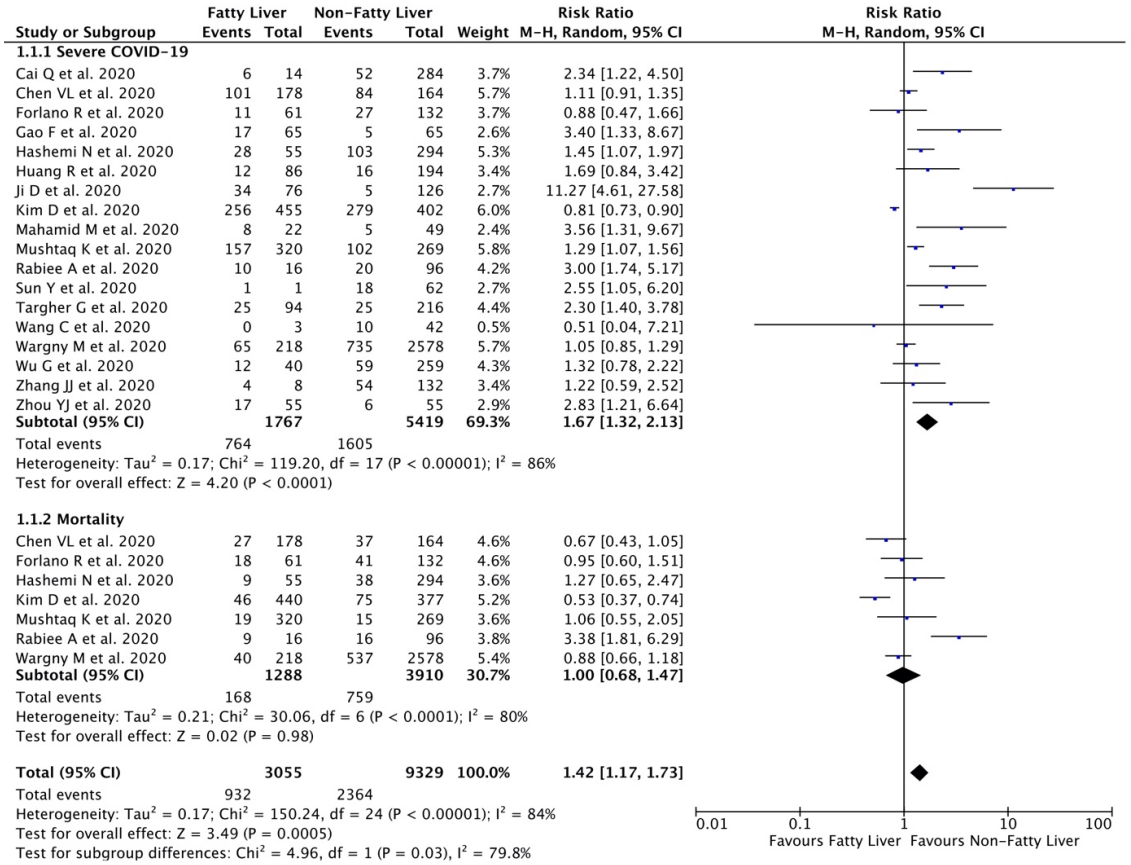

Figure 2. Forest plot demonstrates the association of the non-alcoholic fatty liver disease (NAFLD) with in-hospital outcomes of coronavirus disease 2019 (COVID-19), which comprised of severe COVID-19 and mortality.

Meta-regression

Our meta-regression found that the association of NAFLD and in-hospital outcomes (severity and mortality) of COVID-19 patients was affected by age (p=0.001) (**Figure 3A**) and diabetes (p=0.029) (**Figure 3B**). Dyslipidemia (p=0.530) did not affect the association of NAFLD and in-hospital outcomes (**Figure 3C**).

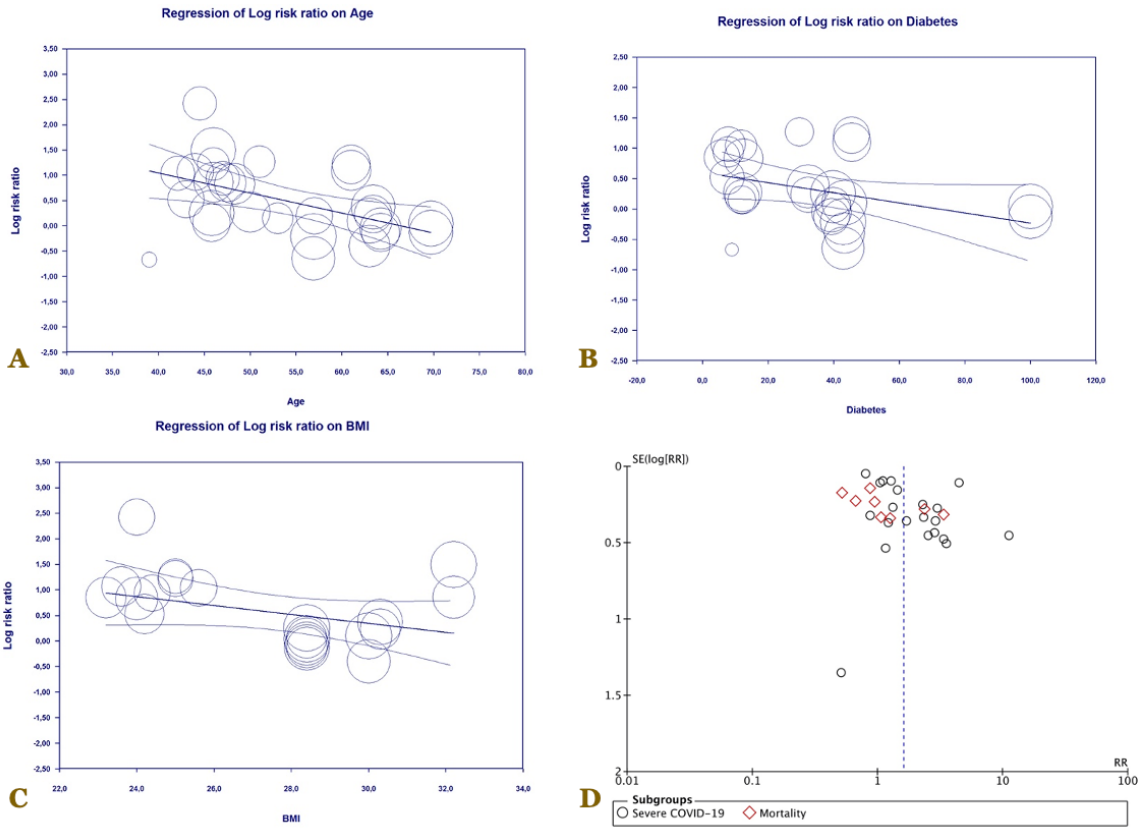

Figure 3. Bubble-plot for Meta-regression and Begg's funnel-plot analysis. Meta-regression analysis showed that the association between non-alcoholic fatty liver disease (NAFLD) and in-hospital outcomes of coronavirus disease 2019 (COVID-19) was affected by age (A) and diabetes (B), but not by dyslipidemia (C). Begg's funnel-plot analysis showed a qualitatively symmetrical inverted funnel-plot for the association between NAFLD and in-hospital outcomes of COVID-19 (severity and mortality) (D).

Subgroup analysis

The RR of COVID-19 in-hospital outcomes in the studies with median age of ≥45 years was lower compared to those studies with median age of <45 years (RR 1.29; 95%CI: 1.07–1.55), p=0.009, I^2=82%, random-effect model vs RR 2.96; 95%CI: 1.03–8.57, p=0.004, I^2=77%, random-effect model, respectively). Moreover, a lower RR has also been shown by studies with the prevalence of diabetes ≥25% when compared to studies with the prevalence of diabetes <25% (RR 1.29; 95%CI: 1.03–1.61, p=0.02, I^2=87%, random-effect model vs RR 1.85; 95%CI: 1.45–2.37, p<0.001, I^2=0%, random-effect modeling, respectively).

Publication bias

Funnel-plot analysis shows symmetrical inverted relation qualitatively linking NAFLD and COVID-19 in-hospital outcomes, noting no implication of publication bias (**Figure 3D**).

Discussion

This paper does not solely analyze the identification between NAFLD and in-hospital outcomes of COVID-19 but further develops the importance of confounding factors for instance age, gender, along comorbid conditions. These factors may also ascertain the connection to severe outcomes. Previously published studies indistinctly mention fatty liver disease's impact on the outcomes. It only shows in a form of an article review wherein liver injury in COVID-19 patients. This result was barely according to a single observational study, which shows conflicting results [32, 33].

Table 3. Additional studies that analyzed relationship between non-alcoholic fatty liver disease (NAFLD) and COVID-19 outcomes (n=7)

Study	Sample size	Design	Outcome Results (Severe COVID-19 and mortality outcomes)
Madan *et al.* [38] 2022	446	Case control	No significant difference in the mortality rate between NAFLD and non-NAFLD (13.24% vs 13.81%; p=0.866) No significant difference in the ICU requirements between NAFLD and non-NAFLD (32.52% vs 39.49%; p=0.752) No significant difference in the ventilatory support between NAFLD and non-NAFLD (9.34% vs 8.91%; p=0.385)
Nath *et al.* [39] 2022	3933	Prospective cohort	The mortality rate was comparable between NAFLD and non-NAFLD group (6.7% vs 6%; p=0.381). In the multivariate analysis, NAFLD was not associated with mortality in COVID-19 patients (OR 1.149; 95% CI: 0.669–1.976, p=0.614).
Okuhama *et al.* [40] 2022	222	Retrospective cohort	Patients with severe COVID-19 had higher prevalence of fatty liver (OR 6.33; 95% CI: 3.37–12.14, p<0.001). In the multivariate analysis, fatty liver on CT-scan was significantly associated with severe COVID-19 (OR 6.20; 95% CI: 2.82–13.62, p<0.001).
Tripon *et al.* [41] 2022	719	Retrospective cohort	In patients with NAFLD, no significant difference was observed in the proportion of patients who experience severe COVID-19 compared to those who experience only mild-to-moderate COVID-19 (59.8% vs 63%, p=0.455) More patients with severe COVID-19 had NAFLD associated with a high fibrosis-4 index (FIB-4): 72.8% vs. 57.9%, respectively (p<0.001)
Vrsaljko *et al.* [42] 2022	216	Prospective cohort	Patients with NAFLD more frequently required high-flow nasal cannula or non-invasive ventilation than those without NAFLD (21.66% vs 10.42%; p=0.289) No significant differences in the requirement for invasive mechanical ventilation between NAFLD and non-NAFLD groups (5% vs 3.12%) No significant differences in the in-hospital mortality between NAFLD and non-NAFLD groups (6.67% vs 3.12%; p=0.3529)
Wang *et al.* [43] 2021	218	Retrospective cohort	No significant differences were observed between NAFLD and non-NAFLD patients in terms of severe COVID-19 (22.1% vs 16.7%; p=0.316). The mortality rate did not differ significantly between subjects with NAFLD and those without NAFLD (0% vs 1.5%; p=0.251). In the normal BMI group, after adjusting for age, gender, hypertension, cardiovascular disease, diabetes, and chronic liver disease, it has been revealed that NAFLD was significantly associated with severity of COVID-19 (HR 3.26; 95% CI: 1.17–9.04, p=0.023).
Yoo *et al.* [44] 2021	74244	Retrospective cohort	In matched cohort, patients with NAFLD had a higher risk of severe COVID-19 disease progression than patients without NAFLD (0.8% vs 0.6%; aOR 1.41; 95% CI: 1.08–1.83). Progression to severe COVID-19 was more commonly observed on patients with NAFLD than those without NAFLD (aOR 1.35; 95% CI: 1.05–1.71).

COVID-19: coronavirus disease 2019; CT-scan: computed-tomography scan; ICU: intensive care unit; HR: hazard ratio; NAFLD: non-alcoholic fatty liver disease; OR: odds ratio

These 18 comprehensive meta-analysis studies show the relation of NAFLD with poor in-hospital outcomes of COVID-19. There are some explanations between this relation. First, NAFLD is related to extra-hepatic signs of metabolic syndrome while obesity, hypertension, diabetes, and dyslipidemia included in metabolic syndrome itself are linked to higher severity and mortality rate of COVID-19 [34]. Concerning the severity of COVID-19 in patients with NAFLD may be caused by the relation to metabolic syndrome as mentioned before. Second, in normal conditions, the cholangiocytes and hepatocytes expressed ACE2 in low level. Nevertheless, in chronic liver damage, including NAFLD, the level of ACE2 has been shown to increase [32, 35]. Thus, increase levels of ACE2 in NAFLD patients also increase the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and predispose them to develop severe outcomes. Finally, a lower percentage of *Bacteroides* and higher levels of *Prevotella* and *Porphyromonas* species leads to the development of gut dysbiosis in patients with NAFLD [34]. Some experimental and clinical studies proposed that through the gut-lung axis, gut microbiota represents an essential role in sepsis and ARDS pathogenesis. Furthermore, gut microbiota also operates the regulation of immune response, preferably through T-regulatory cells [36, 37]. Accordingly, gut dysbiosis will develop into severe outcomes such as sepsis and ARDS.

To increase the relevance of the results from our study, we have performed additional searching process for studies which analyzed the relationship between NAFLD and COVID-19 outcomes (severity and mortality). We have found seven additional studies that published between 2021–2022 (**Table 3**) [38-44]. Out of seven studies, four of them were retrospective cohort, two were prospective cohort, and the remaining one study was case-control study. These studies showed conflicting results regarding the relationship between NAFLD and severity or mortality outcomes in patients with COVID-19. From a total of six studies that reported the severe COVID-19 outcome, three studies did not show any significant difference between patients with NAFLD and those without NAFLD, while three other studies showed that NAFLD was associated with higher severity of COVID-19 when compared to non-NAFLD group. In terms of mortality outcome, all four studies that reported this outcome showed no significant difference in the proportion of patients who were died during the follow-up period between NAFLD and non-NAFLD group. These conflicting results indicate that further studies are still required to confirm the relationship between NAFLD and COVID-19 outcomes.

This study has some limitations. The limitation of data on the NAFLD/diabetic/dyslipidemia medications in included studies makes it unable to be analyzed. Moreover, any heterogeneity found in our study was presumably generated by diverse demographic characteristics among the studies included. However, we assume this study could still give advanced insight into additional risk stratification for COVID-19.

Conclusions

Patients with NAFLD should be encouraged to take extra forethought in reducing the risk of exposure. Patients with suspected COVID-19 infection should also be closely observed for the appropriate detection of disease progression. Certainly, the NAFLD shall be a consideration to risk stratification models for COVID-19 in the prospect.

Ethics approval

Not required

Acknowledgments

None.

Conflict of interest

All the authors declare that there are no conflicts of interest.

Funding

This study received no external funding.

Underlying data

All data underlying the results are available from the corresponding author upon reasonable request.

How to cite

Kurniawan A, Hariyanto TI. Non-alcoholic fatty liver disease (NAFLD) and COVID-19 outcomes: A systematic review, meta-analysis, and meta-regression. Narra J 2023; 3 (1): e102 - http://doi.org/10.52225/narra.v3i1.102.

References

1. Hariyanto TI, Rizki NA, Kurniawan A. Anosmia/hyposmia is a good predictor of coronavirus disease 2019 (COVID-19) infection: a meta-analysis. Int Arch Otorhinolaryngol 2021; 25(01):e170-e174.
2. Soeroto AY, Yanto TA, Kurniawan A, Hariyanto TI. Efficacy and safety of tixagevimab-cilgavimab as pre-exposure prophylaxis for COVID-19: A systematic review and meta-analysis. Rev Med Virol 2023;33(2):e2420.
3. Yang J, Zheng Y, Gou X, *et al*. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis 2020; 94:91-95.
4. Permana H, Audi Yanto T, Ivan Hariyanto T. Pre-admission use of sodium glucose transporter-2 inhibitor (SGLT-2i) may significantly improves Covid-19 outcomes in patients with diabetes: A systematic review, meta-analysis, and meta-regression. Diabetes Res Clin Pract 2023 ;195:110205.
5. Wang Q, Davis PB, Gurney ME, Xu R. COVID-19 and dementia: Analyses of risk, disparity, and outcomes from electronic health records in the US. Alzheimers Dement 2021;17(8):1297-1306.
6. Wang Y, Xie Y, Hu S, *et al*. Systematic review and meta-analyses of the interaction between HIV infection And COVID-19: Two years' evidence summary. Front Immunol 2022 10;13:864838.
7. Liu Y, Pan Y, Yin Y, *et al*. Association of dyslipidemia with the severity and mortality of coronavirus disease 2019 (COVID-19): a meta-analysis. Virol J 2021;18(1):157.
8. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY) 2020;12(7):6049-6057..
9. Gold MS, Sehayek D, Gabrielli S, *et al*. COVID-19 and comorbidities: a systematic review and meta-analysis. Postgrad Med 2020;132(8):749-755.
10. Nseir W, Mograbi J, Amara A, *et al*. Non-alcoholic fatty liver disease and 30-day all-cause mortality in adult patients with community-acquired pneumonia QJM 2019; 112(2):95-99.
11. Moher D, Liberati A, Tetzlaff J, *et al*. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLOS Medicine 2009; 6(7):e1000097.
12. Margulis AV, Pladevall M, Riera-Guardia N, *et al*. Quality assessment of observational studies in a drug-safety systematic review, comparison of two tools: the Newcastle-Ottawa Scale and the RTI item bank. Clin Epidemiol 2014; 6:359-368.
13. Melsen W, Bootsma M, Rovers M, *et al*. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014; 20(2):123-129.
14. Cai Q, Huang D, Ou P, *et al*. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy 2020; 75(7):1742-1752.
15. Chen VL, Hawa F, Berinstein JA, *et al*. Hepatic steatosis is associated with increased disease severity and liver injury in coronavirus disease-19. Dig Dis Sci 2021; 66:3192-3198.
16. Forlano R, Mullish BH, Mukherjee SK, *et al*. In-hospital mortality is associated with inflammatory response in NAFLD patients admitted for COVID-19. PLoS One 2020; 15(10):e0240400.
17. Gao F, Zheng KI, Wang XB, *et al*. Metabolic associated fatty liver disease increases coronavirus disease 2019 disease severity in nondiabetic patients. J Gastroenterol Hepatol 2021; 36(1):204-207.
18. Hashemi N, Viveiros K, Redd WD, *et al*. Impact of chronic liver disease on outcomes of hospitalized patients with COVID-19: A multicentre United States experience. Liver Int 2020; 40(10):2515-2521.
19. Huang R, Zhu L, Wang J, *et al*. Clinical features of patients with COVID-19 with nonalcoholic fatty liver disease. Hepatol Commun 2020; 4(12):1758-1768.

20. Liu X, Wang X-J. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. J Genet Genomics 2020;47(2):119-121.
21. Kim D, Adeniji N, Latt N, *et al.* Predictors of outcomes of COVID-19 in patients with chronic liver disease: US multi-center study. Cli Gastroenterol Hepatol 2021; 19(7):1469-1479. e1419.
22. Mahamid M, Nseir W, Khoury T, *et al.* Nonalcoholic fatty liver disease is associated with COVID-19 severity independently of metabolic syndrome: a retrospective case-control study. Eur J Gastroenterol Hepatol 2021; 33(12):1578-1581.
23. Mushtaq K, Khan MU, Iqbal F, *et al.* NAFLD is a predictor of liver injury in COVID-19 hospitalized patients but not of mortality, disease severity on the presentation or progression–The debate continues. J Hepatol 2021; 74(2):482-484.
24. Rabiee A, Sadowski B, Adeniji N, *et al.* Liver injury in liver transplant recipients with coronavirus disease 2019 (COVID-19): US multicenter experience. Hepatology 2020; 72(6):1900-1911.
25. Sun Y, Dong Y, Wang L, *et al.* Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. J Autoimmun 2020; 112:102473.
26. Targher G, Mantovani A, Byrne CD, *et al.* Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. Gut 2020; 69(8):1545-1547.
27. Wang C, Deng R, Gou L, *et al.* Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 2020; 8(9):593.
28. Wargny M, Potier L, Gourdy P, *et al.* Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. Diabetologia 2021; 64:778-794.
29. Wu G, Yang P, Xie Y, *et al.* Development of a clinical decision support system for severity risk prediction and triage of COVID-19 patients at hospital admission: An international multicentre study. Eur Respir J 2020; 56(2).
30. Zhang J-j, Dong X, Cao Y-y, *et al.* Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020; 75(7):1730-1741.
31. Zhou YJ, Zheng KI, Wang XB, *et al.* Metabolic-associated fatty liver disease is associated with severity of COVID-19. Liver Int 2020; 40(9):2160-2163.
32. Musa S. Hepatic and gastrointestinal involvement in coronavirus disease 2019 (COVID-19): What do we know till now? Arab J Gastroenterol 2020; 21(1):3-8.
33. El Kassas M, Abdelkader H, Medhat MA. COVID-19 in Egypt: Through crisis to adaptation; a gastroenterologist' s perspective. Arab J Gastroenterol 2020; 21(3):207.
34. Grabherr F, Grander C, Effenberger M, *et al.* Gut dysfunction and non-alcoholic fatty liver disease. Front Endocrinol 2019; 10:611.
35. Paizis G, Tikellis C, Cooper ME, *et al.* Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. Gut 2005; 54(12):1790-1796.
36. Dhar D, Mohanty A. Gut microbiota and Covid-19- possible link and implications. Virus Res 2020; 285:198018.
37. Hariyanto TI, Prasetya IB, Kurniawan A. Proton pump inhibitor use is associated with increased risk of severity and mortality from coronavirus disease 2019 (COVID-19) infection. Dig Dis 2020; 52(12):1410-1412.
38. Madan K, Rastogi R, Bhargava R, *et al.* Is fatty liver associated with increased mortality and morbidity in coronavirus disease 2019 (COVID-19) pneumonia? J Clin Exp Hepatol 2022;12(5):1320-1327.
39. Nath P, Kumar R, Mallick B, *et al.* Effect of nonalcoholic fatty liver disease (NAFLD) on COVID-19: A single-center study of 3983 patients with review of literature. Cureus 2022;14(7):e26683.
40. Okuhama A, Hotta M, Ishikane M, *et al.* Fatty liver on computed tomography scan on admission is a risk factor for severe coronavirus disease. J Infect Chemother 2022;28(2):217-223.
41. Tripon S, Bilbault P, Fabacher T, *et al.* Abnormal liver tests and non-alcoholic fatty liver disease predict disease progression and outcome of patients with COVID-19. Clin Res Hepatol Gastroenterol 2022;46(5):101894.
42. Vrsaljko N, Samadan L, Viskovic K, *et al.* Association of nonalcoholic fatty liver disease with COVID-19 severity and pulmonary thrombosis: CovidFAT, a prospective, observational cohort study. Open Forum Infect Dis 2022 9;9(4):ofac073.
43. Wang G, Wu S, Wu C, *et al.* Association between non-alcoholic fatty liver disease with the susceptibility and outcome of COVID-19: A retrospective study. J Cell Mol Med 2021;25(24):11212-11220.
44. Yoo HW, Jin HY, Yon DK, *et al.* Non-alcoholic fatty liver disease and COVID-19 susceptibility and outcomes: A Korean nationwide cohort. J Korean Med Sci 2021;36(41):e291.