REVIEW

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

Harapan Harapan1,2,3 | Jonny Karunia Fajar4 | Supriono Supriono5 | Gatot Soegiarto6 | Laksmi Wulandari7 | Fiha Seratin8 | Nyoman Gede Prayudi9 | Dara Puspita Dewi10 | Maria Theresia Monica Elsina11 | Lasarus Atamou11 |
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1Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
2Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
3Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia
4Brawijaya Internal Medicine Research Centre, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
5Department of Internal Medicine, Division of Gastro-Entero-Hepatology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
6Department of Internal Medicine, Division of Allergy & Immunology, Universitas Airlangga, Surabaya, Indonesia
7Department of Pulmonology and Respiratory Medicine, Universitas Airlangga, Surabaya, Indonesia
8Department of Paediatric, Faculty of Medicine, Universitas Padjajaran, Bandung, Indonesia
9Department of Urology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia
10Faculty of Public Health, Universitas Indonesia, Depok, Indonesia
11Faculty of Nursing, Universitas Indonesia, Depok, Indonesia
12Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia
13Faculty of Medicine, Universitas Indonesia, Depok, Indonesia
14Department of Nursing, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
15Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia
16Master Program of Biology, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Banda Aceh, Indonesia
17Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia
18Department of Internal Medicine, RSUD Bangil, Pasuruan, Indonesia
19Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
20Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

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.
The involvement of liver in SARS 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 and involves multiple organs including lung, kidney, heart, neurologic system, gastrointestinal system and liver. 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 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. The involvement of liver in SARS-CoV-2 infection is mystifying, 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.

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, liver involvement was reported to cause poor prognosis of COVID-19 patients. Moreover, liver involvement has been included in predicting the outcomes of patients with COVID-19. 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.

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 and involves multiple organs including lung, kidney, heart, neurologic system, gastrointestinal system and liver. 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 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. The involvement of liver in SARS-CoV-2 infection is mystifying, 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.

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METHODS

2.1 Study design and eligibility criteria

A systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis 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.

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; (6) the incidence of ALI; (6) the factors associated with ALI; and (7) severity and mortality rate of COVID-19 patients with and without ALI.
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. 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. 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. 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 (\( p < 0.10 \)). 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
### 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): $-125; 95\% \text{ CI}: -207, -43$, 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).

### 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

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**TABLE 1** Baseline characteristics of articles included in our analysis

| Author and years | Country | Study design | Study group comparation | Sample size | Quality (NOS) |
|------------------|---------|--------------|-------------------------|-------------|--------------|
| 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 | ALI           | Non-ALI         | Point estimate | 95%CI          | p Egger | p Het  | p-value |
|---------------------------------|-----|-------|---------------|----------------|----------------|----------------|---------|--------|---------|
| ALI prevalence                   | 16  | Random| 1254 (20.05)  | 4999 (79.94)   | 22.8%<sup>a</sup> | 14.1, 34.6     | 1.176   | <0.0001| <0.0001 |
| **ALI predictors**              |     |       |               |                |                |                |         |        |         |
| Age (years), mean ± SD          | 5   | Random| 55.2 ± 8.8    | 53.6 ± 10.2    | 1.76<sup>b</sup> | −3.26, 6.78    | 0.326   | 0.0030 | 0.4660  |
| Male, n (%)                     | 6   | Fixed | 194 (71.9)    | 1334 (48.5)    | 2.70<sup>c</sup> | 2.03, 3.60     | 0.172   | 0.318  | <0.0001 |
| BMI (kg/m²), mean ± SD          | 2   | Fixed | 28.5 ± 3.5    | 26.5 ± 4.9     | 2.63<sup>d</sup> | 0.97, 4.30     | <0.0001 | 0.3630 | 0.0020  |
| Diabetes mellitus, n (%)        | 6   | Fixed | 56 (20.7)     | 828 (30.1)     | 0.72<sup>e</sup> | 0.52, 0.99     | <0.0001 | 0.8450 | 0.0450  |
| Coronary artery disease, n (%)  | 4   | Fixed | 10 (9.7)      | 77 (10.4)      | 1.26<sup>f</sup> | 0.60, 2.63     | <0.0001 | 0.8520 | 0.5450  |
| Hypertension, n (%)             | 5   | Random| 105 (40.4)    | 1309 (48.5)    | 1.31<sup>g</sup> | 0.67, 2.54     | 0.5790  | 0.0220 | 0.4260  |
| Liver disease, n (%)            | 4   | Random| 15 (7.2)      | 110 (4.2)      | 2.98<sup>h</sup> | 1.00, 8.88     | 0.8400  | 0.0630 | 0.0500  |
| Leucocyte (cells/µl), mean ± SD | 3   | Random| 7983 ± 3953   | 5553 ± 1700    | 2432<sup>i</sup> | −89, 4954      | 0.4550  | <0.0001| 0.0590  |
| Neutrophils (cells/µl), mean ± SD| 3  | Random| 5556 ± 2833   | 3893 ± 1334    | 166<sup>j</sup> | −29, 362       | 0.4400  | <0.0001| 0.0970  |
| Lymphocytes (cells/µl), mean ± SD| 4  | Random| 1097 ± 128   | 1222 ± 89      | −125<sup>k</sup> | −207, −43      | 0.8610  | <0.0001| 0.0090  |

Prognosis

| Study group                     |     |       |               |                |                |                |         |        |         |
|---------------------------------|-----|-------|---------------|----------------|----------------|----------------|---------|--------|---------|
| Severe versus non severe        | 5   | Fixed | 140 (27.80)  | 97 (11.90)     | 3.61<sup>b</sup> | 2.60, 5.02     | 0.2810  | 0.2060 | <0.0001 |
| Mortality                       | 8   | Random| 252 (28.77)  | 445 (24.07)    | 1.38<sup>b</sup> | 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.

<sup>a</sup>Event rate.
<sup>b</sup>Odds ratio.
<sup>c</sup>Mean difference.

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 Supriono. Design: Jonny Karunia Fajar. Control/supervision: Supriono Supriono, Gatot Soegiarto, Laksmi Wulandari. Data collection/processing: Fiha Seratin, Nyoman Gede Prayudi, Daru Puspita Dewi, Maria Theresia Monica Elsina, Lasarus Atamou, Sinta Wiranata, Dhipto Pemi Aprianto, Erlin Friska, D. Fitria Sari Firdaus, Makdum Alaidin, Firdha Aprillia Wardhani, Nurdina Wahyu Hidayati, Yeni Hendriyanti, Kristia Wardani, Arde Evatta, Reizal Audi Manungan, Wiryawan Pradipo, Ade Rahmawati, Fredo Tamara, Aditya Indra Mahendra, Budi Santoso, Chandra Adi Irawan Primasaty, Nindy Tji tonganata, 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 Soe giarto, 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.

ORCID

Harapan Harapan https://orcid.org/0000-0001-7630-8413
Gatot Soe giarto https://orcid.org/0000-0002-9197-3873

References

1. Keam S, Megawati D, Patel SK, Tiwari R, Dhama K, Harapan H. Immunopathology and immunotherapeutic strategies in severe acute respiratory syndrome coronavirus 2 infection. Rev Med Virol. 2020;30:e2123. doi:10.1002/rmv.2123
2. Harapan H, Itoh N, Yufika A, et al. Coronavirus Disease 2019 (COVID-19): a literature review. J Infect Public Health. 2020;13:667-673. doi:10.1016/j.jiph.2020.03.019
3. Thakur V, Ratho RK, Kumar P, et al. Multi-organ involvement in COVID-19: beyond pulmonary manifestations. J Clin Med. 2021;10:446. doi:10.3390/jcm10030446
4. Carfi A, Bernabei R, Landi F, et al. Persistent symptoms in patients after acute COVID-19. J Am Med Assoc. 2020;324:603-605. doi:10.1001/jama.2020.12603
5. Chen TWD, Chen H, Yan W, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368:m1295. doi:10.1136/bmj.m1295
6. Zhou P, Yang X-L, Wang X-G, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-273.
7. Nguyen-Contant P, Embong AK, Kanagala P, et al. S protein-reactive IgG and memory B cell production after human SARS-CoV-2 infection includes broad reactivity to the S2 subunit. mBio. 2020;11. doi:10.1128/mBio.01991-20
8. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver involvement in patients with COVID-19: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5:667-678. doi:10.1016/s2468-1253(20)30126-6
9. Chen Y, Zhou X, Yan H, et al. CANTP Score: a tool to predict severe COVID-19 on admission. Front Med. 2021;8:608107. doi:10.3389/fmed.2021.608107
10. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Open Med 2009;3:e123-30.
11. European Association for the Study of the Liver. Electronic address easlofficce(easlofficece), Clinical Practice Guidelines Panel, et al. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66:1047-1081. doi:10.1016/j.jhep.2016.12.003
12. Stang A. Critical evaluation of the Newcastle–Ottawa Scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25:603-605. doi:10.1007/s10654-010-9491-z
13. Fabrini M, IImawan M, Fajar JK, et al. Persistence of long COVID symptoms in COVID-19 survivors worldwide and its potential pathogenesis: a systematic review and meta-analysis. Nam J. 2021;1:e36. doi:10.52225/narraj.v1i2.36
14. Bloom PP, Meyerowitz EA, Reinus Z, et al. Liver biochemistries in hospitalized patients with COVID-19. Hepatology. 2021;73:890-900. doi:10.1002/hep.33126
15. Cai Q, Huang D, Yu H, et al. COVID-19: abnormal liver function tests. J Hepatol. 2020;73:566-574. doi:10.1016/j.jhep.2020.04.006
16. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. Allergy. 2020;75:1742-1752. doi:10.1111/all.14309
17. Chen F, Chen W, Chen J, et al. Clinical features and risk factors of COVID-19-associated liver injury and function: a retrospective analysis of 830 cases. Ann Hepatol. 2021;21:100267. doi:10.1016/j.aohep.2020.09.011
18. Chow M, Tang Z, Radcliffe C, et al. Significant liver injury during hospitalization for COVID-19 is not associated with liver insufficiency or death. Clin Gastroenterol Hepatol. 2021;19:2182-2191. doi:10.1016/j.cgh.2021.05.022
19. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver functional abnormality. Clin Gastroenterol Hepatol. 2020;18:1561-1566. doi:10.1016/j.cgh.2020.04.002
20. Mishra K, Naffouj S, Gorgis S, et al. Liver injury as a surrogate for inflammation and predictor of outcomes in COVID-19. Hepatol Commun. 2021;5:24-32. doi:10.1002/hepc.41586
21. Phipps MM, Barraza LH, LaSota ED, et al. Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a large U.S. cohort. Hepatology. 2020;72:807-817. doi:10.1002/hep.31404
22. Piano S, Dalbeni A, Vettore E, et al. Abnormal liver function tests predict transfer to intensive care unit and death in COVID-19. Liver Int. 2020;40:2394-2406. doi:10.1111/liv.14565
23. Qi X, Liu C, Jiang Z, et al. Multicenter analysis of clinical characteristics and outcomes in patients with COVID-19 who develop liver injury. J Hepatol. 2020;73:455-458. doi:10.1016/j.jhep.2020.04.010
24. Sarin SK, Choudhury A, Lau GK, et al. Pre-existing liver disease is associated with poor outcome in patients with SARS CoV2 infection; the APCOLIS Study (APASL COVID-19 Liver Injury Spectrum Study). Hepatol Int. 2020;14:690-700. doi:10.1007/s12072-020-10072-8
25. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80:639-645. doi:10.1016/j.jinf.2020.03.019
26. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of non-ICU hospitalized patients with coronavirus disease 2019 and liver injury: a retrospective study. Liver Int. 2020;40:1321-1326. doi:10.1111/liv.14449
27. Gao Q, Bao L, Mao H, et al. Development of an inactivated vaccine candidate for SARS-CoV-2. Science. 2020;369:77-81. doi:10.1126/science.abc1932
28. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-1062. doi:10.1016/S0140-6736(20)30566-3
29. Ahmed J, Rizwan T, Malik F, et al. COVID-19 and liver injury: a systematic review and meta-analysis. Cureus. 2020;12:e9424. doi:10.7759/cureus.9424
30. Hamming I, Timens W, Bulthuis ML, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004;202:631-637. doi:10.1002/path.1570
31. Patel SK, Velkoska E, Burrell LM. Emerging markers in cardiovascular disease: where does angiotensin-converting enzyme 2 fit in? Clin Exp Pharmacol Physiol. 2013;40:551-559. doi:10.1111/1440-1681.12069
32. Mjaess G, Karam A, Aoun F, Alabisini S, Roumeguère T. COVID-19 and the male susceptibility: the role of ACE2, TMRSS2 and the androgen receptor. Prog Urol. 2020;30:484-487. doi:10.1016/j.purol.2020.05.007
33. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12:8. doi:10.1038/s41368-020-0074-x
34. Wu ZH, Yang DL. A meta-analysis of the impact of COVID-19 on liver dysfunction. Eur J Med Res. 2020;25:54. doi:10.1186/s40001-020-00454-x
35. Wong YJ, Tan M, Zheng Q, et al. A systematic review and meta-analysis of the COVID-19 associated liver injury. Ann Hepatol. 2020;19:627-634. doi:10.1016/j.aohep.2020.08.064
36. Sharma A, Jaiswal P, Kerakhan Y, et al. Liver disease and outcomes among COVID-19 hospitalized patients—a systematic review and meta-analysis. Ann Hepatol. 2021;21:100273. doi:10.1016/j.aohep.2020.10.001
37. Yang Z, Xu M, Yi JQ, et al. Clinical characteristics and mechanism of liver damage in patients with severe acute respiratory syndrome. Hepatobiliary Pancreat Dis Int. 2005;4:60-63.
38. Hojyo S, Uchida M, Tanaka K, et al. How COVID-19 induces cytokine storm with high mortality. Inflamm Regen. 2020;40:37. doi:10.1186/s41368-020-00146-3

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