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LETTER TO THE EDITOR

Chronic liver disease independently associated with COVID-19 severity: evidence based on adjusted effect estimates

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Recently, a meta-analysis by Kovalic et al. reported that chronic liver disease was significantly associated with severe coronavirus disease 2019 (COVID-19) and mortality [1]. This is an interesting study. However, the pooled effect on the association between chronic liver disease and severe COVID-19 was estimated based on un-adjusted effect sizes in Kovalic et al.'s study [1]. It has been considered that several factors such as gender, age and certain comorbidities significantly influenced COVID-19 outcomes [2–5]. This suggests that these factors might modulate the relationship between chronic liver disease and COVID-19 severity. Therefore, it is urgently required to clarify this association by performing a quantitative meta-analysis based on adjusted effect estimates.

Electronic databases including PubMed, Web of Science and EMBASE were searched up to December 10, 2020 using the terms: "SARS-CoV-2", "COVID-19", "chronic liver disease", "cirrhosis", "hepatitis", "liver cancer" and "nonalcoholic fatty liver disease". Only studies reporting the relationship between chronic liver disease and COVID-19 severity by adjusted effect estimates were included. Case reports, reviews, duplicate publications, errata and studies without sufficient data were excluded. The heterogeneity was detected by I^2 statistics. The pooled effect sizes with 95% confidence interval (CI) were estimated. Publication bias was evaluated by Begg's test and Egger's test. Sensitivity analysis, subgroup analysis and meta-regression analysis were also performed. All data were analyzed using Stata 12.1. $p < 0.05$ was considered statistical significance.

Figure S1 shows the flow diagram of study selection. 29 articles with 90,095 confirmed COVID-19 patients were included. The characteristics of the included studies are summarized in Table 1. Our meta-analysis based on adjusted effect estimates demonstrated that COVID-19 patients with chronic liver disease tended to develop severe outcome compared to those without (pooled effect size = 1.52, 95% CI: 1.14–2.02, Fig. 1a) and had a significantly increased risk for mortality compared to those without (pooled effect size = 1.36, 95% CI: 1.22–1.53, Fig. 1b). Sensitivity analysis exhibited that our findings were stable (Fig. 1c). Subgroup analyses by sample size and study design exhibited consistent results (Table S1 and Figure S2–3). But inconsistent results were observed in subgroup analyses by age, male percentage, effect estimate and region (Table S1 and Figure S4–7). Meta-regression analysis showed that the tested variables such as sample size, age, male percentage, effect estimate, study design and region might not be the source of heterogeneity (Table S1). Begg's test and Egger's test suggested that there might be potential publication bias (Figure S8).

This meta-analysis has several limitations. First, inconsistent results were observed in subgroup analyses by age, male percentage and region. Thus, the findings should be cautiously extrapolated to whole population. Second, most of the included studies are retrospective, further well-designed studies with more prospective literatures are warranted to confirm our findings. Third, publication bias might

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Table 1 Main characteristics of the studies included in this meta-analysis

Author	Country	No. of cases	Male percentage (%)	Age[§]	Study design	Adjusted-effect size (95% CI)	Adjusted risk factors
Hashemi et al. (PMID: 32585065)	USA	363	55.4	63.4 ± 16.5	Retrospective study	OR: 2.00 (0.94–4.28)	Age, obesity, male, cardiac diseases, hypertension, diabetes, hyperlipidemia, pulmonary disorders
Ji et al. (PMID: 32597048)	Korea	7341	40.5	47.05 ± 19.0	Retrospective study	OR: 1.031 (0.469–2.265) OR: 0.592 (0.082–4.289)	Endocrinopathy, cardiac disease, chronic respiratory disease, renal disease, disease of digestive system, chronic neurologic disease, malignancy, musculoskeletal and rheumatologic disease, hematologic disease, obesity, nutritional deficiency, mental and behavioral disorders, immune deficiency
Salacup et al. (PMID: 32617986)	USA	242	50.8	66 ± 14.75	Retrospective study	OR: 2.605 (0.389–17.428)	Age, BMI, sex, ethnicity, COPD or asthma, diabetes mellitus, hypertension, heart failure, CKD
Shah et al. (PMID: 32620056)	USA	522	41.8	63 (50–72)	Retrospective study	OR: 1.89 (0.23–15.44)	Age, BMI, gender, race, all the baseline comorbidities
Shang et al. (PMID: 32653423)	China	584	47.4	59 (25–75)	Retrospective study	HR: 1.365 (0.452–4.119)	Sex, age, hypertension, CVD, diabetes, chronic respiratory diseases, CKD, acute kidney injury, acute liver injury, respiratory failure, acute cardiac injury
Berenguer et al. (PMID: 32758659)	Spain	3979	61	70 (56–80)	Retrospective study	HR: 2.03 (1.31–3.13)	Sex, age, arterial hypertension, obesity, dementia, chronic neurological disorder, active cancer, dyspnoea, confusion, low age-adjusted SaO2 on room air, higher white cell blood count, higher neutrophil-to-lymphocyte ratio, lower platelet count, international normalized ratio, estimated glomerular filtration rate, concentrations of C-reactive protein
Yu et al. (PMID: 32777639)	China	1561	50	62 (50–70)	Retrospective study	OR: 0.75 (0.23–2.44)	Age, sex, smoking history, COPD, hypertension, CVD, cerebrovascular disease, diabetes, tuberculosis, malignant tumor, CKD, prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen, fibrin(ogen) degradation products, d-dimer
Posso et al. (PMID: 32782092)	Spain	834	46.5	78.2 ± 9.8	Retrospective study	OR: 1.24 (0.39–3.95)	CKD, heart failure, malignancy, obesity, diabetes, hypertension, chronic respiratory disease, age, gender
Gupta et al. (PMID: 32818209)	USA	2626	57	65.35 ± 17.59	Retrospective study	OR: 0.917 (0.492–1.709)	Age, sex, first BMI assessment, race and ethnicity, insurance, New York City borough of residence, history of hypertension, diabetes, coronary artery disease, heart failure, stroke or transient ischemic attack, atrial arrhythmias, chronic lung disease, CKD, outpatient use of beta-blockers, ACEi, ARBs, oral anticoagulants, P2Y12 receptor inhibitors
Emami et al. (PMID: 32835530)	Iran	1239	55.9	51.48 ± 19.54	Not clearly reported	HR: 0.807 (0.35–1.15)	Age, diabetes mellitus, CVD, CKD, cancer, HIV, smoking, asthma, immunodeficiency disease
Feng et al. (PMID: 32850926)	China	114	62.3	63.96 ± 13.41	Prospective study	HR: 0.997 (0.128–7.760)	Age, sex

Table 1 (continued)

Author	Country	No. of cases	Male percentage (%)	Age[§]	Study design	Adjusted-effect size (95% CI)	Adjusted risk factors
Li et al. (PMID: 32855361)	China	104	62.5	59 ± 12.9	Retrospective study	RR: 1.19 (0.45–3.19)	Not explicitly reported
Mahamid et al. (PMID: 32868652)	Israel	71	38.2	51.0 ± 21.7	Retrospective study	OR: 3.29 (3.28–3.58) OR: 3.25 (3.09–3.47)	Obesity, metabolic syndrome, diabetes, smoking
Reilev et al. (PMID: 32887982)	Denmark	11,122	42.2	48 (33–62)	Population-based study	OR: 1.8 (1.0–3.3)	Age, sex
Yan et al. (PMID: 32949175)	China	1103	48.6	63 (51–71)	Retrospective study	HR: 1.84 (0.44–7.73)	Age, male, diabetes, hypertension, COPD, chronic heart diseases, CKD, cerebrovascular diseases, hyperlipidemia, tumor, C-reactive protein, d-dimer
Ioannou et al. (PMID: 32965502)	USA	10,131	91	64.86 ± 17.26	Longitudinal cohort study	HR: 1.55 (1.16–2.07)	All sociodemographic characteristics, comorbid conditions, symptoms
Forlano et al. (PMID: 33031439)	UK	193	62.7	65.97 ± 18.64	Retrospective study	OR: 1.47 (0.57–3.9)	Male gender, presence of type-2 diabetes, hypertension, dyslipidemia
Lee YR et al. (PMID: 33053932)	Korea	1005	35.9	61 (48–72)	Retrospective study	HR: 2.86 (1.04–9.30)	Age, BMI, smoking history, diabetes mellitus, hypertension, CVD, COPD, chronic renal disease, fever/chill, cough, shortness of breath
Clift et al. (PMID: 33082154)	UK	10,776	55.3	69.63 ± 17.91	Population-based cohort study	HR: 1.85 (1.15–2.29) HR: 1.29 (0.83–2.02)	Age, BMI, townsend score (linear), ethnic group, domicile (residential care, homeless, neither), and a range of conditions and treatments
Omrani et al. (PMID: 33076848)	Qatar	1409	82.8	39 (30–50)	Retrospective study	OR: 2.463 (0.716–8.465)	Age, sex, BMI (defined as body weight in kilograms divided by squared height in meters), and co-existing diabetes mellitus, systemic hypertension, coronary artery disease, CKD
Kolhe et al. (PMID: 33125416)	UK	1161	56.6	72.10 ± 16.01	Retrospective study	OR: 4.37 (1.27–15.1)	Age, sex, ethnicity, myocardial infarction, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, chronic lung disease, connective tissue disorder, diabetes with complications, paraplegia, CKD, dementia, cancer
An et al. (PMID: 33127965)	Korea	10,237	39.9	44.97 ± 19.79	Retrospective study	HR: 0.76 (0.37–1.57)	Age, sex, income level, residence, household type, disability, symptom, infection route
Liu et al. (PMID: 33141117)	China	744	58.4	64 (54–73)	Retrospective study	HR: 0.56 (0.23–1.36)	Age, sex, APACHE II score, COPD, diabetes, hypertension, chronic cardiac disease, CKD, immunosuppression, stroke, malignancy, fever at admission, systolic pressure at admission, leukocytes, hemoglobin, platelets, lymphocytes, d-dimer, total bilirubin, serum creatinine, procalcitonin, corticosteroids, antiviral, human immunoglobulin

Table 1 (continued)

Author	Country	No. of cases	Male percentage (%)	Age[§]	Study design	Adjusted-effect size (95% CI)	Adjusted risk factors
Rubio-Rivas et al. (PMID: 33137919)	Spain	12,066	58.5	67 ± 16	Retrospective study	OR: 1.20 (1.00–1.44)	Age, gender, BMI, clusters, arterial hypertension, diabetes mellitus, hyperlipidemia, COPD, ischemic cardiopathy, chronic heart failure, CKD, active cancer, charlson's index, heart rate upon admission, respiratory rate upon admission > 20 bpm, PaO2/FiO2 upon admission, laboratory test upon admission, treatments during admission
Guo et al. (PMID: 33154656)	China	350	49.4	43 (32–56)	Retrospective study	OR: 2.30 (0.48–10.90)	Age, sex, Wuhan exposure, family cluster case, smoking, comorbidity, hypertension, diabetes, CVD, CKD, cerebral infarction
Tang et al. (PMID: 33153910)	USA	752	39.9	71.16 ± 51.68	Retrospective study	HR: 0.94 (0.29–3.02)	Age, sex, race, facility
Lee SG et al. (PMID: 33218161)	Korea	7399	40.1	47.1 ± 19.0	Retrospective study	OR: 1.01 (0.58–1.74)	Influenza, tuberculosis, COPD, pneumonia, asthma, diabetes mellitus, CKD, hypertension, CVDs, malignancies, HIV infection, lopinavir/ritonavir, hydroxychloroquine, ribavirin, type I interferon, human immunoglobulin G, oseltamivir, antibiotics, age, male, DG area
Bauer et al. (PMID: 33220171)	USA	1449	36.5	54.7 ± 22.5	Retrospective study	OR: 2.14 (0.76–6.07)	Hypertension, diabetes, chronic respiratory disease, arterial disease, congestive heart failure, CKD, cancer, immunosuppression
Galiero et al. (PMID: 33301529)	Italy	618	61.3	65 ± 15.2	Retrospective study	OR: 5.88 (2.39–14.46)	Age, sex, GCS/15, respiratory severity scale, chronic cardiac disease, CKD, chronic respiratory disease, malignancies

ACEi angiotensin-converting enzyme inhibitors, *APACHE* acute physiology and chronic health evaluation, *ARBs* angiotensin receptor blockers, *BMI* body mass index, *CI* confidence interval, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CVD* cardiovascular disease, *CVDs* cardiovascular/cerebrovascular diseases, *DG* Daegu city and Gyeongsangbuk-do province, *FiO2* fraction of inspired oxygen, *GCS* Glasgow Coma Score, *HIV* human immunodeficiency virus, *HR* hazard ratio, *OR* odds, ratio, *PaO2* arterial partial pressure of oxygen, *RR* relative ratio, *SaO2* arterial oxygen saturation. [§]The values of age are presented as mean ± standard deviation (SD) or median (interquartile range, IQR)

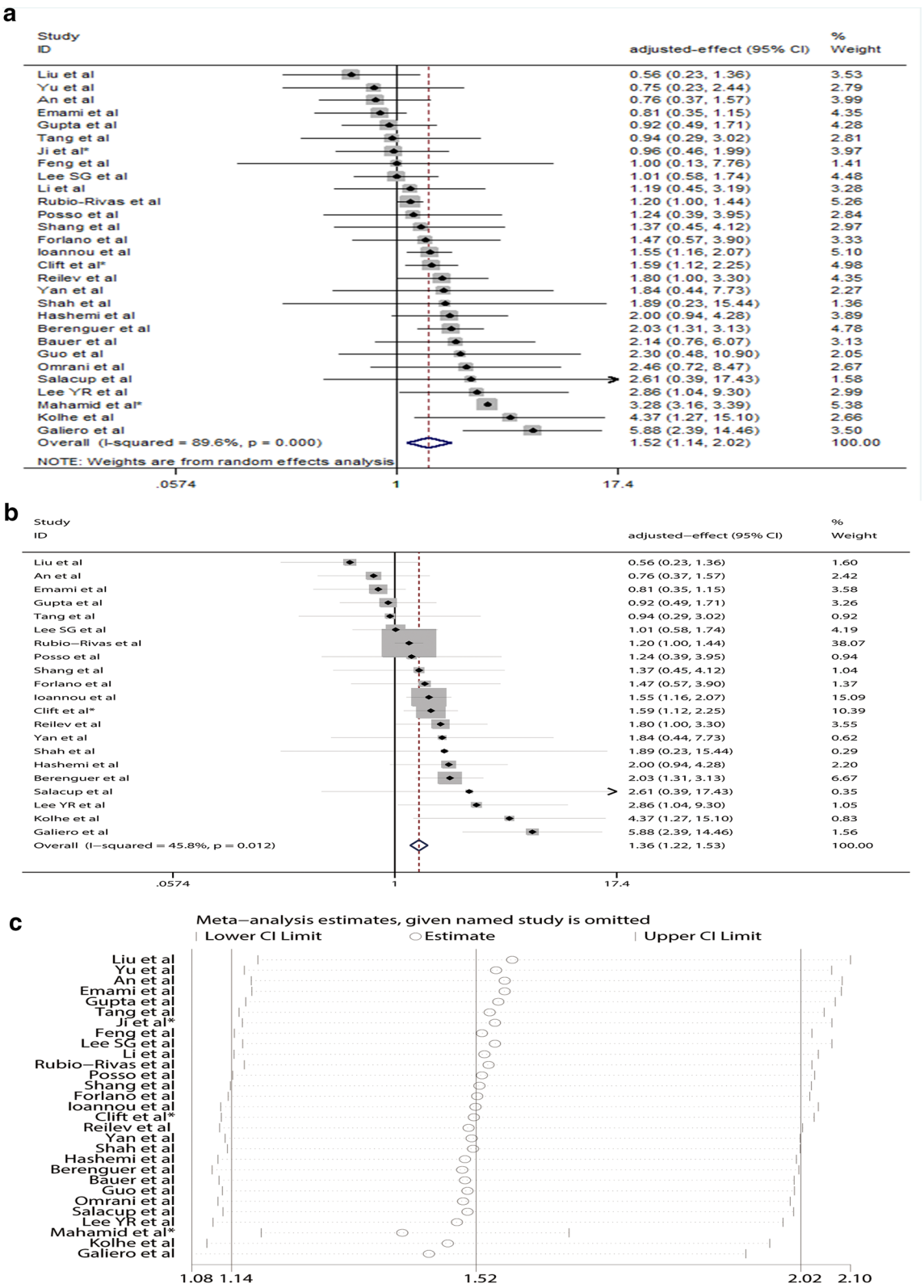

Fig. 1 **a** The forest plot on the association between chronic liver disease and severe coronavirus disease 2019 (COVID-19) on the basis of 29 studies with 90,095 cases reporting adjusted effect estimates; **b** The forest plot on the association between chronic liver disease and COVID-19 mortality; **c** Leave-one-out sensitivity analysis indicated that our results were stable and robust. *Indicates that the combined value was calculated on the basis of subgroups

exist although we tried to search potential articles in electronic databases.

In summary, our study indicated that chronic liver disease was independently associated with COVID-19 severity and mortality, especially among aged individuals, male-dominated population, USA and Europe. Proper management of COVID-19 patients with chronic liver disease is highly recommended to prevent severe situations and mortality.

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Author contributions Haiyan Yang and Yadong Wang designed this study. Jie Xu and Xuan Liang performed literature search. Haiyan Yang and Jie Xu performed data extraction. Jie Xu, Haiyan Yang, Xuan Liang and Li Shi performed statistical analyses. Haiyan Yang, Jie Xu and Yadong Wang wrote and reviewed the manuscript. All the authors approved the final version of this manuscript.

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Data availability All data relevant to this study are included in this article or uploaded as supplementary information.

Compliance with ethical standards

Conflict of interest The authors Haiyan Yang, Jie Xu, Xuan Liang, Li Shi and Yadong Wang have no any potential conflict of interest regarding this submitted manuscript.

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