Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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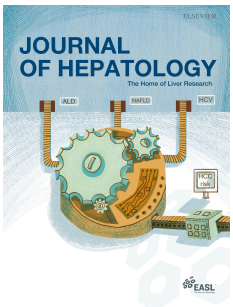

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Ying Wang, Yadong Wang, Guangcai Duan, Haiyan Yang

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NAFLD was independently associated with severe COVID-19 among younger patients rather than older patients: A meta-analysis

Ying Wang[1], Yadong Wang[2], Guangcai Duan[1], Haiyan Yang[1*]

[1]Department of Epidemiology, School of Public Health, Zhengzhou University, Zhengzhou 450001, China

[2]Department of Toxicology, Henan Center for Disease Control and Prevention, Zhengzhou 450016, China.

***Corresponding author:** Haiyan Yang, Department of Epidemiology, School of Public Health, Zhengzhou University, No. 100 of Science Avenue, Zhengzhou 450001, China. Phone: 86-371-67781248; Fax: 86-371-67781248. E-mail address: yhy@zzu.edu.cn.

Running head: NAFLD and severe COVID-19

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Author contributions: Haiyan Yang and Guangcai Duan conceptualized the study. Ying Wang and Yadong Wang performed literature search and data extraction. Ying Wang and Yadong Wang analyzed the data. Ying Wang and Haiyan Yang wrote the manuscript. All the authors approved the final manuscript.

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Data availability statement: The data that support the findings of this study are included in this article and available from the corresponding author upon reasonable request.

To the Editor,

In the Journal of Hepatology, Ji et al reported that the presence of non-alcoholic fatty liver disease (NAFLD) was significantly associated with an increased risk for the progression of coronavirus disease 2019 (COVID-19) in multivariate model [1], however, Marjot et al [2] and Mushtaq et al [3] reported opposite findings that the presence of NAFLD was not significantly associated with COVID-19 mortality, disease severity or disease progression in multivariate model. This suggests whether the presence of NAFLD was an independent predictor for severe COVID-19 is still inconclusive. The EASL position in Marjot et al's paper noted that patients with NAFLD were at increased risk for developing severe COVID-19 which might be attributed to the presence of other high-risk comorbidities [4]. Taken together, we conducted this meta-analysis of risk factors-adjusted effect sizes to determine whether the presence of NAFLD was significantly independently associated with more severe COVID-19.

This meta-analysis was performed in accordance with the preferred reporting item for systematic reviews and meta-analysis (PRISMA) guidelines [5]. The literature was searched in the online databases of Web of Science, PubMed, Elsevier ScienceDirect, Wiley Library, EMBASE, Springer Link, Scopus and Cochrane Library for potentially eligible articles which were published between December 10, 2019 and September 7, 2022. The keywords were used: ("NAFLD" OR "non-alcoholic fatty liver disease" OR "MAFLD" OR "metabolic associated fatty liver disease") and ("2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR "2019 novel coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus disease 2019"). The exposure group was COVID-19 patients with NAFLD and the control group was COVID-19 patients without NAFLD. The outcome of interest was

severe COVID-19 (which was reported as severe/critical illness, severity/progression, intensive care unit (ICU) admission, need for invasive mechanical ventilation (IMV) and mortality, etc. in the original articles). We included all peer-reviewed articles in English providing the risk factors-adjusted effect sizes of the association between NAFLD and severe COVID-19 by multivariate model. We excluded case reports, reviews, preprints, study protocol, editorial, commentary, errata, and studies with un-adjusted effect sizes or without available data. Two independent researchers conducted literature retrieval and data extraction. Any disagreements were settled by discussion between the researchers until the consensus was achieved. In order to find additional pertinent studies, the listed references of the included studies and relevant reviews were further scanned and manually retrieved.

The Stata 11.2 software was used for statistical analyses. The pooled odds ratio (OR) and 95% confidence interval (CI) were estimated by a random-effects model [6]. The Cochran's Q test and I^2 test were applied to assess statistical heterogeneity. A leave-one-out sensitivity analysis was utilized to evaluate the influences of individual studies on the overall results. Publication bias was assessed by Egger's test [7] and Begg's test [8]. Subgroup analysis was conducted by age (mean/median), male proportion and study design. Probability value less than 0.05 was deemed statistically significant.

A total of eighteen eligible studies with 22,056 cases were included in this meta-analysis. Our results indicated the presence of NAFLD was significantly independently associated with more severe COVID-19 based on risk factors-adjusted effect sizes (pooled OR = 1.76, 95% CI: 1.24-2.49, Figure 1A). Subgroup analyses by male proportion (pooled OR = 1.64, 95% CI: 1.18-2.26 for ≥ 50% and 2.25, 95% CI: 1.21-4.17 for < 50%) and study design (pooled OR = 1.87, 95% CI: 1.22-2.88 for retrospective studies and 1.40, 95% CI: 1.15-1.70 for the others)

yielded consistent results. Subgroup analysis by age (mean/median) showed the presence of NAFLD was significantly independently associated with more severe COVID-19 among younger patients (pooled OR = 2.08, 95% CI: 1.33-3.27 for < 60 years, Figure 1B), but not among older patients (pooled OR = 1.37, 95% CI: 0.97-1.93 for ≥ 60 years, Figure 1C). Sensitivity analysis exhibited deleting each individual study once had no significant impacts on the overall results (Figure 1D, 1E and 1F). Egger's test (P = 0.003) and Begg's test (P = 0.005) demonstrated publication bias might exist presently.

Although the pooled OR was calculated on the basis of the risk factors-adjusted effects sizes (mainly adjusting age, sex, smoking, obesity, diabetes and hypertension), other factors (such as SARS-CoV-2 variants, status of vaccination and medication) [9, 10] might certainly play an important role in modifying the association between NAFLD and severe COVID-19. Unfortunately, few included studies provided the information of SARS-CoV-2 variants, status of vaccination and medication. We could not assess the impacts of SARS-CoV-2 variants, status of vaccination and medication on the association between NAFLD and severe COVID-19 presently, which should be addressed in the future when more data are available.

In conclusion, this meta-analysis of risk factors-adjusted effect sizes indicated the presence of NAFLD was significantly independently associated with more severe COVID-19 among younger patients rather than older patients. Future well-designed studies with comprehensive measurements of potential confounding factors are warranted to verify our findings.

References:

[1] Ji D, Qin E, Xu J, Zhang D, Cheng G, Wang Y, et al. Non-alcoholic fatty liver diseases in patients with COVID-19: A retrospective study. Journal of hepatology. 2020;73(2):451-453.

[2] Marjot T, Buescher G, Sebode M, Barnes E, Barritt ASt, Armstrong MJ, et al. SARS-CoV-2 infection in patients with autoimmune hepatitis. Journal of hepatology. 2021;74(6):1335-1343.

[3] Mushtaq K, Khan MU, Iqbal F, Alsoub DH, Chaudhry HS, Ata 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. Journal of hepatology. 2021;74(2):482-484.

[4] Marjot T, Eberhardt CS, Boettler T, Belli LS, Berenguer M, Buti M, et al. Impact of COVID-19 on the liver and on the care of patients with chronic liver disease, hepatobiliary cancer, and liver transplantation: An updated EASL position paper. Journal of hepatology. 2022;77(4):1161-1197.

[5] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 2009;6(7):e1000100.

[6] Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiologic reviews. 1987;9:1-30.

[7] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical research ed). 1997;315(7109):629-634.

[8] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088-1101.

[9] Cornberg M, Eberhardt CS. Protected or not protected, that is the question - First data on COVID-19 vaccine responses in patients with NAFLD and liver transplant recipients. Journal of hepatology. 2021;75(2):265-266.

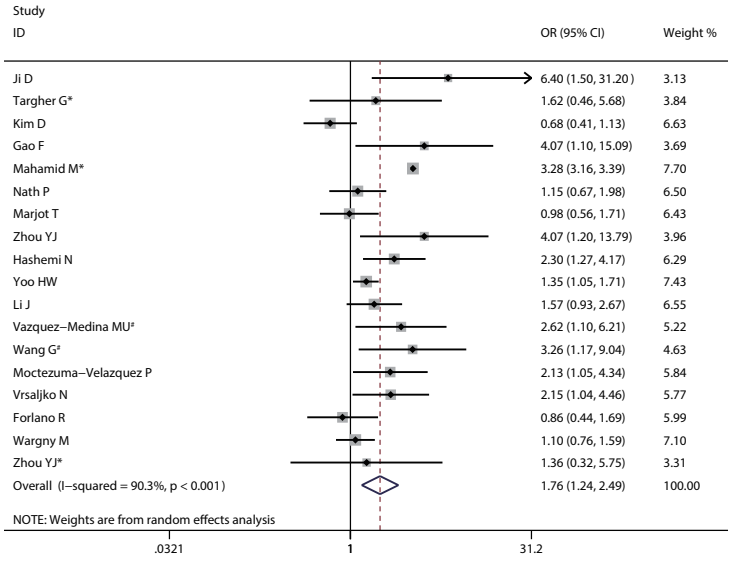
[10] Cornberg M, Buti M, Eberhardt CS, Grossi PA, Shouval D. EASL position paper on the use of COVID-19 vaccines in patients with chronic liver diseases, hepatobiliary cancer and liver transplant recipients. Journal of hepatology. 2021;74(4):944-951.

Figure legend:

Figure 1: Forest plot demonstrated that the presence of non-alcoholic fatty liver disease (NAFLD) was significantly independently associated with more severe coronavirus disease 2019 (COVID-19) on the basis of eighteen eligible articles reporting risk factors-adjusted effect sizes (A). Subgroup analysis by age (mean/median) showed that the presence of NAFLD was significantly independently associated with more severe COVID-19 among younger patients (< 60 years) (B), but not among older patients (≥ 60 years) (C). Leave-one-out sensitivity analysis exhibited that omitting any single study once had no significant impacts on the overall results (D for total studies, E for < 60 years, and F for ≥ 60 years). * indicates combined effect sizes were calculated from subgroups. # indicates that the study used the hazard ratio (HR) to assess the effect size. The publication bias may favour the publication of positive studies which leads to an overestimation of the positive association

149 between NAFLD and severe COVID-19 and affects the validity and generalisation of the
150 conclusion.

A



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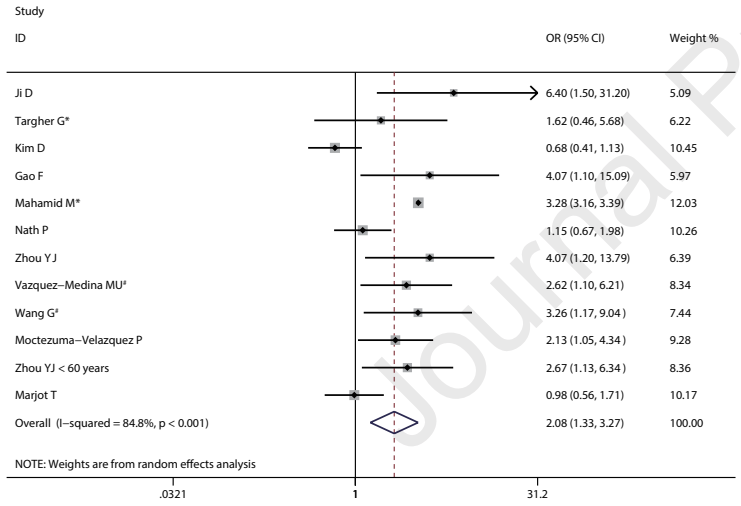

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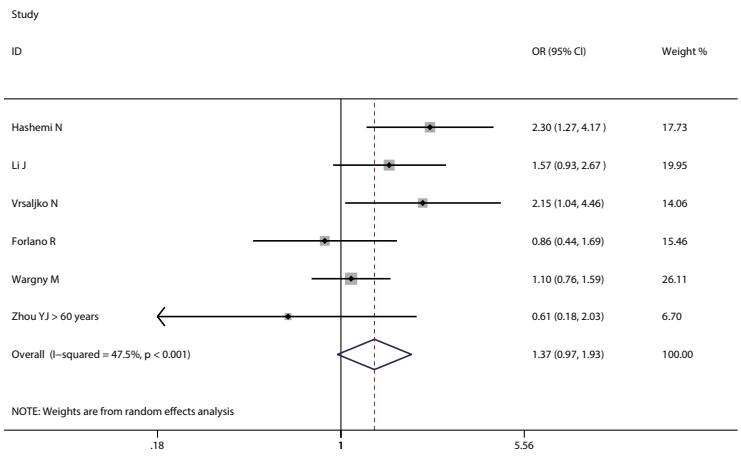

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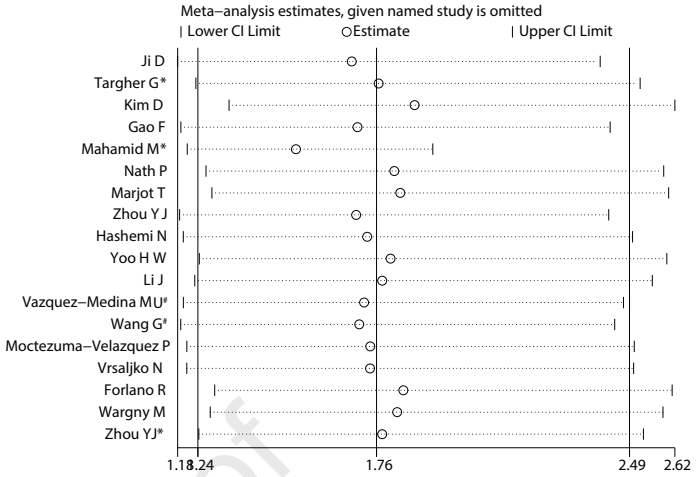

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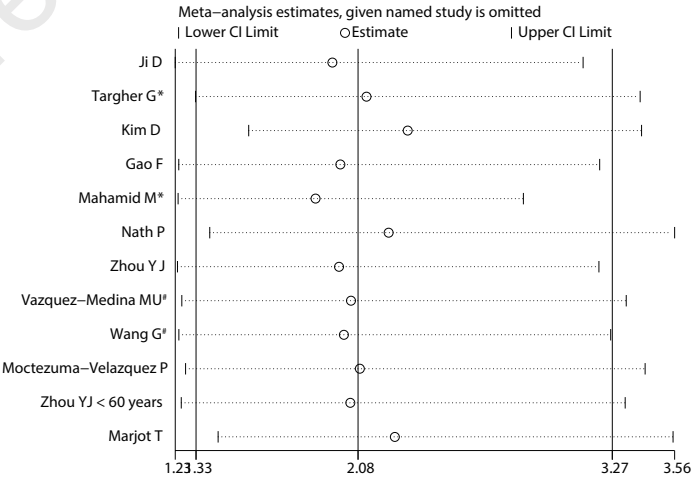

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