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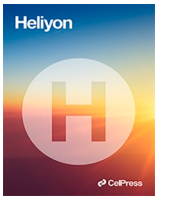

Association between acute liver injury & severity and mortality of COVID-19 patients: A systematic review and meta-analysis

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ABSTRACT

Background: Acute liver injury (ALI), a complication often seen in COVID-19 patients, can lead to severe liver damage, multi-organ failure, acute vascular events, and can potentially escalate to patient mortality. Given this, we initiated a meta-analysis to investigate the correlation between ALI and adverse outcomes in COVID-19 patients.
Methods: We conducted an exhaustive search of databases, including Medline, Embase, PubMed Central, ScienceDirect, Google Scholar, and the Cochrane Library, from the November 2019 until January 2022. The quality of the included studies was evaluated using the Newcastle Ottawa (NO) scale. Our meta-analysis was carried out using a random-effects model and results were presented as pooled odds ratios (ORs) with their corresponding 95% confidence intervals (CIs).
Results: Our analysis incorporated 20 studies involving a total of 13,850 participants, predominantly from China and the United States. According to the NO scale, the majority of these studies were categorized as low-quality. Patients with ALI faced approximately 7 times higher odds of severe COVID-19 symptoms (pooled OR = 7.09; 95%CI: 4.97 to 10.12) and over 5 times higher odds of mortality (pooled OR = 5.50; 95%CI: 3.37 to 8.99) when compared to those without ALI.
Conclusion: Our findings affirm that ALI is a potent predictor of adverse outcomes, including severity and mortality, among COVID-19 patients. Recognizing and promptly addressing ALI in COVID-19 patients could be pivotal in improving prognosis and tailoring individualized patient management strategies. This underscores the need for clinicians to be vigilant about liver complications in the COVID-19 patients and integrate appropriate interventions in the treatment paradigm.

1. Introduction

The coronavirus disease 2019 (COVID-19) remains a pressing public health crisis. As of June 2023, it has resulted in approximately 690 million cases and 6.89 million fatalities [1]. SARS-CoV-2, the causative agent of COVID-19, belongs to the Coronaviridae family and is an enveloped virus with a positive-sense, single-stranded RNA genome [2]. Primarily, this virus is associated with mild

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infections in the human upper respiratory and gastrointestinal tracts [2]. However, despite a generally low mortality rate, specific demographics, such as the elderly and those with pre-existing conditions, face a higher risk of severe illness, complications, and increased mortality [3].

One of the severe complications arising from COVID-19 includes multi-organ failure, among which liver damage is particularly concerning [4,5]. The liver, vital for immune homeostasis, frequently manifests damage in COVID-19 cases, as highlighted by numerous global studies. Notably, Greenough et al. pinpointed SARS-CoV proteins in the liver cells of infected individuals, a finding later echoed in autopsy results [6,7]. These proteins suggest a two-fold mechanism behind liver injury: either through the direct viral invasion of liver cells or an immunopathological response spurred by unchecked inflammation [8].

Adding complexity to this, research has shed light on SARS-CoV-2's ability to disrupt bile duct functions, an essential facet of liver health. This disruption is attributed to the virus binding to bile duct cells via Angiotensin-converting enzyme-2 (ACE-2) receptors [9, 10]. These receptors are not only paramount for liver regeneration but also play a critical role in modulating immune responses. Importantly, their overstimulation by the virus may amplify disease severity. Concurrently, a virus-induced cytokine storm could potentially wreak havoc on various organs, including the heart, liver, and kidneys [11,12].

Highlighting the clinical ramifications, Lu et al. elucidated the relationship between decreased lymphocyte count, elevated C-reactive protein levels, and liver injury in COVID-19 cases [13]. The liver repercussions in these patients typically align more with hepatocellular damage than cholestatic [14]. Furthermore, around 60% of COVID-19 patients showcase abnormal liver parameters, with variations noted between 14% and 53% [8]. More so, patients with severe disease presentations often demonstrate elevated liver enzymes such as ALT or AST, hypoalbuminemia, heightened γGT, and marginally increased bilirubin levels [15–19]. Intriguingly, a significant discrepancy exists in the elevated AST levels between severe (45.5%) and mild COVID-19 cases (15.0%) [2].

While numerous studies have delved into the nuances of slightly abnormal liver parameters in COVID-19, a discernible gap exists in understanding the implications of acute liver injury (ALI) and its influence on COVID-19 progression [20–22]. ALI, when coupled with COVID-19, can escalate the severity, leading to extensive liver damage, multi-organ failure, vascular complications, and even death [23]. Alarmingly, our literature exploration revealed an absence of systematic reviews focusing on impact of ALI on COVID-19 patients. Hence, our review seeks to elucidate the association between ALI and its consequential effects on severity and mortality in COVID-19 patients.

2. Methods

2.1. Eligibility criteria

Design: We included observational studies (case-control, cohort, cross-sectional studies) in our analysis. Our focus was on published literature; therefore, unpublished or grey literature was excluded. Our inclusion criteria encompassed both retrospective and prospective observational studies. The reason for this diverse inclusion is to capture a comprehensive understanding of the association between ALI and COVID-19 outcomes. However, it's noteworthy that retrospective studies, being based on past data, may carry inherent biases related to data collection and reporting. In contrast, prospective studies, which follow participants forward in time, might provide more accurate and unbiased data. Hence, the type of study can significantly influence the strength and interpretation of the associations observed.

Participants: We incorporated studies conducted on COVID-19 patients. Studies conducted on COVID-19 patients with specific comorbidities were not included.

Exposure: We included studies reporting outcomes among acute liver injury (ALI) and non-ALI patients. Studies applying any standard criteria or upper limit of any standard criteria for ALI diagnosis were eligible. The standard guidelines used are provided in **Supplementary File 1**.

Outcomes: We considered (a) severity of the COVID-19 condition, and (b) mortality as the outcomes. The COVID-19 condition severity can be assessed based on the following parameters: respiratory rate (RR) $>$ 30 breaths/min, oxygen saturation (SpO2) $<$ 93%, oxygenation index (PaO2/FiO2) $\leq$ 300 mmHg, requirement of intensive care unit (ICU), or mechanical ventilation [24].

Search Strategy: A comprehensive electronic search was performed across PubMed Central, Embase, Medline, ScienceDirect, Cochrane library, and Google Scholar, using Medical subject headings (MeSH) search and field search. The search spanned from November 2019 until January 2022 and was restricted to English language. A detailed list of search terms and Boolean operators is provided in **Supplementary File 1.**

2.2. Study selection

The study selection began with an initial screening of titles, keywords, and abstracts, carried out independently by two reviewers (YK & MK). Studies that passed the first phase were then thoroughly examined by two investigators in the second stage of screening. Here, we shortlisted full-text studies that satisfied the eligibility criteria for further analysis. In case of disagreements, they were resolved via discussions with a third reviewer (VH).

2.3. Data collection

Data extraction was performed by two investigators (KG & MK), utilizing a pre-defined semi-structured data collection form developed at the protocol stage. This data included information about authors, journal details, publication year, study design, setting,

country, sample size in exposed and non-exposed groups, outcome definitions, mean age, and the number of events in both groups. The first author (YK) was responsible for data entry, while another author (VH) validated the entries to ensure their correctness.

2.4. Assessment of bias risk

A thorough evaluation of the bias risk was independently carried out by two authors (KG & MK). We utilized the reputable Newcastle Ottawa (NO) scale for this purpose, which assesses potential bias across three domains, namely Selection (awarding a maximum of four stars), Comparability (a maximum of two stars), and Outcome (a maximum of two stars). The total score ranged from zero to eight stars, with scores of 7–8 stars indicating "good" quality, scores of 5–6 stars suggesting "satisfactory" quality, and scores of 0–4 stars denoting "unsatisfactory" quality [25].

2.5. Data synthesis

All analyses were performed in STATA version 14.2 (StataCorp, CollegeStation, TX, USA). Given the dichotomous nature of the outcomes, we recorded the number of events and the sample size in each group, interpreting the final estimate in terms of the odds ratio (OR). To compensate for methodological heterogeneity, we utilized a random effects model with inverse variance [26].

The presence of heterogeneity was verified using a chi-square test and quantified via the I^2 statistic. We used forest plots to provide a visual representation of both study-specific and pooled estimates. The sensitivity analysis was undertaken to examine the robustness of our findings. In essence, by removing one study at a time, we gauged how each individual study impacted the pooled results, thereby identifying potential outliers or influential studies that might skew our findings. For the subgroup analysis, our primary aim was to identify potential reasons for heterogeneity. Divergent geographical regions, varied criteria defining ALI, and distinct severity criteria across studies can be sources of such heterogeneity. These analyses were paramount to ensure that our conclusions were drawn from a cohesive and consistent pool of data.

Due to the lack of diversity in the study designs - only one study was prospective while the remaining were retrospective - an analysis based on study design was not feasible. We conducted a univariable meta-regression with study-level characteristics, using variables with a p-value less than 0.20 for multivariable meta-regression, to discern potential sources of heterogeneity between studies.

Publication bias, a concern in systematic reviews, arises when studies with statistically significant results are more likely to be published and cited. This can potentially skew the review findings. In our assessment, visual inspections of funnel and Doi plots provide

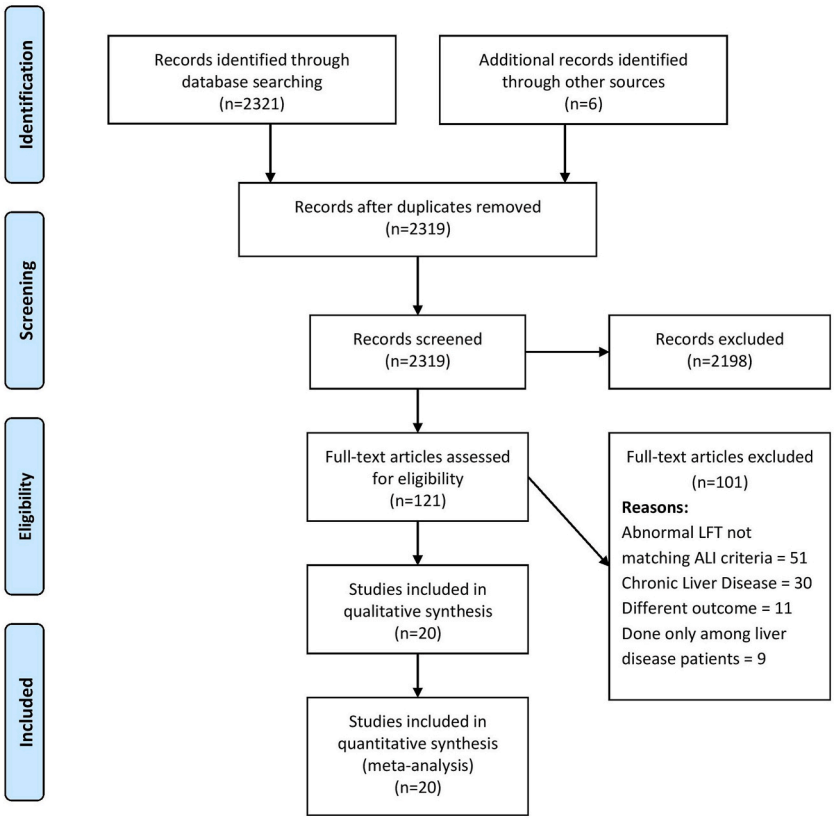

Fig. 1. PRISMA flowchart.

Table 1
Characteristics of the included studies (N = 20).

Author and Year	Country	Study design	Sample size	ALI criteria	Outcome assessed	COVID-19 Severity criteria	Quality of the study[a]
Anastasiou 2021 [23]	Germany	Retrospective	65	EASL clinical practical guidelines on the management of acute liver failure (Patients with liver injury showing disorder of coagulation (INR ≥1.5) and jaundice (total bilirubin level ≥51 μmol/L) within 26 weeks of the onset of illness)	Mortality	NA	High
Cai 2020 [28]	China	Retrospective	318	Total bilirubin level of ≥3 mg/dl, ALT >5 time normal and ALP >2 times normal	Severity	Patients with RR > 30 breaths/min, SpO2 < 93% or PaO2/FiO2 ≤ 300 mmHg	Low
Chen 2020 [29]	China	Retrospective	274	Total bilirubin level of ≥3 mg/dl, ALT >5 time normal and ALP >2 times normal	Mortality	NA	Low
Chew 2021 [44]	USA	Retrospective	834	American College of Gastroenterology Guidelines (AST ≥5 times normal)	Mortality	NA	Low
Choron 2021 [37]	USA	Retrospective	103	ALT and/or AST ≥15 times normal	Mortality	NA	Low
Da 2020 [35]	USA	Retrospective	176	American College of Gastroenterology Guidelines (ALT/AST ≥3 times normal)	Severity, Mortality	Patients with RR > 30 breaths/min, SpO2 < 93% or PaO2/FiO2 ≤ 300 mmHg	Low
Ding 2020 [34]	China	Retrospective	1869	EASL clinical practical guidelines on the management of acute liver failure (Patients with liver injury showing disorder of coagulation (INR ≥1.5) and jaundice (total bilirubin level ≥51 μmol/L) within 26 weeks of the onset of illness)	Severity, Mortality	Invasive mechanical ventilation requirement	Low
Fu 2020 [30]	China	Prospective	355	ALT >5 times the normal limit	Mortality	NA	High
Goel 2020 [31]	USA	Retrospective	552	ALP >3 times the normal limit	Mortality	NA	Low
Pazoki 2021 [42]	Iran	Retrospective	176	AASLD clinical practice guidelines for the liver diseases (ALT or AST ≥3 x ULN, ALP or total bilirubin ≥2 x ULN)	Severity, Mortality	Oxygen saturation ≤93, or > 50% lung involvement on imaging, dyspnea, septic shock, respiratory failure, or multiple organ dysfunction/ failure	High
Phipps 2020 [32]	USA	Retrospective	1929	ALT >5 times the normal limit	Severity, Mortality	ICU admission	Low
Richardson 2020 [15]	USA	Retrospective	2628	ALT/AST >15 times ULN	Mortality	NA	Low
Roedl 2021 [43]	Germany	Retrospective	72	Total bilirubin ≥2 mg/dl or elevation of ALT/AST levels >20-fold ULN	Severity, Mortality	Invasive mechanical ventilation requirement	Low
Sarin 2020 [33]	13 Asian countries	Retrospective	43	Total bilirubin level of ≥3 mg/dl or ALT/AST/SAP/GGT >2 times normal or PT-INR 1.5 times normal	Severity, Mortality	Patients with RR > 30 breaths/min, SpO2 < 93% or PaO2/FiO2 ≤ 300 mmHg	Low
Shao 2021 [39]	China	Retrospective	1466	ALT/AST >2 times ULN and ALP/ GGT >2 times ULN	Severity, Mortality	ICU admission	Low
Siddiqui 2021 [40]	USA	Retrospective	1935	Peak levels of ALT/AST 3 times the ULN level or peak ALP/total bilirubin levels 2 times the ULN level	Severity, Mortality	Invasive mechanical ventilation requirement	Low
Tijera 2021 [38]	Mexico	Retrospective	166	AST >5 times the normal limit	Severity	Invasive mechanical ventilation requirement	High
Yitao 2021 [41]	China	Retrospective	257	ALI >3 times the ULN or ALP >2 times the ULN or total bilirubin >2 times the ULN	Severity	Patients with RR > 30 breaths/min, SpO2 < 93% or PaO2/FiO2 ≤ 300 mmHg	Low
Zhang 2021 [45]	China	Retrospective	440	Chinese guidelines for the COVID-19-related liver injury (ALT and/or AST ≥3 ULN, or total bilirubin ≥2 times ULN)	Severity, Mortality	ICU admission	Low
Zhou 2021 [36]	China	Retrospective	186	American College of Gastroenterology Guidelines (ALT/AST ≥3 times normal)	Mortality	NA	Low

[a] Based on Newcastle Ottawa Scale; NA – Not applicable; USA – United States of America; INR – International Normalized Ratio; ALT – Alanine aminotransferase; AST – Aspartate aminotransferase; ALP – Alkaline Phosphatase; RR – Respiratory rate; SpO2 – oxygen saturation; PaO2/FiO2 - ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen; EASL - European Association for the Study of the Liver; AASLD – American Association for the Study of Liver Diseases clinical practice guidelines for the liver diseases; ULN – Upper Limit Normal.

preliminary insights, while the statistical methods, like Egger's test and Luis Furuya-Kanamori asymmetry index (LFK index) offer more concrete evidence of such bias [26,27]. A notable publication bias could suggest that our meta-analysis results are based on a potentially unrepresentative subset of all relevant studies. In such cases, the interpretations and conclusions drawn must be approached with added caution.

3. Results

3.1. Selection of studies

A total of 2321 records were retrieved through our systematic search, 121 of which were deemed relevant for full-text retrieval. During the second screening stage, 20 studies encompassing 13,850 participants met the eligibility criteria [15,23,28–45](Fig. 1).

3.2. Characteristics of studies

Almost all the included studies were of a retrospective or cross-sectional nature, with the exception of Fu et al. (2020) [30], which was a prospective case cohort study. The majority of the studies were conducted in China (8 studies) and the United States of America (7 studies). The total number of participants in the included studies was 13,850, with sample sizes ranging from 43 to 2628. Of the 20 studies included, 12 reported on severity, and 17 reported on mortality following COVID-19 (**Table-1**). The majority (16 out of 20) of the included studies were deemed low quality according to the NO assessment checklist.

3.3. Relationship between ALI and COVID-19 consequences

3.3.1. Severity

From the 12 studies that reported severity outcomes for both groups in our analysis, the pooled OR was found to be 7.09 (95%CI: 4.97 to 10.12; I2 = 68.6%) (Fig. 2), demonstrating that the likelihood of ALI patients experiencing a severe form of COVID-19 is seven times greater than that of non-ALI patients. A subgroup analysis by study region demonstrated the highest correlation between ALI and

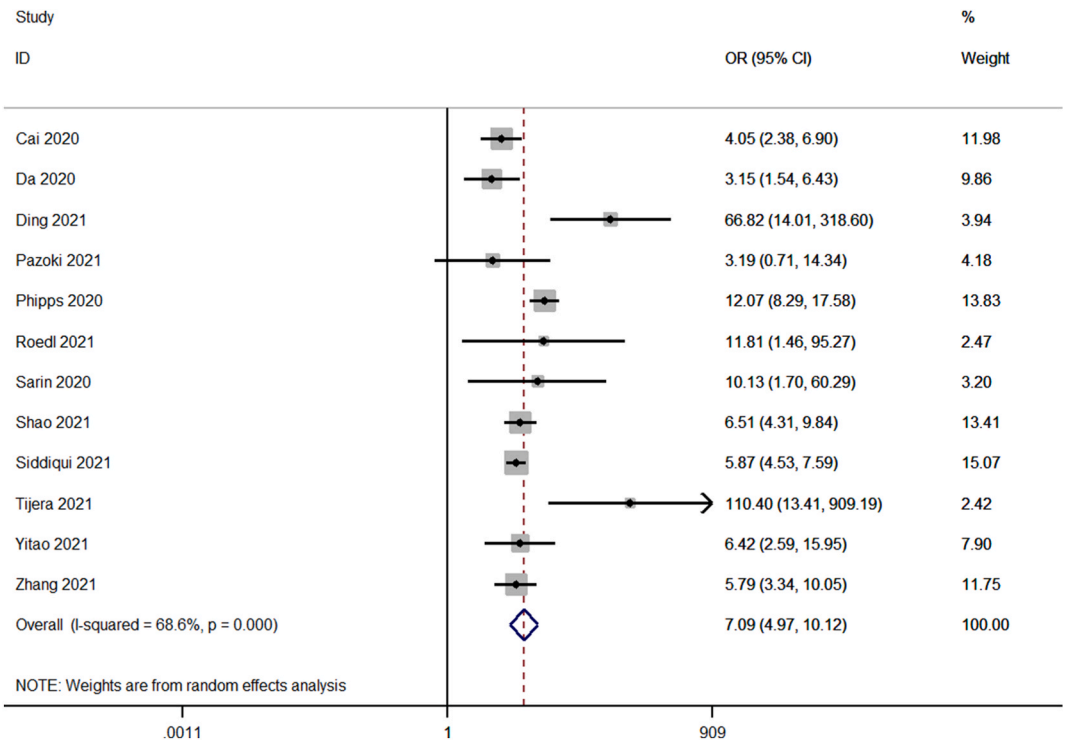

Fig. 2. Forest plot showing the association between acute liver injury and COVID-19 severity.

COVID-19 severity in American studies (pooled OR = 8.08; 95%CI: 3.98–16.41), followed by Asian (pooled OR = 6.83; 95%CI: 4.30–10.87) and Europe/Middle East studies (pooled OR = 5.00; 95%CI: 1.47–17.00) **(Supplementary Fig. 1).**

An analysis based on ALI criteria showed that studies setting a higher upper limit normal (ULN) for diagnosis (>15 times the ULN: pooled OR = 11.40, 95%CI: 3.70–35.12; >5 times the ULN: [pooled OR = 11.81, 95%CI: 1.46–95.27) resulted in the highest pooled estimate compared to studies setting a lower ULN for diagnosis (>2 times the ULN: pooled OR = 6.66, 95%CI: 4.45–9.95; >3 times the ULN: pooled OR = 5.50, 95%CI: 4.44–6.81) **(Supplementary Fig. 2).**

A subgroup analysis based on the COVID-19 severity definition indicated that the criteria for invasive mechanical ventilation (pooled OR = 23.33; 95%CI: 4.58–118.72) yielded the highest combined estimate, followed by ICU admission (pooled OR = 7.88; 95% CI: 4.93–12.69) and standard severity criteria based on RR/SpO2/PaO2/FiO2 (pooled OR = 4.19; 95%CI: 2.90–6.04) **(Supplementary Fig. 3).** The meta-regression model with ALI criteria and severity criteria accounted for approximately 20% of the heterogeneity discovered in the review.

The funnel plot exhibited no asymmetry **(Supplementary Fig. 4),** which was statistically confirmed by Egger's test (p = 0.39), while the Doi plot revealed significant asymmetry with an LFK index of 2.26 **(Supplementary Fig. 5).** Sensitivity analysis demonstrated no single study effects on the combined effect size **(Supplementary Fig. 6).**

3.3.2. Mortality

Our analysis included 17 studies that reported on the mortality outcome for both groups. The pooled OR was 5.51 (95%CI: 3.37 to 8.99; $I^2 = 84.9\%$), showing a significant correlation between ALI and mortality among COVID-19 patients (Fig. 3). A subgroup analysis by study region showed that studies conducted in the Asian region (pooled OR = 9.73; 95%CI: 4.08–23.22) had the highest correlation between ALI and COVID-19 mortality, followed by Europe/Middle East (pooled OR = 5.43; 95%CI: 1.91–15.44) and America (pooled OR = 3.42; 95%CI: 1.79–6.53) **(Supplementary Fig. 7).** An analysis based on the ALI criteria indicated substantial variation in the combined estimate **(Supplementary Fig. 8).**

The meta-regression model with geographical region and ALI criteria was able to account for about 71% of the total heterogeneity. The funnel plot showed signs of asymmetry (Supplementary Fig. 9), while the Doi plot exhibited minor asymmetry (Supplementary Fig. 10). The observed asymmetry in the funnel plot and the Doi plot for mortality estimates warrants further examination. Funnel plot asymmetry can be indicative of publication bias, where smaller studies reporting larger effect sizes are less likely to be published. This phenomenon can stem from various factors, such as selective outcome reporting, selective analysis reporting, or a genuine heterogeneity across the study spectrum.

The Doi plot and the associated LFK index provide a more granular insight into funnel plot asymmetry. An LFK index exceeding 1

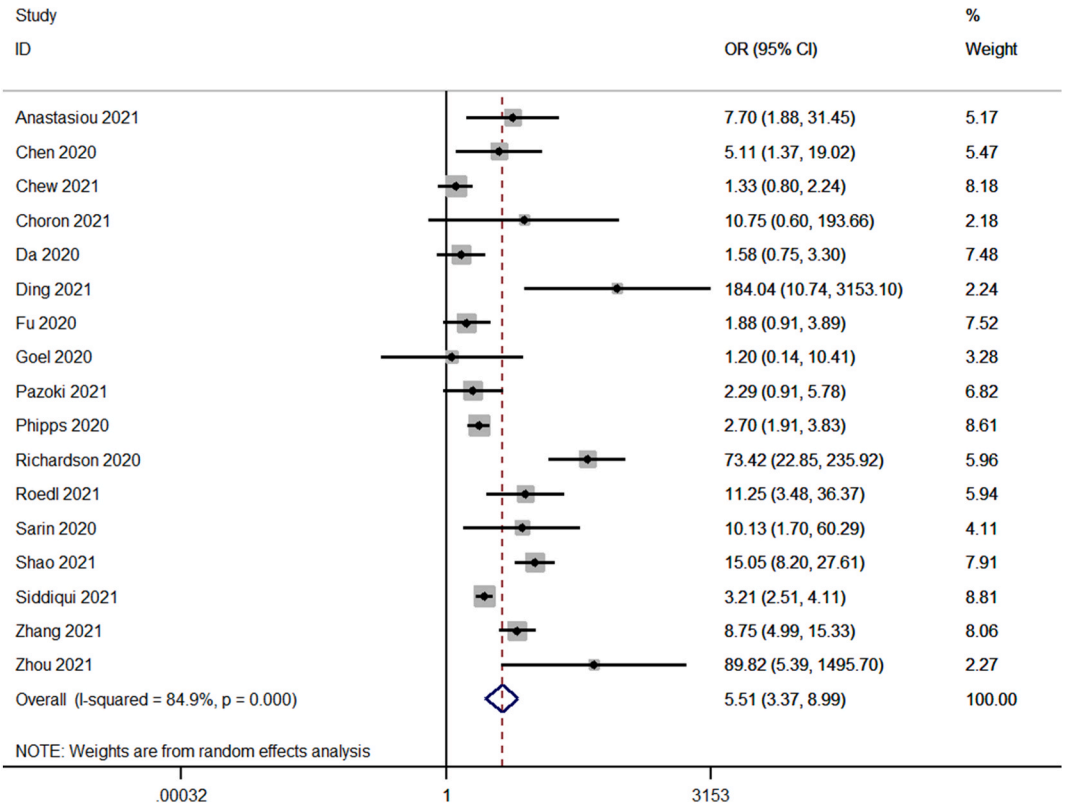

Fig. 3. Forest plot showing the association between acute liver injury and mortality amongst COVID-19 patients.

suggests potential asymmetry. In our analysis, an LFK index of 1.60 could point toward minor publication bias or other underlying heterogeneities. For instance, it's plausible that some studies, especially those with more remarkable findings, got published more promptly, while others with less significant findings did not get published or were delayed.

While our Egger's test for the mortality outcome showed a borderline significance ($p = 0.09$), which suggests the presence of small study effects, it's critical to approach these findings with caution. Potential sources of bias, such as methodological differences between small and large studies or the presence of true clinical or methodological heterogeneity, should also be considered.

Sensitivity analysis demonstrated no single study effects on the overall estimate (Supplementary Fig. 11).

4. Discussion

4.1. Review overview and contextualization

The ongoing COVID-19 pandemic has brought liver function abnormalities to the forefront as a significant concern for infected patients. This issue is not an isolated physiological response; there is a theorized higher risk of adverse events among COVID-19 patients with abnormal liver function compared to those who maintain normal liver function throughout the course of their disease. Yet, the extent of this risk, specifically the relationship between acute liver injury (ALI) and adverse outcomes among COVID-19 patients, remains uncertain.

Prompted by this need for clarity, we initiated this comprehensive review to study the association between ALI and the severity and mortality outcomes of COVID-19 patients. Our review found 20 studies that fulfilled the eligibility criteria of our review. These studies were primarily conducted in two countries that have been significantly impacted by the pandemic - China and the United States of America. The designs of the majority of these studies were retrospective or cross-sectional in nature, but it's important to note that they were of lower quality as evaluated using the NO scale, a widely recognized tool for assessing the quality of nonrandomized studies in meta-analyses.

4.2. Summary of findings and comparison with existing literature

In the course of our review, we found that ALI had a significant association with the severity (pooled OR = 7.09; 95%CI: 4.97 to 10.12) and mortality (pooled OR = 5.51; 95%CI: 3.37 to 8.99) among the COVID-19 patients. This finding echoes the results from earlier reviews that assessed the impact of abnormal liver function - specifically levels above the upper limit of normal - with COVID-19 outcomes. These prior reviews [46–51], [46–51] similar to ours, also reported a parallel direction of association.

However, our study unveiled a critical finding - the magnitude of the association in our study was noticeably higher compared to these previous reviews. This indicates that ALI exerts a more serious impact on the adverse outcomes in COVID-19 patients when compared to abnormal liver function tests, which merely indicate levels just above the upper limit of liver enzymes [46–51].

The intricate and exact mechanism behind the association between ALI and COVID-19 is yet to be definitively deciphered. Several theories have been proposed regarding the impact of SARS-CoV-2 on the liver [52–54]. One of these proposed theories suggests that SARS-CoV-2 directly affects hepatocytes and the biliary epithelium by targeting ACE-2 receptors. Enhanced immune response leading to liver injury and immune-mediated destruction is another widely accepted theory. The potential toxicity of certain drugs like antivirals, acetaminophen, and hydroxychloroquine also remains a plausible hypothesis. However, our review could not definitively establish a causation link between ALI and adverse outcomes due to the still unclear pathogenesis behind ALI.

4.3. Study limitations

Our review, while comprehensive, was not without its limitations. One significant drawback was that most of the studies included in our review were deemed to be of lower quality, which potentially places a constraint on the generalizability of our findings. Furthermore, a considerable proportion of the studies included in our review, as well as the previous ones, did not employ any uniform criteria for the measurement of ALI. This lack of consistency could complicate the interpretation of findings in the pooled analysis, considering the heterogeneity of exposure categorizations. Funnel plot and Doi plot showed presence of asymmetry for mortality outcome, indicating a possibility of publication bias. The implications of these observations are paramount. If publication bias is indeed present, our mortality estimates might be slightly inflated, as studies showing a stronger correlation between ALI and mortality might be overrepresented in our sample. Future research and meta-analyses on this topic should be aware of this potential bias and aim to include a broader range of studies to mitigate such effects.

4.4. Implications for practice

The findings of our review carry significant implications for clinical practice. Although it's widely known that patients with any liver pathology may experience adverse outcomes, the magnitude of risk was observed to nearly double in the presence of ALI. This underscores the crucial role of intensive care and additional attention for such patients who are most likely to experience severe morbidity and mortality. Therefore, healthcare providers should consider an early intervention with advanced lines of management to pre-emptively counter any potential adverse clinical outcomes.

From a clinical perspective, these findings could influence a series of management decisions for COVID-19 patients with ALI. Monitoring liver function tests more frequently, adjusting drug dosages that are metabolized by the liver, or considering alternative

therapeutic agents might become paramount for these patients. [55] Additionally, healthcare systems could consider creating specialized treatment pathways or guidelines to manage COVID-19 patients exhibiting signs of ALI, ensuring that they receive tailored care which addresses their unique risk profile.

4.5. Implications for future research

While our results provide crucial insights into the association of ALI and adverse COVID-19 outcomes, they also underscore the need for further investigation. In particular, a higher number of longitudinal studies are necessary to establish the temporality of association and the causal link between acute liver damage and COVID-19 related mortality. Such research would build on our work, providing key insights that could be instrumental in improving the management of COVID-19 patients and potentially preventing numerous fatalities worldwide. Consequently, a deeper understanding of the impact of ALI on COVID-19 outcomes may serve as a stepping stone towards better therapeutic strategies and improved patient prognosis in the face of this global pandemic.

Moreover, there remains a need for studies focusing on potential interventions that could mitigate the effects of ALI in COVID-19 patients, and whether early therapeutic interventions specifically targeting liver injury could alter the disease trajectory. Research should also look into the genetic, environmental, or pre-existing clinical factors that might predispose certain individuals to ALI upon contracting COVID-19.

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Ethical approval

This article does not contain any studies with human participants performed by any of the authors.

Informed consent

Not applicable.

Author contribution statement

Yuvaraj Krishnamoorthy: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
Monica Karunakaran, Karthika Ganesh: Performed the experiments; Analyzed and interpreted the data.
Vishnu Shankar Hariharan: Contributed analysis tools and data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

First Author Yuvaraj Krishnamoorthy is Associate Editor for Heliyon Journal.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20338.

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