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

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

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15 <b>Running head:</b> NAFLD and severe COVID-19
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16 Key words: non-alcoholic fatty liver disease, coronavirus disease 2019, worse outcomes,

17 meta-analysis, independent risk factor

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## 45 To the Editor,

In the Journal of Hepatology, Ji et al reported that the presence of non-alcoholic fatty liver 46 disease (NAFLD) was significantly associated with an increased risk for the progression of 47 coronavirus disease 2019 (COVID-19) in multivariate model [1], however, Marjot et al [2] 48 and Mushtaq et al [3] reported opposite findings that the presence of NAFLD was not 49 significantly associated with COVID-19 mortality, disease severity or disease progression in 50 multivariate model. This suggests whether the presence of NAFLD was an independent 51 52 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 53 COVID-19 which might be attributed to the presence of other high-risk comorbidities [4]. 54 55 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 56 more severe COVID-19. 57

This meta-analysis was performed in accordance with the preferred reporting item for 58 systematic reviews and meta-analysis (PRISMA) guidelines [5]. The literature was searched 59 in the online databases of Web of Science, PubMed, Elsevier ScienceDirect, Wiley Library, 60 EMBASE, Springer Link, Scopus and Cochrane Library for potentially eligible articles which 61 were published between December 10, 2019 and September 7, 2022. The keywords were 62 used: ("NAFLD" OR "non-alcoholic fatty liver disease" OR "MAFLD" OR "metabolic 63 associated fatty liver disease") and ("2019-nCoV" OR "SARS-CoV-2" OR "COVID-19" OR 64 "2019 novel coronavirus" OR "severe acute respiratory syndrome coronavirus 2" OR 65 "coronavirus disease 2019"). The exposure group was COVID-19 patients with NAFLD and 66 the control group was COVID-19 patients without NAFLD. The outcome of interest was 67

severe COVID-19 (which was reported as severe/critical illness, severity/progression, 68 intensive care unit (ICU) admission, need for invasive mechanical ventilation (IMV) and 69 mortality, etc. in the original articles). We included all peer-reviewed articles in English 70 providing the risk factors-adjusted effect sizes of the association between NAFLD and severe 71 COVID-19 by multivariate model. We excluded case reports, reviews, preprints, study 72 protocol, editorial, commentary, errata, and studies with un-adjusted effect sizes or without 73 available data. Two independent researchers conducted literature retrieval and data extraction. 74 Any disagreements were settled by discussion between the researchers until the consensus 75 was achieved. In order to find additional pertinent studies, the listed references of the 76 included studies and relevant reviews were further scanned and manually retrieved. 77

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<sup>2</sup> 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  $\geq$  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 91 92 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 93 among older patients (pooled OR = 1.37, 95% CI: 0.97-1.93 for  $\geq$  60 years, Figure 1C). 94 Sensitivity analysis exhibited deleting each individual study once had no significant impacts 95 on the overall results (Figure 1D, 1E and 1F). Egger's test (P = 0.003) and Begg's test (P =96 0.005) demonstrated publication bias might exist presently. 97

Although the pooled OR was calculated on the basis of the risk factors-adjusted effects 98 sizes (mainly adjusting age, sex, smoking, obesity, diabetes and hypertension), other factors 99 (such as SARS-CoV-2 variants, status of vaccination and medication) [9, 10] might certainly 100 play an important role in modifying the association between NAFLD and severe COVID-19. 101 Unfortunately, few included studies provided the information of SARS-CoV-2 variants, status 102 of vaccination and medication. We could not assess the impacts of SARS-CoV-2 variants, 103 status of vaccination and medication on the association between NAFLD and severe 104 COVID-19 presently, which should be addressed in the future when more data are available. 105

In conclusion, this meta-analysis of risk factors-adjusted effect sizes indicated the 106 presence of NAFLD was significantly independently associated with more severe COVID-19 107 among younger patients rather than older patients. Future well-designed studies with 108 comprehensive measurements of potential confounding factors are warranted to verify our 109 findings. 110

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### 137 **Figure legend**:

Figure 1: Forest plot demonstrated that the presence of non-alcoholic fatty liver disease 138 (NAFLD) was significantly independently associated with more severe coronavirus disease 139 2019 (COVID-19) on the basis of eighteen eligible articles reporting risk factors-adjusted 140 effect sizes (A). Subgroup analysis by age (mean/median) showed that the presence of 141 NAFLD was significantly independently associated with more severe COVID-19 among 142 younger patients (< 60 years) (B), but not among older patients ( $\geq$  60 years) (C). 143 Leave-one-out sensitivity analysis exhibited that omitting any single study once had no 144 significant impacts on the overall results (D for total studies, E for < 60 years, and F for  $\ge 60$ 145 years). \* indicates combined effect sizes were calculated from subgroups. # indicates that the 146 study used the hazard ratio (HR) to assess the effect size. The publication bias may favour the 147 publication of positive studies which leads to an overestimation of the positive association 148

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

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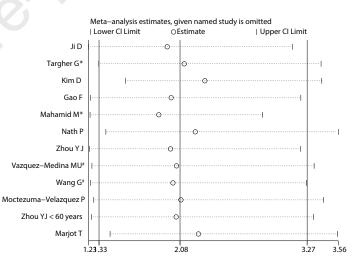
Study		
ID	OR (95% CI)	Weight
d il	★ 6.40 (1.50, 31.20)	3.13
Targher G*	1.62 (0.46, 5.68)	3.84
Kim D 🛛	0.68 (0.41, 1.13)	6.63
Gao F	<b>4.07</b> (1.10, 15.09)	3.69
Mahamid M*	<ul> <li>3.28 (3.16, 3.39)</li> </ul>	7.70
Nath P	1.15 (0.67, 1.98)	6.50
Marjot T	0.98 (0.56, 1.71)	6.43
Zhou YJ	4.07 (1.20, 13.79)	3.96
Hashemi N -	2.30 (1.27, 4.17)	6.29
Yoo HW	1.35 (1.05, 1.71)	7.43
u) 🚽	1.57 (0.93, 2.67)	6.55
Vazquez–Medina MU <sup>#</sup>	2.62 (1.10, 6.21)	5.22
Wang G <sup>#</sup>	<ul> <li>3.26 (1.17, 9.04)</li> </ul>	4.63
Moctezuma–Velazquez P	2.13 (1.05, 4.34)	5.84
Vrsaljko N	2.15 (1.04, 4.46)	5.77
Forlano R	0.86 (0.44, 1.69)	5.99
Wargny M 🛛 🔸 🚽	1.10 (0.76, 1.59)	7.10
Zhou YJ*	1.36 (0.32, 5.75)	3.31
Overall (I-squared = 90.3%, p < 0.001)	1.76 (1.24, 2.49)	100.00
NOTE: Weights are from random effects analysis		
.0321 1	31.2	

Meta-analysis estimates, given named study is omitted | Lower CI Limit OEstimate | Upper Cl Limit Ji D ۰I Targher G\* Kim D 0 Gao F • 💬 Mahamid M\* 0 -----Nath P 0 Marjot T 0 Zhou Y J 0 -1 Hashemi N . 0 Yoo H W 0 -1 Li J -1 Vazquez–Medina MU<sup>#</sup> • 📀 Wang G<sup>#</sup> ...... Moctezuma–Velazquez P ٠C Vrsaljko N Forlano R 0 Wargny M 0 Zhou YJ\* 1.18.24 1.76 2.49 2.62

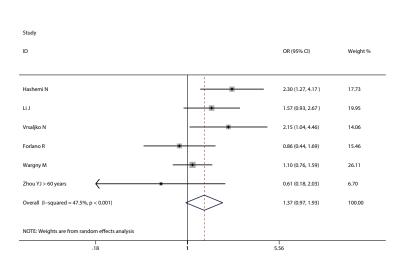
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Study			
ID		OR (95% CI)	Weight %
	,		
Ji D		6.40 (1.50, 31.20)	5.09
Targher G*		1.62 (0.46, 5.68)	6.22
Kim D		0.68 (0.41, 1.13)	10.45
Gao F		4.07 (1.10, 15.09)	5.97
Mahamid M*		3.28 (3.16, 3.39)	12.03
Nath P		1.15 (0.67, 1.98)	10.26
Zhou YJ		- 4.07 (1.20, 13.79)	6.39
Vazquez–Medina MU*		2.62 (1.10, 6.21)	8.34
Wang G <sup>#</sup>		3.26 (1.17, 9.04)	7.44
Moctezuma–Velazquez P		2.13 (1.05, 4.34)	9.28
Zhou YJ < 60 years		2.67 (1.13, 6.34)	8.36
Marjot T		0.98 (0.56, 1.71)	10.17
Overall (I-squared = 84.8%, p < 0.001)	$\Leftrightarrow$	2.08 (1.33, 3.27)	100.00
NOTE: Weights are from random effects analysis			
.0321	1	31.2	



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