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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.
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Authors' contributions

All authors contributed equally on conceptualization, drafting and writing of this reply.

Supplementary data

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Cirrhosis is an independent predictor for COVID-19 mortality: A meta-analysis of confounding cofactors-controlled data

To the Editor:
We read with great interest the excellent paper by Marjot *et al.* titled "Outcomes following SARS-CoV-2 infection in patients with chronic liver disease: An international registry study".[1] In this paper, the authors reported that cirrhosis was significantly associated with coronavirus disease 2019 (COVID-19) mortality on multivariable analysis. Meanwhile, other studies have reported that cirrhosis is not significantly associated with the risk for COVID-19 mortality on multivariable analysis.[2–4] This suggested that the association between cirrhosis and COVID-19 mortality remains inconclusive. Therefore, we performed this meta-analysis to clarify the association between cirrhosis and COVID-19 mortality based on confounding cofactors-controlled effect estimates.

A systematic search was performed in PubMed, Web of Science, EMBASE, Springer Link, Wiley Library, Elsevier ScienceDirect and Cochrane Library to identify all relevant studies as of August 12, 2022. The search terms were: "coronavirus disease 2019", "COVID-19", "severe acute respiratory syndrome coronavirus 2", "SARS-CoV-2", "mortality", "cirrhosis" and "liver cirrhosis". We included the articles reporting the confounding cofactors-controlled effect estimates on the association between cirrhosis and COVID-19 mortality. We excluded preprints, reviews, duplications, errata, case reports and studies reporting the confounding cofactors-uncontrolled effect estimates. We also examined the reference lists of reviews and retrieved original literature to identify all relevant articles. Two authors independently performed literature search and data extraction. Any discrepancy was resolved by consulting the third author. This meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[5]

Heterogeneity was assessed by using the I^2 statistic and Cochran's Q test. The pooled effects and 95% CIs were

estimated using a random-effect model. Publication bias was evaluated by Begg's test. Sensitivity analysis, subgroup analysis and meta-regression were also performed. All statistical analyses were conducted by Stata 11.2 software. p <0.05 was considered statistically significant.

We included 29 articles including data on 6,872,587 individuals with COVID-19. Our meta-analysis indicated that individuals with COVID-19 and cirrhosis had a significantly increased risk of mortality compared to those without cirrhosis based on confounding cofactors-controlled effect estimates

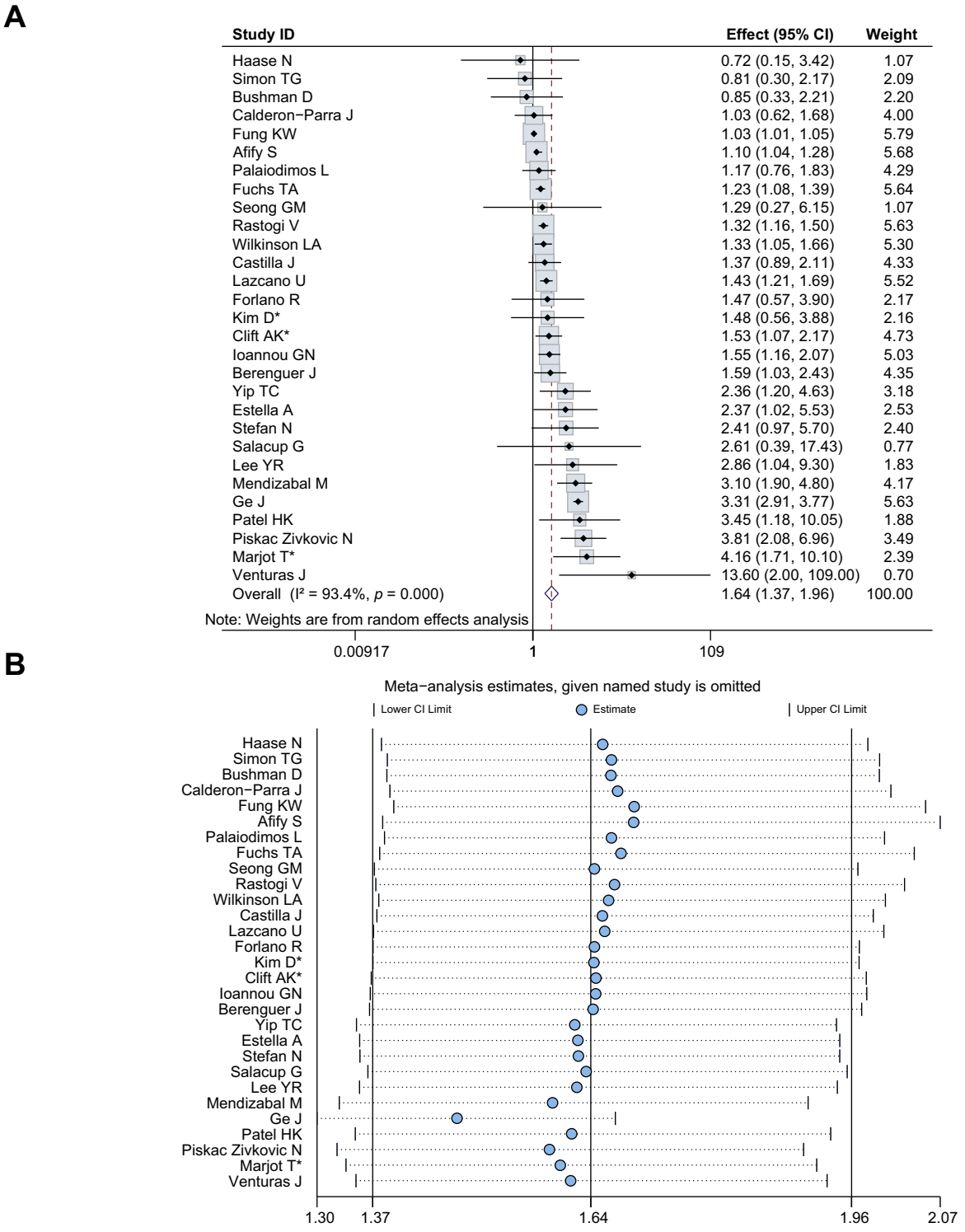

Fig. 1. Forest plots of pooled effect size and sensitivity analysis of the association between cirrhosis and COVID-19 mortality. (A) Forest plot presenting the pooled effect size on the association between cirrhosis and COVID-19 mortality, on the basis of confounding cofactors-controlled data, *indicates combined effects based on subgroups; (B) A sensitivity analysis (based on omitting a single study each time) showed that our results were stable and robust.

(pooled effect = 1.64, 95% CI 1.37–1.96; Fig. 1A). Sensitivity analysis indicated our results were robust (Fig. 1B). We observed consistent results in the subgroup analyses by age (pooled effect = 2.10, 95% CI 1.47–2.99 for age <60, and pooled effect = 1.33, 95% CI 1.17–1.50 for age ≥60), proportion of males (pooled effect = 2.00, 95% CI 1.32–3.04 for proportion of males <50%, and pooled effect = 1.52, 95% CI 1.29–1.80 for proportion of males ≥50%), sample size (pooled effect = 1.86, 95% CI 1.26–2.75 for <3,000 cases, and pooled effect = 1.57, 95% CI 1.24–1.99 for ≥3,000 cases), study design (pooled effect = 1.46, 95% CI 1.25–1.71 for retrospective study, and pooled effect = 1.89, 95% CI 1.32-2.69 for prospective study) and setting (pooled effect = 1.42, 95% CI 1.23–1.64 for studies with all patients, and pooled effect = 1.76, 95% CI 1.27–2.45 for studies with hospitalized patients). Meta-regression indicated that no tested factors contributed to heterogeneity (age, $p = 0.068$; proportion of males, $p = 0.093$; sample size, $p = 0.459$; study design, $p = 0.676$; setting, $p = 0.217$). Begg's test indicated that there was no publication bias in this meta-analysis ($p = 0.138$).

Cirrhosis is the end stage of many chronic liver diseases.[6] Immune dysfunction associated with cirrhosis and fragile physiological buffering may increase susceptibility to severe COVID-19, meanwhile, SARS-CoV-2 infection can precipitate new or worsening acute hepatic decompensation and acute-on-chronic liver failure in individuals with cirrhosis, leading to adverse outcomes.[7] This is consistent with our study showing that cirrhosis was an independent predictor of COVID-19 mortality. But this is a very superficial view, as other factors[8–10] will certainly play a role. The stage of cirrhosis (*e.g.*, Child-Pugh and model for end-stage liver disease [MELD] score) is as important as the pandemic itself (the impact of the different SARS-CoV-2 variants and the impact of vaccination also play a role). Unfortunately, of the studies we included, only five studies described the stage of cirrhosis at baseline by different methods such as Child-Pugh score, MELD score, and chronic liver failure organ failure (CLIF-OF) score, etc. Few included studies addressed the effects of different SARS-CoV-2 variants and vaccination on the association between cirrhosis and COVID-19 mortality. Thus, limited data prevented us from performing further analysis.

In conclusion, this meta-analysis based on confounding cofactors-controlled data indicated that cirrhosis was an independent predictor for COVID-19 mortality. The analysis confirmed what the recent EASL position paper noted.[7] Further well-designed studies based on prospective study estimates are warranted to confirm our findings. We hope that the data from this quantitative meta-analysis will contribute to more accurate elaboration and substantiation of the study by Marjot *et al.*[1]

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Authors' contributions

Haiyan Yang conceptualized the study. Ying Wang and Mengke Hu performed literature search and data extraction. Ying Wang analyzed the data. Ying Wang and Mengke Hu wrote the manuscript. All the authors approved the final manuscript.

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.

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Supplementary data

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Relationship between non-alcoholic fatty liver disease and atrial fibrillation: Assessment of latest evidence

To the Editor:

We read with great interest the study by van Kleef *et al.*, which suggested that higher liver stiffness instead of ultrasonography-diagnosed hepatic steatosis was significantly correlated with atrial fibrillation (AF).[1] We believe that this study provided the most current evidence to improve the management of cardiovascular risk in patients with fatty liver disease; however, there are some issues worth discussing.

First, the relatively low incidence rate of AF (10.2 per 1,000 person-years) in this study may result in an inability to detect a modest association between hepatic steatosis and AF. Second, the study population was older and had a high prevalence of chronic comorbidities such as hypertension and diabetes. Although these factors were adjusted for in the study, older people and individuals with diabetes or hypertension are more likely to be treated with a range of medications that may reduce the risk of cardiovascular diseases including AF. The information on the use of these medications was missing in the study. Not only that, but there was also a higher risk of developing incident type 2 diabetes and hypertension in patients with non-alcoholic fatty liver disease (NAFLD),[2] the current study only screened for these comorbidities at baseline, and data on the occurrence of comorbidities during the follow-up period were not available. Finally, the relatively short follow-up period may contribute to some AF cases being missed.

We also noticed another recent large prospective population-based cohort study that identified NAFLD based on fatty liver index (FLI) and indicated NAFLD being positively correlated with AF risk.[3] These divergent results might be attributed to differences in study populations, study designs, covariate adjustments, and different diagnostic methods for NAFLD. The relationship between FLI and increased AF risk might be due to the metabolically unhealthy components of FLI. Moreover, the current European guidelines recommend imaging modalities rather than non-invasive scoring as first-line diagnostic tools for steatosis in clinical practice.[4]

Thus, to further evaluate the association of the diseases, we conducted a meta-analysis that investigated the associations between imaging-identified NAFLD and AF risk. The literature search was performed using PubMed, Embase, and Web of Science to identify all relevant articles until 20 July 2022. The following studies were included: (1) cohort studies of adult participants (≥18 years) that reported the association between NAFLD and AF risk; (2) studies in which the diagnosis of NAFLD was imaging (mainly ultrasound) based, excluding other competing causes of chronic liver disease (such as heavy alcohol consumption); (3) studies that quantified the outcome with multivariable-adjusted effect estimates (odds ratios [ORs]), relative risks [RRs], or hazard ratios [HRs]) with the corresponding 95% CIs. The methodological quality of the included studies was evaluated based on the Newcastle-Ottawa Quality Assessment Scale. To further eliminate confounding factors, the adjusted RRs and 95% CIs were extracted for the analyses. The reported HRs were considered equal to RRs, and ORs were converted to RRs according to the method given by Zhang *et al.*[5] A random-effects model was used if interstudy heterogeneity existed.

Four high quality prospective cohort studies involving 9,243 participants were selected.[1,6–8] The combined results showed no significant difference in the risk of AF between individuals with imaging-defined NAFLD and those without NAFLD after multivariable adjustment (RR = 1.38, 95% CI 0.81−2.35; p = 0.234; Fig. 1A), with significant heterogeneity among studies (I^2 = 72.9%, p = 0.011). Subsequently, we performed another meta-analysis by pooling the minimally adjusted RRs (adjusted for sex and age), and the results demonstrated that NAFLD was not associated with an increased risk of AF without adjusting for other cardiovascular risk factors (RR 1.43, 95% CI 0.90−2.28; p = 0.131; I^2 = 75.1%; Fig. 1B). Among the four included studies, three used ultrasonography to diagnose fatty liver and the fourth used computed tomography. The non-significant association we observed between NAFLD and the risk of incident AF was consistent for different NAFLD definitions. The subgroup analysis indicated significantly increased AF risk in the subgroup of 'sample <2,000,' while no significant association was observed in the subgroups of 'general population' and 'sample ≥2,000.' Additionally, a sensitivity analysis conducted by removing individual studies at a time revealed that the results were not materially altered.