Received: 9 May 2020 | Accepted: 20 May 2020

DOI: 10.1002/jmv.26055

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

COVID-19 and liver dysfunction: A systematic review and meta-analysis of retrospective studies

Mohanad Youssef[1] | Mohammad H Hussein[1] | Abdallah S Attia[1] | Rami M Elshazli[2] | Mahmoud Omar[1] | Ghassan Zora[1] | Ashraf S Farhoud[1] | Ahmad Elnahla[1] | Areej Shihabi[1] | Eman A Toraih[1,3] | Manal S Fawzy[4,5] | Emad Kandil MD, MBA, FACS, FACE[6]

[1]Department of Surgery, Tulane University, School of Medicine, New Orleans, Louisiana

[2]Department of Biochemistry and Molecular Genetics, Faculty of Physical Therapy, Horus University—Egypt, New Damietta, Egypt

[3]Genetics Unit, Department of Histology and Cell Biology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[4]Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

[5]Department of Biochemistry, College of Medicine, Northern Border University, Arar, Saudi Arabia

[6]Division of Endocrine and Oncologic Surgery, Department of Surgery, Tulane University, School of Medicine, New Orleans, Louisiana

Correspondence
Prof Emad Kandil, MD, MBA, FACS, FACE, Department of Surgery, Tulane University, School of Medicine, New Orleans, LA 70112, USA.
Email: ekandil@tulane.edu

Abstract

Recently, Coronavirus Disease 2019 (COVID-19) pandemic is the most significant global health crisis. In this study, we conducted a meta-analysis to find the association between liver injuries and the severity of COVID-19 disease. Online databases, including PubMed, Web of Science, Scopus, and Science direct, were searched to detect relevant publications up to 16 April 2020. Depending on the heterogeneity between studies, a fixed- or random-effects model was applied to pool data. Publication bias Egger's test was also performed. Meta-analysis of 20 retrospective studies (3428 patients), identified that patients with a severe manifestation of COVID-19 exhibited significantly higher levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin values with prolonged prothrombin time. Furthermore, lower albumin level was associated with a severe presentation of COVID-19. Liver dysfunction was associated with a severe outcome of COVID-19 disease. Close monitoring of the occurrence of liver dysfunction is beneficial in early warning of unfavorable outcomes.

KEYWORDS

COVID-19, liver function, meta-analysis, outcome, SARS-CoV-2

1 | INTRODUCTION

In December 2019, a novel virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as a causative pathogen for a cluster of pneumonia initially detected in Wuhan City, China.[1] As of 3 May 2020, the World Health Organization has reported Worldwide 3 267 184 confirmed cases and 229 971 deaths. The United States has reported 1 067 127 confirmed cases and 57 406 deaths.[2]

Coronavirus Disease 2019 (COVID-19) is typically characterized by the symptoms of viral pneumonia, such as fever, fatigue, dry cough, anosmia, and headache, which may evolve to respiratory failure.[3,4] The pathogen, however, displays a wide range of severity causing difficulty in determining infection outcome. COVID-19 may cause hepatic, intestinal, and respiratory diseases, and lead to respiratory distress syndrome, organ failure, and even death in severe cases.[5,6]

Currently, studies about the relationship between underlying mechanisms of COVID-19 and liver dysfunction are limited. COVID-19 uses the angiotensin-converting enzyme 2 (ACE2) as the binding site to enter the host cell in the lungs, kidneys, and heart.[7] Chai et al[8] found that both liver cells and bile duct cells express ACE2. However,

Abbreviations: ACE2, angiotensin-converting enzyme 2; AKI, acute kidney injury; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; COVID-19, Coronavirus Disease 2019; PT, prothrombin time; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SMD, the standardized mean difference; TSA, trial sequential analysis.

the ACE2 expression of bile duct cells is much higher than that of liver cells.[9] These findings suggest that liver injury in patients with COVID-19 may be the result of damage to bile duct cells. Various studies have reported the laboratory findings and the clinical characteristics associated with different degrees of liver dysfunction in patients with COVID-19 disease.[10-15]

However, to date, there is still limited research regarding the concomitant association between the COVID-19 and the hepatobiliary system. Therefore, by meta-analyzing data in the observational studies available so far, our study aimed to assess liver dysfunction among patients infected with SARS-CoV-2 to investigate the potential relationship between acute liver injury and COVID-19.

2 | METHODS

2.1 | Literature search strategy

A comprehensive literature review of all qualifying studies was conducted to identify the association of COVID-19 with acute liver injury based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16] Two authors (RE, MY) independently screened the following medical electronic database: PubMed, Web of Science, Scopus, and Science direct for relevant data published up to 16 April 2020, using a combination of the following keywords and medical subjects headings (MeSHs): ("COVID-19" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus SARS-CoV-2" OR "2019-nCoV" OR "Wuhan coronavirus" OR "Wuhan pneumonia") AND ("Liver" OR "Acute Liver injury" OR "Liver enzymes" Chronic Liver") AND ("outcome" OR "survival" OR "mortality" OR "complications" Or "infection"). The reference list of previous studies and systematic reviews were also searched for identifying eligible studies. The identified records were screened for the inclusion criteria specified for the present systematic review and meta-analysis.

2.2 | Eligibility criteria

We applied the following criteria to all extracted studies: (a) Types of studies: observational, retrospective cohort, prospective case-control, or clinical trials reporting laboratory features of COVID-19 patients, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, albumin, and prothrombin time (PT); (b) Subjects: diagnosed patients with COVID-19, and (c) Severity: mild cases of COVID-19 disease with patients that do not require extraordinary measures to manage the diseases and severe cases of COVID-19 infection who developed COVID-related complications such as acute respiratory distress syndrome (ARDS) and respiratory failure, or expired. Exclusion criteria were as follows: (a) duplicate data (b) case reports, series, abstract-only articles, conference article and comment, editorials and expert opinions (c) studies with insufficient outcome data, and (d) preprints (articles in the peer-review stage).

2.3 | Data extraction

Data extraction was conducted by four authors (MY, GZ, AA, and AF). The process included using a two-step approach: first, we screened titles and abstracts for eligibility according to the study objective, and second, we screened the full-text article of relevant abstracts.

2.4 | Quality assessment

The Newcastle-Ottawa Scale was used for assessing the quality of eligible manuscripts. Publication bias was assessed with the Newcastle-Ottawa Quality Assessment Scale cohort studies.[17]

2.5 | Pairwise comparison and heterogeneity assessment

The pooled estimates were extracted using RevMan version 5.3. Descriptive summary statistics in the form of mean, standard deviation, and range for continuous parametric measures were tabulated. Pairwise comparison between mild and severe COVID-19 patients was performed. Overall pooled odds ratio (OR) or standardized mean difference (SMD) with 95% confidence intervals (CI) were estimated for categorical and quantitative variables, respectively. A Fixed-effects model was employed unless significant heterogeneity was detected. In this case, the Random-effects model has applied.[18] Heterogeneity was considered significant if the I^2 value exceeds 50%, or its P value was less than .1.

Subgroup analyses by the location of the patients, publication date, sample size, and quality score were performed. Sensitivity analysis was carried out by removing one study each time, to reflect its effect size on the overall OR.

Publication bias was assessed via Begg's funnel plot and Egger's linear regression approach using Comprehensive Meta-analysis software.[19] An asymmetric funnel-shape or a P value less than .1 indicated significant bias.[20]

2.6 | Meta-regression analysis

Meta-regression analysis was employed using OpenMeta Analyst software, taking into consideration the following study characteristics; sample size, mean age of patients, percentage of males, city of the hospital, publication date, and quality score.

2.7 | Trial sequential analysis

To evaluate the reliability of statistical appraisal of this meta-analysis study, we used trial sequential analysis (TSA) software (version 0.9.5.10 beta) by merging several available sample sizes of applicable studies with the threshold of statistical influence to reduce the

unintentional miscalculations and improve the strength of anticipations. We used two-side trials and type I error with a calculated power of 5% and 80%. If the cumulative Z-curve crosses the monitoring boundaries, no additional trials would be required. On the contrary, if the Z-curve did not accomplish the boundary levels, the necessary threshold requires additional records to achieve a prominent significance.

3 | RESULTS

3.1 | Characteristics of the included studies

Following the removal of duplicates (n = 1870), our database search identified 2582 unique citations, of which 186 full-text articles were assessed. A total of 20 eligible retrospective cohort studies, including 3428 positively confirmed COVID-19 patients, were enrolled in the current meta-analysis. The workflow of the process of study selection is demonstrated in Figure 1. All articles were published during the period between 30 January and 16 April 2020. Most of them were from Wuhan city (13), three from Zhejiang, one from Guangdong, one from Hubei, one from Guangdong, and one from Anhui. As depicted in Table 1, the sample size of studies ranged from 21 to 651 cohorts. The mean age of patients was 53.8 years, and 57.8% were men. In the included studies, the severe disease was detected in 36.2% of patients and the average survival rate was 72.18%. All studies except for three scored more than 5 on the scale. Two studies scored a three, and one study scored a two.

3.2 | Pooled analysis of laboratory findings

Table 2 summarizes pairwise comparison, heterogeneity analysis, and publication bias of the meta-analysis. Patients who had severe

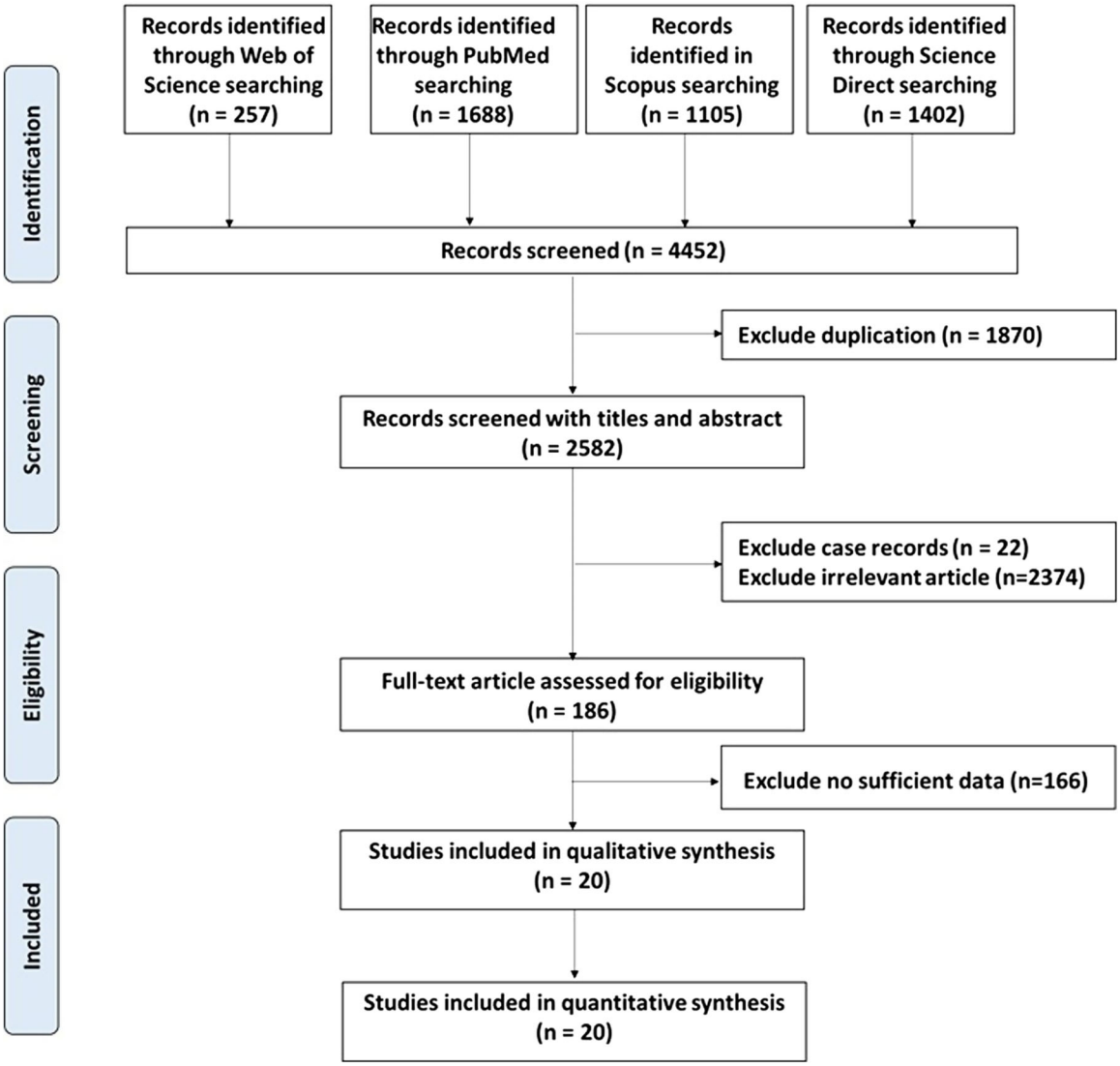

FIGURE 1 The workflow of the selection process

TABLE 1 Characteristics of the included studies

Author	Date of publication	Year	Ref	Journal name	Study	Country	City	Sample Size	Mean age	Male/female	Severe cases (%)	Survival rate (%)	Quality score
Huang[4]	30 Jan	2020	[4]	The Lancet	Retro	China	Wuhun	41	49	30/11	31.7	85.37	7
Wang[21]	7 Feb	2020	[21]	JAMA	Retro	China	Wuhun	138	58.5	75/63	26.1	NA	5
Yang[22]	21 Feb	2020	[22]	The Lancet	Retro	China	Wuhun	52	58.25	35/17	61.5	38.46	6
Liu[23]	28 Feb	2020	[23]	Chin Med J (Engl)	Retro	China	Wuhun	78	51.5	39/39	14.1	NA	5
Ruan[24]	3 Mar	2020	[24]	Intensive Care Med	Retro	China	Wuhun	150	58.5	102/48	45.3	54.67	5
Zhou[25]	11 Mar	2020	[25]	The Lancet	Retro	China	Wuhun	191	60.5	119/72	28.3	71.73	8
Gao[11]	13 Mar	2020	[11]	J Med Virol	Retro	China	Anhui	43	44	26/17	34.9	NA	5
Wu[14]	13 Mar	2020	[14]	JAMA Intern Med	Retro	China	Wuhun	201	53.25	128/73	41.8	78.11	5
Zhang[15]	15 Mar	2020	[15]	Int J Infect Dis	Retro	China	Zhejiang	645	40.77	328/317	88.8	NA	7
Mo[10]	16 Mar	2020	[10]	Clin Infect Dis	Retro	China	Wuhun	155	53.5	86/69	54.8	NA	5
Wang[26]	16 Mar	2020	[26]	Clin Infect Dis	Retro	China	Wuhun	69	53.75	32/37	20.3	92.75	8
Chen[12]	17 Mar	2020	[12]	BMJ	Retro	China	Wuhun	274	59.5	171/103	41.2	58.76	8
Qian[27]	17 Mar	2020	[27]	QJM	Retro	China	Zhejiang	91	57.5	37/54	9.9	NA	3
Qu[28]	17 Mar	2020	[28]	J Med Virol	Retro	China	Guangdong	30	54.72	NA	10.0	NA	2
Deng[29]	20 Mar	2020	[29]	Chin Med J (Engl)	Retro	China	Wuhun	225	54.5	124/101	48.4	51.56	7
Wan[30]	21 Mar	2020	[30]	J Med Virol	Retro	China	Chongqing	135	50	72/63	29.6	99.26	8
Jin[31]	24 Mar	2020	[31]	Gut	Retro	China	Zhejiang	651	45.61	331/320	11.4	NA	8
Chen[13]	27 Mar	2020	[13]	J Clin Invest	Retro	China	Wuhun	21	56.5	17/4	52.4	80.95	6
Pan[32]	14 Apr	2020	[32]	Am J Gastroenterol	Retro	China	Hubei	204	52.9	107/97	50.5	82.35	7
Zhou[33]	16 Apr	2020	[33]	J Infect	Retro	China	Wuhun	34	65	17/17	23.5	NA	3

Abbreviations: Ref, reference number; Retro, retrospective.

TABLE 2 Summarizing results of pooled estimates of liver function tests and clinical parameters of chronic liver patients

Characteristics	Number studies	Sample size			Test of association		Effect size			Heterogeneity		Publication bias
		Total	Mild	Severe	Method	Model	Estimate	95% CI	*P* value	I^2	*P* value	P (Egger's)
Laboratory tests												
ALT	19	3376	1953	1423	SMD, IV	Fixed	0.35	0.27, 0.43	.073	34.13%	<.001	0.279
AST	19	3376	1953	1423	SMD, IV	Random	0.44	0.17, 0.70	<.001	88.80%	.001	0.940
Bilirubin	11	2512	1365	1147	SMD, IV	Random	0.41	0.20, 0.62	<.001	75.02%	<.001	0.773
Albumin	11	2605	1434	1171	SMD, IV	Random	−0.84	−1.20, −0.48	<.001	91.4%	<.001	0.204
PT	10	1300	799	501	SMD, IV	Random	0.62	0.32, 0.91	<.001	81.34%	<.001	0.512
Comorbidities												
Hypertension	13	2141	1024	1117	OR, M-H	Fixed	2.36	1.86, 3.01	.30	14.01%	<.001	0.976
Chronic kidney dis	7	1675	690	985	OR, M-H	Fixed	7.28	3.25, 16.26	.54	0.00%	<.001	0.279
Diabetes	14	2193	1044	1149	OR, M-H	Fixed	2.72	2.05, 3.60	.05	41.58%	<.001	0.453
Cardiovascular dis	12	2327	1086	1241	OR, M-H	Random	5.11	2.03, 12.83	<.001	77.27%	<.001	0.061
Chronic liver dis	9	1659	685	974	OR, M-H	Fixed	1.17	0.66, 2.06	.87	0.00%	.58	0.824
Malignancy	12	2132	990	1142	OR, M-H	Fixed	2.20	1.28, 3.77	.90	0.00%	.004	0.890
Cerebrovascular dis	5	769	435	334	OR, M-H	Fixed	5.73	2.52, 13.04	.20	32.59%	<.001	0.041
Treatment												
Antiviral	10	1685	1002	683	OR, M-H	Random	0.70	0.42, 1.16	.16	62.06	<.001	0.52
Antibiotics	7	1991	1387	604	OR, M-H	Random	2.13	0.86, 5.29	.10	81.93	<.001	0.64
Glucocorticoids	13	2981	1651	1330	OR, M-H	Random	3.17	2.03, 4.97	<.001	73.41	<.001	0.49
Immunoglobulins	6	1101	605	496	OR, M-H	Random	2.75	1.09, 6.94	.032	89.10	<.001	0.32
Outcomes												
ARDS	9	2204	1230	974	OR, M-H	Random	18.84	5.39, 65.87	<.001	89.58%	<.001	0.106
AKI	6	1300	516	784	OR, M-H	Random	7.20	1.38, 37.74	.003	71.59%	<.001	0.511
Sepsis	5	1259	488	771	OR, M-H	Random	21.19	4.21, 106.73	.085	50.99%	<.001	0.680
Acute liver injury	2	1296	649	647	OR, M-H	Fixed	1.93	1.11, 3.34	.60	0.00%	.001	NA
Myocardial injury	3	464	334	130	OR, M-H	Random	11.19	0.44, 285.9	<.001	90.44%	<.001	0.408
Mortality	11	1563	922	641	OR, M-H	Random	55.22	12.62, 241.66	<.001	90.82%	<.001	0.282

Abbreviations: AKI, acute kidney injury; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; CI, confidence interval; I^2, the ratio of true heterogeneity to total observed variation; IV, inverse variance; M-H, Mantel-Haenszel; OR, odds ratio; PT, prothrombin time; SMD, standardized mean difference.

presentations of COVID disease had higher levels of AST (SMD = 0.36; 95% CI = 0.27; 0.44; $P < .001$), ALT (SMD = 0.44; 95% CI = 0.35, 0.52; $P < .001$), bilirubin (SMD = 0.40; 95% CI = 0.31, 0.50; $P < .001$), and PT (SMD = 0.69; 95% CI = 0.57, 0.81; $P < .001$). In contrast, lower albumin level was associated with severe presentation (SMD = −0.68; 95% CI = −0.7, −0.58; $P < .001$) (Figure S1). Apart from ALT data, significant heterogeneity was detected in laboratory results. Subgroup analysis by the origin of the hospital, publication date, sample size, and quality score of the studies failed to resolve the obvious heterogeneity.

3.3 | Pooled analysis of comorbidities

The analysis showed that patients with hypertension (OR = 2.37; 95% CI = 1.86-3.01; $P < .001$), chronic kidney disease (OR = 7.28; 95% CI = 3.26-16.26; $P < .001$), and diabetes (OR = 2.72; 95% CI = 2.06-3.61; $P < .001$) were nearly twofold more risk to develop severe presentation of COVID-19. Patients with underlying cardiovascular disease or cerebrovascular disease were five-times more liable to develop severe phenotype (OR = 5.11; 95% CI = 2.04-12.83; $P < .0001$ and OR = 5.73; 95% CI = 2.52-13.04; $P < .0001$, respectively). Cancer patients also exhibited severe manifestations of the disease (OR = 2.20; 95% CI = 1.28-3.78; $P = .004$) (Figure S2). Apart of cardiovascular disease, homogeneity between studies was detected.

3.4 | Pooled analysis of treatment

A total of 17 studies reported treatment to be administered to COVID-19 patients. On comparison between the two groups, severe patients were nearly three times more likely to receive steroids (OR = 3.17; 95% CI = 3.02-4.97; $P < .001$) and immunoglobulins (OR = 2.75; 95% CI = 1.09-6.94; $P = .032$). Sensitivity analysis revealed that the studies of Wang[21] and Zhang[15] contributed in the significant heterogeneity observed in treatment results (Table 2).

3.5 | Pooled analysis of COVID-19 outcomes

Our analysis confirmed that patients with severe COVID-19 disease had higher odds of developing ARDS (OR = 18.84; 95% CI = 5.39-65.87; $P < .0001$) and sepsis (OR = 21.19; 95% CI = 4.21-106.7; $P < .001$). Similarly, acute liver injury (OR = 1.93; 95% CI = 1.12-3.34; $P = .001$) and acute kidney injury (OR = 7.2; 95% CI = 1.38-37.74; $P < .001$) were more prevalent among patient with severe disease. Moreover, our analysis revealed that mortality was more likely to occur among patients with severe COVID-19 patients (OR = 55.22; 95% CI = 12.62-241.66; $P < .001$) (Figure S3). Considerable heterogeneity was observed for the outcomes. Meta-regression analysis for study characteristics showed higher odds of mortality in articles involving Wuhun hospitals (coefficient = 4.30; 95% CI = 3.07-5.54; $P < .001$) (Table S1).

3.6 | Publication bias

The funnel plot of laboratory and clinical parameters is shown in Figure S4. Egger's test showed no publication bias for all variables ($P > .1$) except for two; cardiovascular and cerebrovascular diseases ($P = .061$ and $.041$) (Table 2).

3.7 | Trial sequential analysis

We applied TSA on mortality rate available among all eligible articles of COVID-19 patients with a mild and severe exhibition and indicated that the cumulative Z-curve transverses the monitoring boundaries before reaching the required sample size and achieving considerable significant and so no further studies are necessary (Figure 2).

4 | DISCUSSION

Our meta-analysis including 3428 subjects from 20 retrospective studies explored the potential relationship between liver injury and the severity of COVID-19 disease. We found that liver dysfunction seemed to be higher in patients with severe outcomes from COVID-19 infection.

Our results were in agreement with a previous study review.[36] Previously, liver injury has been reported as an important risk factor for severe outcome and death in SARS and Middle East Respiratory Syndrome.[35,37-39]

Patients in our study who had severe presentations of COVID-19 disease had higher levels of AST, ALT, bilirubin, and lower albumin levels. Our results are consistent with recent studies on COVID-19 disease that showed that the incidence of liver injury ranged from 58% to 78%, mainly indicated by elevated AST, ALT, and total bilirubin levels accompanied by slightly decreased albumin levels.[40,41] In a recent study, Guan et al[42] documented that higher serum levels of AST were observed in nearly 18% of patients with nonsevere COVID-19 disease and approximately 56% of patients with severe COVID-19 infection. Moreover, in that study, higher serum levels of ALT were also observed in nearly 20% of patients with nonsevere COVID-19 presentation, and approximately 28% of patients with severe COVID manifestation.[42] Similar findings in Huang et al[4] were also observed, where patients with severe COVID-19 features had an increased incidence of liver injury.

Postmortem liver biopsies specimens were observed in deceased COVID-19 patients. The findings showed mild lobular and portal activity along with microvascular stenosis, indicating the injury could have been caused by either COVID-19 disease or drug-induced liver injury.[3] Similar to the treatment of SARS, steroids, antivirals, and antibiotics are widely used for the treatment of COVID-19.[34,43,44] These drugs are all potential causes of liver injury during COVID-19 treatment but have not yet been evident.[22] A recent study reported that the liver injury observed in COVID-19 patients might be caused

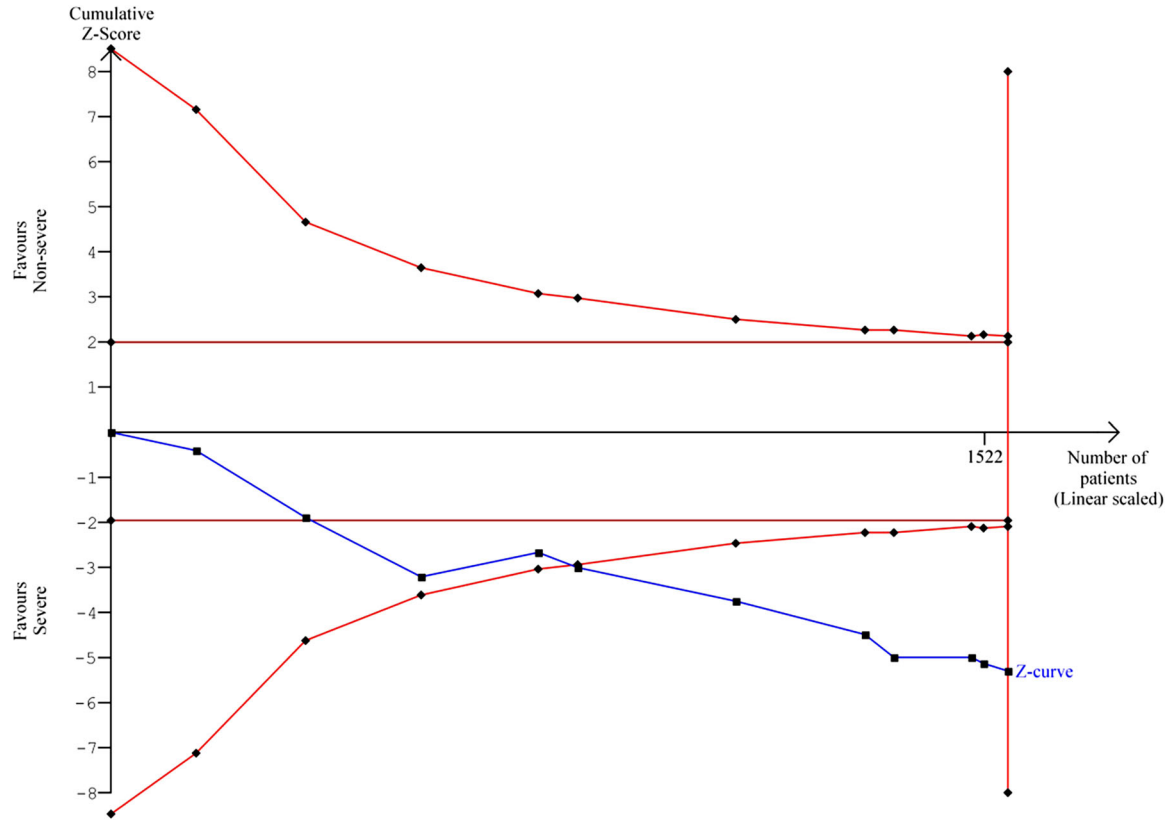

FIGURE 2 Trial sequential analysis for mortality

by lopinavir, which is used as an antiviral for the treatment of SARS-CoV-2 infection.[45] It is worth noting that the specific underlying causes of liver injury and elevated levels of liver enzymes in COVID-19 patients are still limited. However, collectively the proposed mechanisms might include "hyperactivated immune responses and cytokine storm-related systemic inflammation, psychological stress, drug toxicity, and progression of pre-existing liver diseases" as detailed by Li and Fan.[46]

Further studies are needed to investigate the mechanisms of liver dysfunction in COVID-19 disease as a direct outcome of infection and the possible effects that treatment has on the liver.

Limitations of our study include the following; First, all the studies included in this meta-analysis used a case-control or cohort design, which are susceptible to recall and selection biases. Second, we could not distinguish if the liver dysfunction in COVID-19 patients was an acute liver injury or exacerbated chronic liver disease. Last, the enrolled studies focused on Chinese patients, which restricted a more precise estimation of liver dysfunction in the context of other races.

5 | CONCLUSIONS

In this meta-analysis, we comprehensively analyzed liver dysfunction in accordance with the severity of clinical outcomes in COVID-19 patients. Liver dysfunction was associated with severe COVID-19 infection. Patients presented with abnormal liver function tests are at higher risk of severe clinical outcomes. Close monitoring of the presence of liver dysfunction may be beneficial as an early indicator of worse outcomes. This may serve to better prepare the treatment of patients.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

MY, ASA, RE: study design; MY, ASA, MO, GZ, AE, AS: study identification and data extraction; MH, RE, EAT: statistical analysis; MH, RE, EAT, MSF: data interpretation; MY, ASA, RE, MO, GZ, AF, EAT, MSF: original draft preparation. All authors revised and approved the final version of the manuscript.

ORCID

Mohammad H Hussein https://orcid.org/0000-0001-8278-7094
Abdallah S Attia https://orcid.org/0000-0003-2163-0637
Rami M Elshazli http://orcid.org/0000-0002-3381-2641
Mahmoud Omar http://orcid.org/0000-0001-7917-7973
Ghassan Zora https://orcid.org/0000-0002-4586-1918
Ahmad Elnahla https://orcid.org/0000-0002-6973-5561
Eman A Toraih http://orcid.org/0000-0001-9267-3787
Manal S Fawzy http://orcid.org/0000-0003-1252-8403

REFERENCES

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513. https://doi.org/10.1016/S0140-6736(20)30211-7
2. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation Report—84. *World Heal Organ*. 2020;323:1122. https://doi.org/10.1001/jama.2020.2633
3. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8:420-422. https://doi.org/10.1016/S2213-2600(20)30076-X
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395:497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
5. Peiris J, Lai S, Poon L, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet*. 2003;361:1319-1325. https://doi.org/10.1016/S0140-6736(03)13077-2
6. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382:727-733. https://doi.org/10.1056/NEJMoa2001017
7. Hoffmann M, Kleine-Weber H, Krueger N, Mueller MA, Drosten C, Poehlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. *bioRxiv*. 2020. https://doi.org/10.1101/2020.01.31.929042
8. Chai X, Hu L, Zhang Y, et al. Specific ACE2 expression in cholangiocytes may cause liver damage after 2019-nCoV Infection. *bioRxiv*. 2020. https://doi.org/10.1101/2020.02.03.931766
9. Banales JM, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol*. 2019;16:269-281. https://doi.org/10.1038/s41575-019-0125-y
10. Mo P, Xing Y, Xiao Y, et al. Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China. *Clin Infect Dis*. 2020. https://doi.org/10.1093/cid/ciaa270
11. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol*. 2020:jmv.25770. https://doi.org/10.1002/jmv.25770
12. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020:m1091. https://doi.org/10.1136/bmj.m1091
13. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest*. 2020;130:2620-2629. https://doi.org/10.1172/JCI137244
14. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020. https://doi.org/10.1001/jamainternmed.2020.0994
15. Zhang X, Cai H, Hu J, et al. Epidemiological, clinical characteristics of cases of SARS-CoV-2 infection with abnormal imaging findings. *Int J Infect Dis*. 2020;94:81-87. https://doi.org/10.1016/j.ijid.2020.03.040
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097. https://doi.org/10.1371/journal.pmed.1000097
17. 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. https://doi.org/10.1007/s10654-010-9491-z
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
19. Pierce CA, Software Review: Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2007). Comprehensive Meta-Analysis (Version 2.2.027) [Computer software]. Englewood, NJ: Biostat. Organizational Research Methods, 2008. 11(1): p. 188-191. https://doi.org/10.1177/1094428106296641
20. Elshazli RM, Toraih EA, Elgaml A, Kandil E, Fawzy MS. Genetic polymorphisms of TP53 (rs1042522) and MDM2 (rs2279744) and colorectal cancer risk: an updated meta-analysis based on 59 case-control studies. *Gene*. 2020;734:144391.
21. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA—J Am Med Assoc*. 2020;323:1061. https://doi.org/10.1001/jama.2020.1585
22. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8:475-481. https://doi.org/10.1016/S2213-2600(20)30079-5
23. Liu W, Tao ZW, Wang L, et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. *Chin Med J (Engl)*. 2020;133:1032-1038. https://doi.org/10.1097/CM9.0000000000000775
24. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46:846-848. https://doi.org/10.1007/s00134-020-05991-x
25. 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. https://doi.org/10.1016/S0140-6736(20)30566-3
26. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical features of 69 cases with Coronavirus Disease 2019 in Wuhan, China. *Clin Infect Dis*. 2020;ciaa272. https://doi.org/10.1093/cid/ciaa272
27. Qian GQ, Yang NB, Ding F, et al. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-centre case series. *QJM*. 2020;113:474–481. https://doi.org/10.1093/qjmed/hcaa089
28. Qu R, Ling Y, Zhang Y, et al. Platelet-to-lymphocyte ratio is associated with prognosis in patients with coronavirus disease-19. *J Med Virol*. 2020:jmv.25767. https://doi.org/10.1002/jmv.25767
29. Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 (COVID-19) in Wuhan, China: a retrospective study. *China Med J (Engl)*. 2020:1. https://doi.org/10.1097/CM9.0000000000000824
30. Wan S, Xiang Y, Fang W, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. *J Med Virol*. 2020;92:797–806. https://doi.org/10.1002/jmv.25783
31. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. *Gut*. 2020;69:1002-1009. https://doi.org/10.1136/gutjnl-2020-320926
32. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a Descriptive, cross-sectional, multicenter study. *Am J Gastroenterol*. 2020;115:766-773. https://doi.org/10.14309/ajg.0000000000000620
33. Zhou B, She J, Wang Y, Ma X. The clinical characteristics of myocardial injury in severe and very severe patients with 2019 novel coronavirus disease. *J Infect*. 2020;81:147–178. https://doi.org/10.1016/j.jinf.2020.03.021
34. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. *Liver Int*. 2020;40:998-1004. https://doi.org/10.1111/liv.14435
35. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis*. 2014;29:301-306. https://doi.org/10.1016/j.ijid.2014.09.003
36. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East re-

spiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis*. 2013;13:752-761. https://doi.org/10.1016/S1473-3099(13)70204-4
37. Al-Hameed F, Wahla AS, Siddiqui S, et al. Characteristics and outcomes of middle east respiratory syndrome coronavirus patients admitted to an intensive care unit in Jeddah, Saudi Arabia. *J Intensive Care Med*. 2014;31:344-348. https://doi.org/10.1177/0885066615579858
38. Chang HL, Chen KT, Lai SK, et al. Hematological and biochemical factors predicting SARS fatality in Taiwan. *J Formos Med Assoc*. 2006;105:439-450. https://doi.org/10.1016/S0929-6646(09)60183-2
39. Huang Y, Zhou H, Yang R, Xu Y, Feng X, Gong P. Clinical characteristics of 36 non-survivors with COVID-19 in Wuhan, China. *medRxiv*. 2020. https://doi.org/10.1101/2020.02.27.20029009
40. Zhang B, Zhou X, Qiu Y, et al. Clinical characteristics of 82 death cases from COVID-19. *PLoS ONE*. 2020;15:e0235458. https://doi.org/10.1371/journal.pone.0235458
41. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382:1708-1720. https://doi.org/10.1056/NEJMoa2002032
42. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400-402. https://doi.org/10.1016/S1473-3099(20)30132-8
43. Little P. Non-steroidal anti-inflammatory drugs and covid-19. *BMJ*. 2020;368:m1185. https://doi.org/10.1136/bmj.m1185
44. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNAdependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem*. 2020;295:4773-4779. https://doi.org/10.1074/jbc.AC120.013056
45. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. *SSRN Electron J*. 2020. https://doi.org/10.2139/ssrn.3546077
46. Li J, Fan JG. Characteristics and Mechanism of Liver Injury in 2019 Coronavirus Disease. *J Clin Transl Hepatol*. 2020;8(1):13-17. https://doi.org/10.14218/JCTH.2020.00019

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Youssef M, Hussein M, Attia AS, et al. COVID-19 and liver dysfunction: A systematic review and meta-analysis of retrospective studies. *J Med Virol*. 2020;92:1825–1833. https://doi.org/10.1002/jmv.26055