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SCOPE

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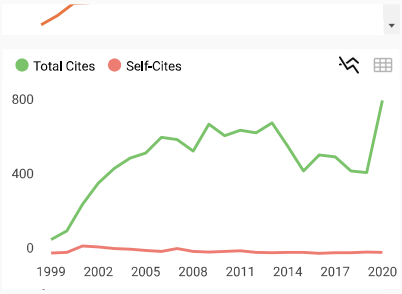

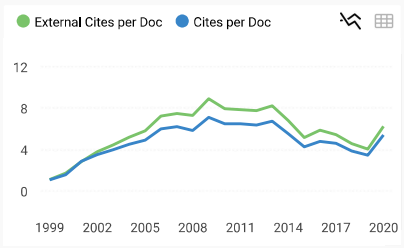

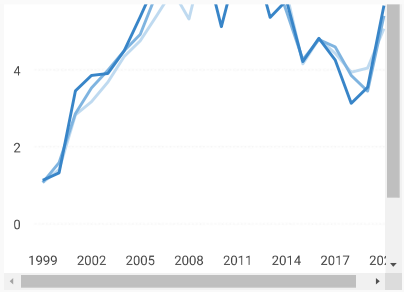

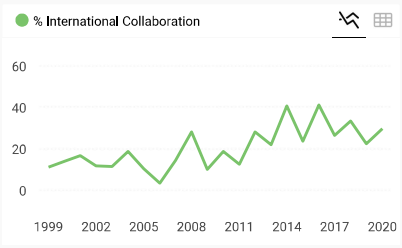

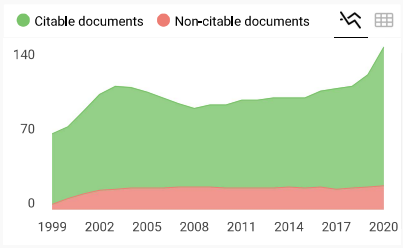

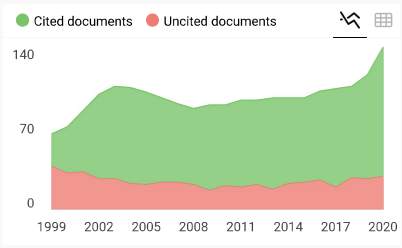

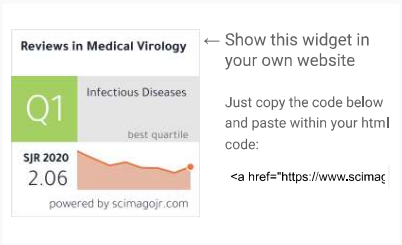

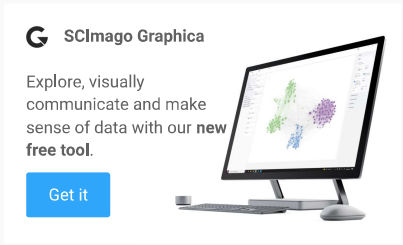

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Effectiveness of public health measures to prevent the transmission of SARS-CoV-2 at mass gatherings: A rapid review

Kieran A. Walsh, Barrie Tyner, Natasha Broderick, Patricia Harrington, Michelle O'Neill, Christopher G. Fawsitt, Karen Cardwell, Susan M. Smith, Máire A. Connolly, Máirín Ryan

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REVIEW

The prevalence, predictors and outcomes of acute liver injury among patients with COVID-19: A systematic review and meta-analysis

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Abbreviations: ACE2, angiotensin-converting enzyme 2; ALI, acute liver injury; BMI, body mass index; CAD, coronary artery disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; NOS, Newcastle–Ottawa Scale; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Summary

The data on the predictors and prognosis of acute liver injury (ALI) among patients in coronavirus disease 2019 (COVID-19) patients are limited. The aim of this study was to determine the prevalence, predictors and outcomes of ALI among patients with COVID-19. A systematic review was conducted up to 10 June 2021. The relevant papers were searched from PubMed, Embase, Cochrane and Web of Science, and the data were analysed using a *Z* test. A total of 1331 papers were identified and 16 papers consisting of 1254 COVID-19 with ALI and 4999 COVID-19 without ALI were analysed. The cumulative prevalence of ALI among patients with COVID-19 was 22.8%. Male and having low lymphocyte levels were more likely to be associated with ALI compared with female and having higher lymphocyte level, odds ratio (OR): 2.70; 95% confidence interval (CI): 2.03, 3.60 and mean difference (MD) −125; 95% CI: −207, −43, respectively. COVID-19 patients with ALI had higher risk of developing severe COVID-19 compared with those without ALI (OR: 3.61; 95% CI: 2.60, 5.02). Our findings may serve as the additional evaluation for the management of ALI in COVID-19 patients.

KEYWORDS
acute liver injury, COVID-19, outcome, predictor, prevalence

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains the major global concern. The pathogenesis of COVID-19 is complicated[1,2] and involves multiple organs including lung, kidney, heart, neurologic system, gastrointestinal system and liver.[3] Although the respiratory tract is the primary target of SARS-CoV-2, more than 50% of COVID-19 patients had nausea, vomiting, diarrhoea and loss of appetite[4] suggesting the involvement of gastrointestinal and hepatobiliary system. A recent study also found that moderate microvascular steatosis was prevalent in liver biopsies of COVID-19 patients, suggesting that liver injury might occur during COVID-19.[5] The involvement of liver in SARS-CoV-2 infection is mystifying,[6] and it was suggested that liver involvement is mediated by several mechanisms, including direct infection of the liver, drug-induced liver injury, systemic inflammatory response or hypoxic hepatitis.[7]

The optimal management of acute liver injury (ALI) in COVID-19 patients remains controversial. Although one recommendation suggested that ALI in COVID-19 is reversible and does not require specific treatment,[7] liver involvement was reported to cause poor prognosis of COVID-19 patients.[8] Moreover, liver involvement has been included in predicting the outcomes of patients with COVID-19.[9] To date, no information is available regarding predictors of when and who among COVID-19 patients will suffer from ALI. In addition, data on the outcomes of COVID-19 patients with ALI are also limited. Therefore, the objective of this study was to determine the prevalence of ALI in COVID-19 patients, predictors of ALI occurrence and prognosis of COVID-19 patients with ALI.

2 | METHODS

2.1 | Study design and eligibility criteria

A systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis[10] was conducted up to 10 June 2021 on four databases including PubMed, Embase, Cochrane and Web of Science. The included papers should: (1) have the design of double-arm analysis such as randomised controlled trial (RCT) and non-RCT or observational studies (case–control, cross-sectional or cohort); (2) report either the prevalence, predictor or the outcome of ALI in COVID-19 patients; (3) contain information about COVID-19 cases diagnosed using RT-PCR from nasopharyngeal or oropharyngeal swab samples; and (4) have sufficient criteria for the diagnosis of ALI.[11]

2.2 | Search strategy and data extraction

All papers in English were searched using Medical Subjects Heading: ("COVID-19" OR "SARS-CoV-2") AND ("acute liver injury" OR "liver dysfunction" OR "liver abnormality") AND ("prevalence" OR "predictor" OR "outcome"). Additional papers from the reference list of the articles were searched and in case of dual duplication, a paper with the higher sample size was included. The following information were collected from each study: (1) first author name and publication year; (2) country and city of origin; (3) study design; (4) study setting; (5) sample size of COVID-19 patients with and without ALI; (5) the incidence of ALI; (6) the factors associated with ALI; and (7) severity and mortality rate of COVID-19 patients with and without ALI. The

definition of variables and study protocols were defined prior to data collection, and a kappa test was used to assess the understanding among investigators.

2.3 | Quality assessment

Potential articles were evaluated for their methodological quality using Newcastle–Ottawa Scale (NOS) that evaluates sample selection, comparison and exposure.[12] The calculation of NOS score was used to classify the quality of articles into low (score 0–3), moderate (score 4–6) and high quality (score 7–9) and only articles with moderate and high quality were included into analysis. All letters to the editor, commentaries, case reports, case series and reviews were excluded.

2.4 | Study variables

ALI refers to an acute abnormality of liver blood tests and the development of a coagulopathy, but does not exhibit any alteration of consciousness in an individual without underlying chronic liver disease.[9] The predictor variables included age, gender, body mass index (BMI), the presence of comorbidities [diabetes mellitus (DM), coronary artery disease (CAD) and hypertension], pre-existing liver disease, as well as the levels of leucocytes, lymphocytes and neutrophils. Those variables were defined after considering the available data.

2.5 | Statistical analysis

To assess the publication bias, an Egger test was applied and a $p < 0.05$ indicated potential publication bias.[13] The heterogeneity among studies was assessed using a Q test and the random effect model was used if the heterogeneity across the studies were observed ($p < 0.10$).[13] The prevalence of ALI, the associated predictors of ALI, and the association between ALI and the clinical outcomes of patients with COVID-19 were determined using a Z test. The summary of statistical analysis was presented in forest plot. A Review Manager (Revman Cochrane, London, UK) version 5.3 was used to analyse the data.

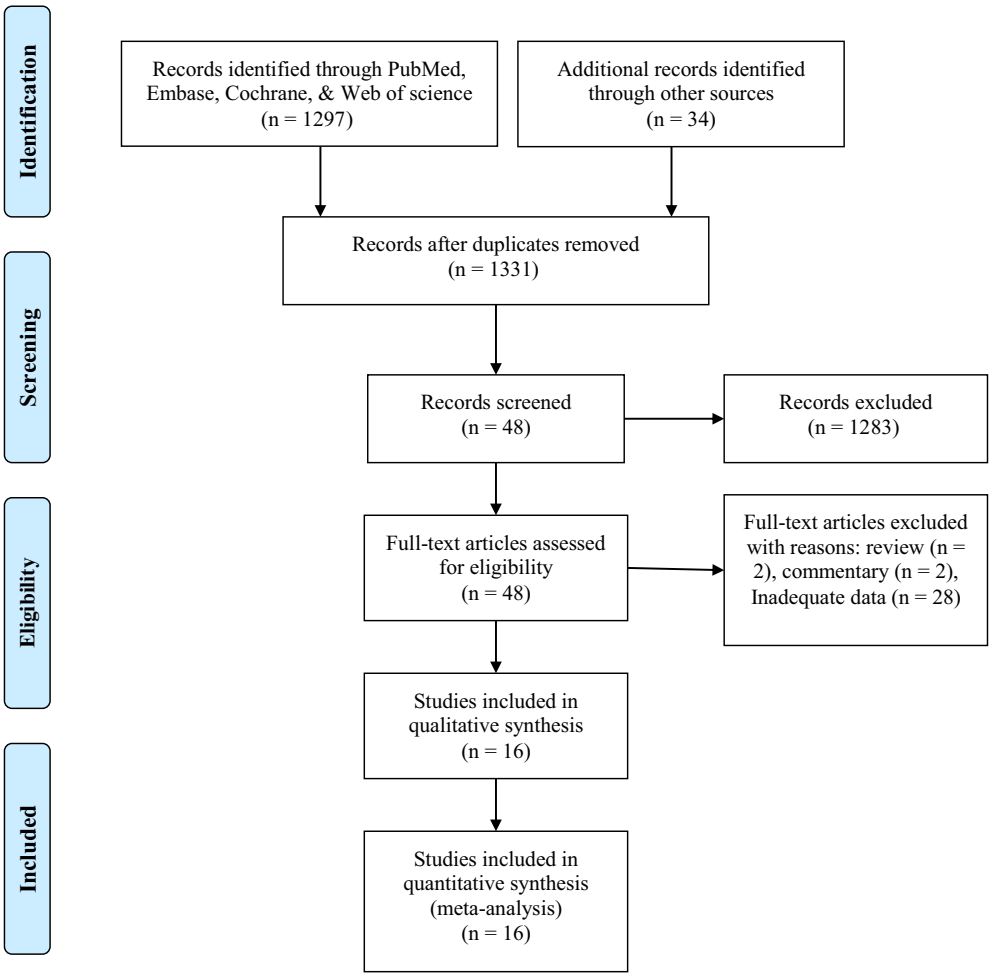

FIGURE 1 A flowchart of article selection

3 | RESULTS

3.1 | Study eligibility results

A total of 1331 papers were identified across the databases of which 1283 papers were excluded due to having irrelevant studies. Full-text assessment was conducted on 48 papers and additional 32 papers were excluded as they did not meet the eligibility criteria (Figure 1). 16 papers consisting of two cross-sectional studies, three prospective studies and 11 retrospective studies were finally included into meta-analysis (Table 1).[5,14-28]

3.2 | The global prevalence, predictors and prognosis of ALI among patients with COVID-19

The included studies comprised 1254 COVID-19 with ALI and 4999 COVID-19 without ALI, and the prevalence of ALI was found to be 22.8% [95% confidence interval (CI): 14.1, 34.6] (Figure 2a). A total of 10 potential predictors of ALI (age, gender, BMI; the presence of DM, CAD, and hypertension, liver disease; as well as the level of white blood cells (WBC), neutrophils and lymphocytes) were analysed (Table 2). Male and having high lymphocyte count were associated with ALI with OR: 2.70; 95% CI: 2.03, 3.60 and mean difference (MD): −125; 95% CI: −207, −43, respectively (Figures 2b,c). Our data suggested that COVID-19 patients with ALI had higher odds of suffering from severe disease compared with those without ALI, OR: 3.61; 95% CI: 2.60, 5.02 (Figure 2d and Table 2).

3.3 | Heterogeneity and potency of bias across the studies

The heterogeneity was identified on data of prevalence of ALI in COVID-19 patients, mortality of COVID-19 and data of some predictors of ALI such as age, hypertension, liver disease, WBC, neutrophils and lymphocytes and therefore random effect model was used while other predictors were and the association between ALI and severity of COVID-19 was assessed using fixed effect model. The potency of publication bias was found in several predictors of ALI including BMI, DM and CAD (Table 2).

4 | DISCUSSION

Our study found that the cumulative prevalence of ALI among patients with COVID-19 was 22.8%. This finding is higher compared with that of a previous meta-analysis using data of five studies (prevalence 15.7%).[29] Our data suggest that male and having high lymphocyte level were associated with ALI. Although the mechanism of ALI in SARS-CoV-2 infection is debatable, it is known that the expression of angiotensin-converting enzyme 2 (ACE2) receptors, the primary receptor for SARS-CoV-2 to enter human cells, was high in

TABLE 1 Baseline characteristics of articles included in our analysis

Author and years	Country	Study design	Study group comparation	Sample size		Quality (NOS)
				ALI	Non-ALI	
Bloom et al. (2021)	US	Prospective cohort	Normal versus hepatocellular injury	10	50	6
Cai et al. (2020)	China	Cross-sectional	Normal liver versus ALI	22	225	6
Cai et al. (2020)	China	Retrospective	Normal liver versus ALI	90	327	6
Chen et al. (2021)	China	Prospective cohort	Normal liver versus ALI	32	603	5
Chen et al. (2020)	China	Retrospective	Normal liver versus ALI	13	261	6
Chew et al. (2021)	China	Retrospective	Normal liver versus ALI	105	729	6
Fan et al. (2020)	China	Cross-sectional	Normal liver versus ALI	55	93	5
Mishra et al. (2020)	US	Retrospective	Normal liver versus ALI	166	162	8
Phipps et al. (2020)	US	Retrospective	Normal liver versus ALI	145	1784	6
Piano et al. (2020)	Italy	Retrospective	Normal liver versus ALI	329	236	6
Qi et al. (2020)	China	Prospective cohort	Non-ALI versus ALI	32	38	5
Sarin et al. (2020)	India	Retrospective	Non-ALI versus ALI	97	88	6
Wang et al. (2020)	China	Retrospective	Normal liver versus ALI	96	243	6
Xie et al. (2020)	China	Retrospective	Non-ALI versus ALI	29	50	6
Yang et al. (2021)	China	Retrospective	Normal liver versus ALI	15	37	7
Zhao et al. (2020)	China	Retrospective	Non-ALI versus ALI	18	73	8

Abbreviations: ALI, acute liver injury; NOS, Newcastle–Ottawa Scale.

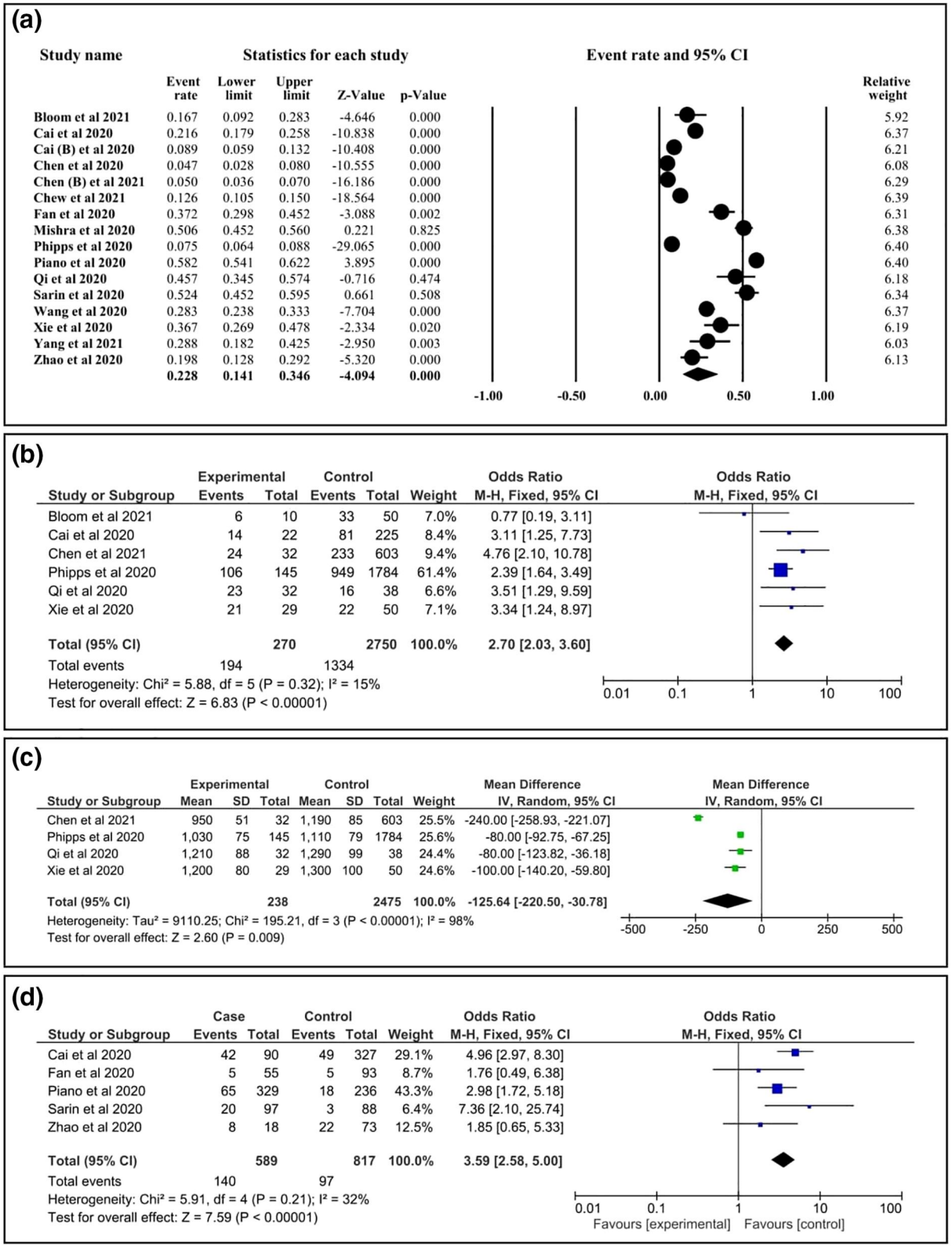

FIGURE 2 The summary of acute liver injury (ALI) in patients with coronavirus disease 2019 (COVID-19). (a) The global prevalence of ALI in patients with COVID-19. (b) Association of gender (male) with ALI in COVID-19 patients. (c) Association of low level of lymphocyte with ALI in COVID-19 patients. (d) Association between ALI and the severity of COVID-19

TABLE 2 The global prevalence, predictors and prognosis of acute liver injury among patients with COVID-19

Variable	NS	Model	Study group		Point estimate	95%CI	*p* Egger	*p* Het	*p*-value
			ALI	Non-ALI					
ALI prevalence	16	Random	1254 (20.05)	4999 (79.94)	22.8%[a]	14.1, 34.6	1.1760	<0.0001	<0.0001
ALI predictors									
Age (years), mean ± SD	5	Random	55.2 ± 8.8	53.6 ± 10.2	1.76[b]	−3.26, 6.78	0.3260	0.0030	0.4660
Male, *n* (%)	6	Fixed	194 (71.9)	1334 (48.5)	2.70[c]	2.03, 3.60	0.1720	0.3180	<0.0001
BMI (kg/m^2), mean ± SD	2	Fixed	28.5 ± 3.5	26.5 ± 4.9	2.63[b]	0.97, 4.30	<0.0001	0.3630	0.0020
Diabetes mellitus, *n* (%)	6	Fixed	56 (20.7)	828 (30.1)	0.72[c]	0.52, 0.99	<0.0001	0.8450	0.0450
Coronary artery disease, *n* (%)	4	Fixed	10 (9.7)	77 (10.4)	1.26[c]	0.60, 2.63	<0.0001	0.8520	0.5450
Hypertension, *n* (%)	5	Random	105 (40.4)	1309 (48.5)	1.31[c]	0.67, 2.54	0.5790	0.0220	0.4260
Liver disease, *n* (%)	4	Random	15 (7.2)	110 (4.2)	2.98[c]	1.00, 8.88	0.8400	0.0630	0.0500
Leucocyte (cells/μl), mean ± SD	3	Random	7983 ± 3953	5553 ± 1700	2432[b]	−89, 4954	0.4550	<0.0001	0.0590
Neutrophils (cells/μl), mean ± SD	3	Random	5556 ± 2833	3893 ± 1334	166[b]	−29, 362	0.4400	<0.0001	0.0970
Lymphocytes (cells/μl), mean ± SD	4	Random	1097 ± 128	1222 ± 89	−125[b]	−207, −43	0.8610	<0.0001	0.0090
Prognosis									
Severe versus non severe	5	Fixed	140 (27.80)	97 (11.90)	3.61[b]	2.60, 5.02	0.2810	0.2060	<0.0001
Mortality	8	Random	252 (28.77)	445 (24.07)	1.38[b]	0.85, 2.25	0.5130	0.0060	0.1940

Abbreviations: ALI, acute liver injury; BMI, body mass index; CI, confidence interval; NOS, Newcastle–Ottawa Scale; NS, number of studies; p Het, p heterogeneity; WBC, white blood cells.

[a]Event rate.

[b]Odds ratio.

[c]Mean difference.

the liver.[30] A previous investigation reported that the expression of ACE2 receptors was higher in male than female[31] and ACE2 expression is mediated by androgen.[32] A study revealed that ACE2 receptors were also expressed in lymphocytes,[33] suggesting that SARS-CoV-2 may also attack lymphocytes leading to decreased numbers. Interestingly, our study also found that patients with higher BMI and DM had higher risk to develop ALI, although the Egger test is insufficient to support the findings. The liver abnormality in patients with the obesity and DM suggested that the metabolic associated steatohepatitis might also affect the involvement of liver injury, and this circumstance might also contribute to the severity of COVID-19 infection.[31] Our findings also showed that COVID-19 patients with ALI had higher risk of developing severe disease, consistent with previous meta-analyses.[29,34-36] Therefore, patients with ALI on initial admission should be strictly monitored since they are at higher risk of developing severe outcomes including death. The involvement of liver could trigger dysregulated immune responses leading to cytokine storm,[37] a pathological state associated with fatal COVID-19 outcomes.[38] This presumably explains why COVID-19 patients with ALI possess higher risk of developing severe conditions.

The present study, to the best of our knowledge, is the first to provide comprehensive data on prevalence, predictors and prognosis of ALI in COVID-19. Robust results indicated that ALI is associated with severe COVID-19. Therefore, some parameters should be monitored during COVID-19 management to anticipate the occurrence of ALI and to prevent severe outcomes. The present data might helpfully be used as the reference for the management of COVID-19 with ALI.

There are some limitations of our study. Potential confounding factors such as previous medication, drug interactions, previous liver disease, status of metabolism and previous history of infectious disease were not reported and therefore could not be controlled. In addition, the heterogeneity of the quality of included articles in our meta-analysis might contribute to certain degree of bias. Furthermore, the limited studies on the topic led us to include only limited number of papers, and therefore the potential for publication bias should be carefully interpreted.

5 | CONCLUSION

The prevalence of ALI among patients with COVID-19 is 22.8%. Male and having lower lymphocyte level are more likely to be associated with ALI. COVID-19 patients with ALI have high risk for severe COVID-19 and therefore should be monitored closely to prevent the development of severe conditions. Nevertheless, further prospective studies are required to provide more robust data and to confirm the findings of the present study.

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CONFLICT OF INTEREST

Authors have no conflict of interest.

ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptual: Harapan Harapan, Jonny Karunia Fajar, Supriono Supriono. *Design*: Jonny Karunia Fajar. *Control/supervision*: Supriono Supriono, Gatot Soegiarto, Laksmi Wulandari. *Data collection/processing*: Fiha Seratin, Nyoman Gede Prayudi, Dara Puspita Dewi, Maria Theresia Monica Elsina, Lasarus Atamou, Sinta Wiranata, Dhito Pemi Aprianto, Erlin Friska, D. Fitria Sari Firdaus, Makdum Alaidin, Firdha Aprillia Wardhani, Nurdina Wahyu Hidayati, Yeni Hendriyanti, Kristia Wardani, Arde Evatta, Reizal Audi Manugan, Wiryawan Pradipto, Ade Rahmawati, Fredo Tamara, Aditya Indra Mahendra, Budi Santoso, Chandra Adi Irawan Primasatya, Nindy Tjionganata, Hendarto Arif Budiman. *Extraction/analysis/interpretation*: Jonny Karunia Fajar, Fredo Tamara, Aditya Indra Mahendra. *Literature review*: Jonny Karunia Fajar, Fredo Tamara, Aditya Indra Mahendra. *Writing the article*: Harapan Harapan, Jonny Karunia Fajar, Fredo Tamara, Aditya Indra Mahendra. *Critical review*: Harapan Harapan, Supriono Supriono, Jonny Karunia Fajar, Gatot Soegiarto, Laksmi Wulandari, Milda Husnah. All authors have read and approved the final draft.

CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

Data used in our study were presented in the main text.

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