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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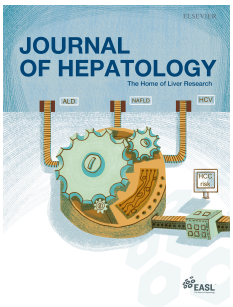

Cirrhosis is an independent predictor for COVID-19 mortality: A meta-analysis of confounding cofactors-controlled data

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

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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,

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 found cirrhosis was significantly associated with coronavirus disease 2019 (COVID-19) mortality in the multivariable analysis. This is an interesting study. To our knowledge, some other studies reported cirrhosis was not significantly associated with the risk for COVID-19 mortality in the multivariable analysis [2-4]. This suggested that the association between cirrhosis and COVID-19 mortality remained to be conclusive. 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% confidence interval (CI) were estimated by 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 twenty-nine articles with 6,872,587 COVID-19 patients. Our meta-analysis indicated that COVID-19 patients with cirrhosis had a significantly increased risk for mortality in comparison to those without cirrhosis based on confounding cofactors-controlled effect estimates (pooled effect = 1.64, 95% CI: 1.37-1.96; Figure 1A). Sensitivity analysis indicated our results were robust (Figure 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 < 3000 cases, and pooled effect = 1.57, 95% CI: 1.24-1.99 for ≥ 3000 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 liver 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 patients with cirrhosis, leading to adverse outcomes [7]. This is consistent with our study 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, model for end-stage liver disease (MELD)) is as important as the ear of the pandemic itself (the impact of the different SARS-CoV-2 variants and the impact of vaccination also play a role). Unfortunately, of the majority of 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, the limited data prevented us from getting further results.

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 of this quantitative meta-analysis will contribute to more accurate elaboration and substantiation of the study provided by Marjot et al [1].

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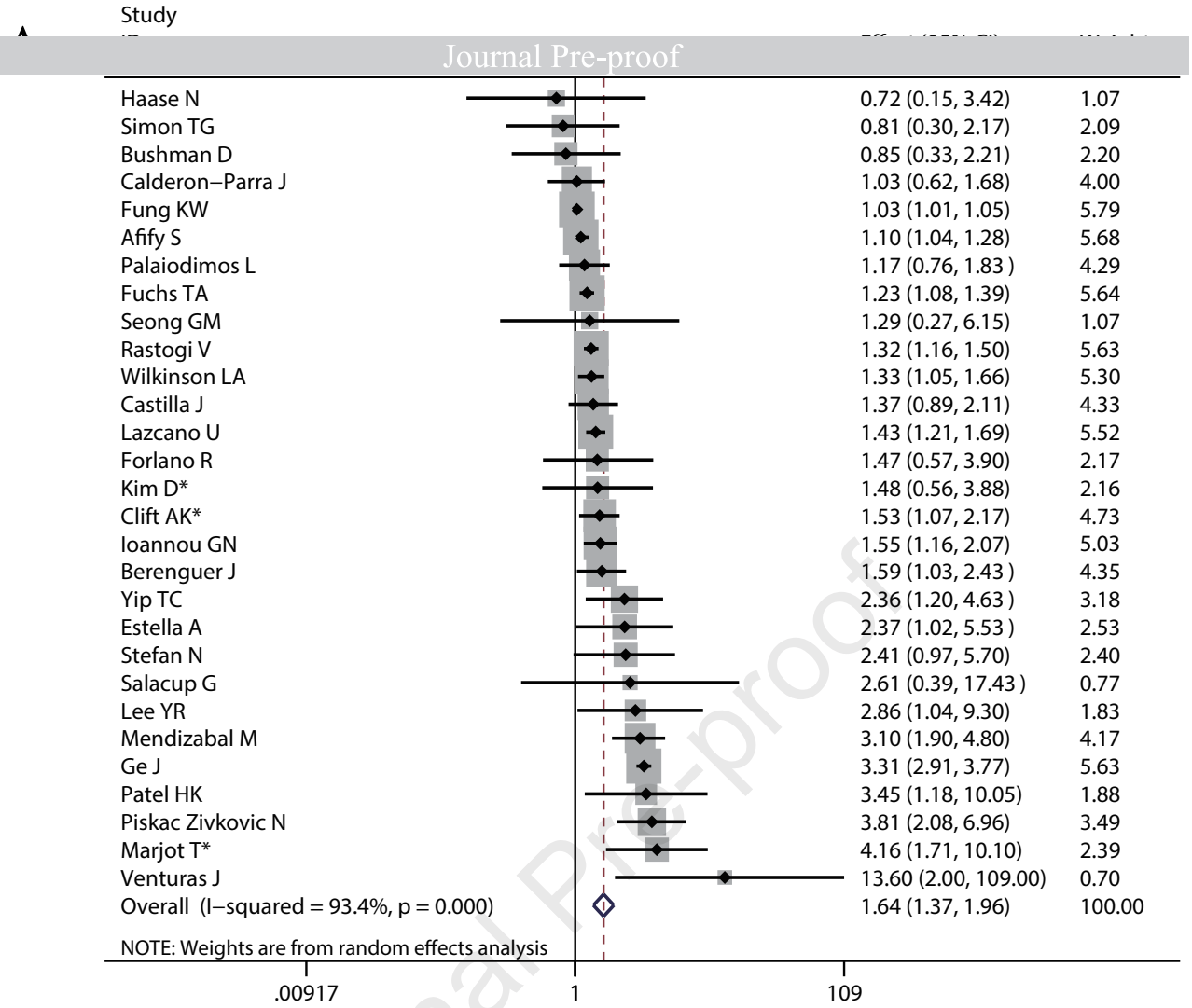
Figure Legend

Figure 1: Forest plot presented the pooled effect size on the association between cirrhosis and COVID-19 mortality on the basis of confounding cofactors-controlled data (A), *indicates combined effects based on subgroups; Sensitivity analysis by omitting single study each time exhibited that our results were stable and robust (B).



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