Review

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Blood biochemical characteristics of patients with coronavirus disease 2019 (COVID-19): a systemic review and meta-analysis

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Abstract

Objectives: Recently, there have been several studies on the clinical characteristics of patients with coronavirus disease 2019 (COVID-19); however, these studies have mainly been concentrated in Wuhan, China; the sample sizes of each article were different; and the reported clinical characteristics, especially blood biochemical indices, were quite different. This study aimed to summarize the blood biochemistry characteristics of COVID-19 patients by performing a systemic review and meta-analysis of published studies.

Methods: Comprehensive studies were screened from PubMed, Embase, and Cochrane Library through March 11, 2020. The inclusion criteria included studies investigating the biochemical indexes of patients with COVID-19. The statistical software R3.6.3 was used for meta-analysis.

Results: Ten studies including 1745 COVID-19 patients met the inclusion criteria for our meta-analysis. Meta-analysis showed that 16% and 20% of patients with COVID-19 had alanine transaminase (ALT) and aspartate aminotransferase (AST) levels higher than the normal range, respectively. Thirty-four percent of patients showed albumin (ALB) levels lower than the normal range, and 6% of patients showed abnormal total bilirubin (TBil) levels. The levels of creatinine (CRE) were increased in 8% of patients. The creatine kinase (CK) level of 13% of patients exceeded the normal range, and 52% of patients had elevated lactate dehydrogenase (LDH) levels. In addition, six studies met the inclusion criteria for the systemic review evaluating the relevance between LDH levels and the severity of COVID-19, and all six studies showed a positive association between these two factors.

Conclusions: Some patients with COVID-19 had different degrees of blood biochemical abnormalities, which might indicate multiple organ dysfunction. Some biochemical indexes, such as abnormal ALB and LDH, could reflect the severity of the disease to a certain extent. These blood biochemical indicators should be considered in the clinical management of the disease.

Keywords: biochemical characteristics; coronavirus disease 2019; meta-analysis; systemic review.

Introduction

At the end of 2019, a cluster of pneumonia cases caused by a novel coronavirus (2019-nCov) were detected in Wuhan, China. Its rapid spread and progression and lack of specific therapeutic strategy resulted in an epidemic [1]. Soon after, this novel virus became a global concern; on January 30, 2020, the World Health Organization (WHO) declared that the epidemic of 2019-nCoV was a public health emergency of international concern (PHEIC), and on February 11, 2020, the WHO designated the disease coronavirus disease 2019 (COVID-19). At present, although the outbreaks in China appear to be under control, the number of confirmed cases is still increasing globally. As of March 11, 2020, 80,955 cases with COVID-19 have been confirmed in China, and 37,364 cases have been confirmed in more than 100 other countries [2]. In addition to the incidence and transmission characteristics, the clinical characteristics and fatality rate of patients, especially severe patients, have been a concern.

Several studies have reported the clinical manifestations and blood biochemical features of patients with COVID-19 [3–5]. However, there were certain differences in the results due to the different designs of studies and insufficient sample sizes. As blood biochemical changes

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play an essential role in estimating the patients' condition and prognosis, directing treatment, and even evaluating the curative effect, we aim to conduct a systematic review and meta-analysis of the published studies to obtain more persuasive conclusions on the biochemical characteristics of patients with COVID-19.

Materials and methods

Search strategy

Two authors independently searched published studies in PubMed, Embase, and Cochrane Library through March 11, 2020, with no language restrictions. The keywords included: ("2019 novel coronavirus" OR "2019-nCoV" OR "COVID-19") AND ("clinical characteristics" OR "clinical features" OR "biochemical").

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies investigating the clinical and blood biochemical characteristics of COVID-19 patients and (2) studies with sufficient data on biochemical indexes in patients with COVID-19.

The exclusion criteria were as follows: (1) reviews, case reports, letters, comments, or non-human studies; (2) studies about neonates, pregnant women, and children; and (3) studies lacking relevant data.

Data extraction and quality assessment

Data were extracted independently using a predefined data extraction form by two investigators. We extracted the following information from each included study: (1) the study's general characteristics, including the first author's name and country; (2) subject characteristics, including the number of cases, age, and sex; (3) abnormal blood biochemical levels, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), total bilirubin (TBil), blood urea nitrogen (BUN), creatinine (CRE), creatine kinase (CK), and lactate dehydrogenase (LDH).

The quality of each study was independently assessed by two investigators using the Newcastle-Ottawa Scale (NOS) [6]. Studies with seven stars or more were identified as high quality, those with between five and seven stars were identified as moderate quality, and those with fewer than five stars were identified as low quality.

Statistical analysis

All statistical analyses were performed using R3.6.3 software (Wolfgang Viechtbauer). The "meta" package was applied to calculate the proportion of patients with abnormal biochemical parameters resulting from COVID-19, and data are shown in the forest plot. The I^2 statistic was used to ascertain the heterogeneity, and I^2 values of 0–25%, 25–50%, 50–75%, and >75% indicated insignificant, low, moderate, and high heterogeneity, respectively [7]. A random-effect model was chosen if the heterogeneity was moderate or high; otherwise, a fixed-effect model was selected [8].

Three univariate meta-regression analyses were used for exploring the potential source of heterogeneity: (1) female proportion; (2) age; and (3) the number of cases. Publication bias was assessed using a funnel plot. Egger's test was not performed in the meta-analysis of each biochemical index due to the inclusion of fewer than 10 studies [9].

Additionally, a meta-analysis about the differences in LDH levels between non-severe and severe patients was not performed because the included studies only provided the median value of LDH and had different reference ranges due to different detection methods.

Results

Analysis of the included literature

According to the inclusion and exclusion criteria, 10 studies were included, and data were extracted from 1745 patients for meta-analysis [10–19]. The flow diagram for inclusion and exclusion of studies is shown in Figure 1. Among the studies, seven were about ALT abnormalities, nine were about AST abnormalities, six were about ALB abnormalities, seven were about TBil abnormalities, four were about BUN abnormalities, nine were about serum CRE abnormalities, and eight were about CK and LDH abnormalities. The detailed characteristics of the studies are shown in Tables 1 and 2.

Additionally, to review the differences in LDH levels between non-severe and severe patients, data were extracted from six studies including 497 patients based on the inclusion and exclusion criteria [15, 16, 20–23]. The clinical parameters of the studies are presented in Table 3.

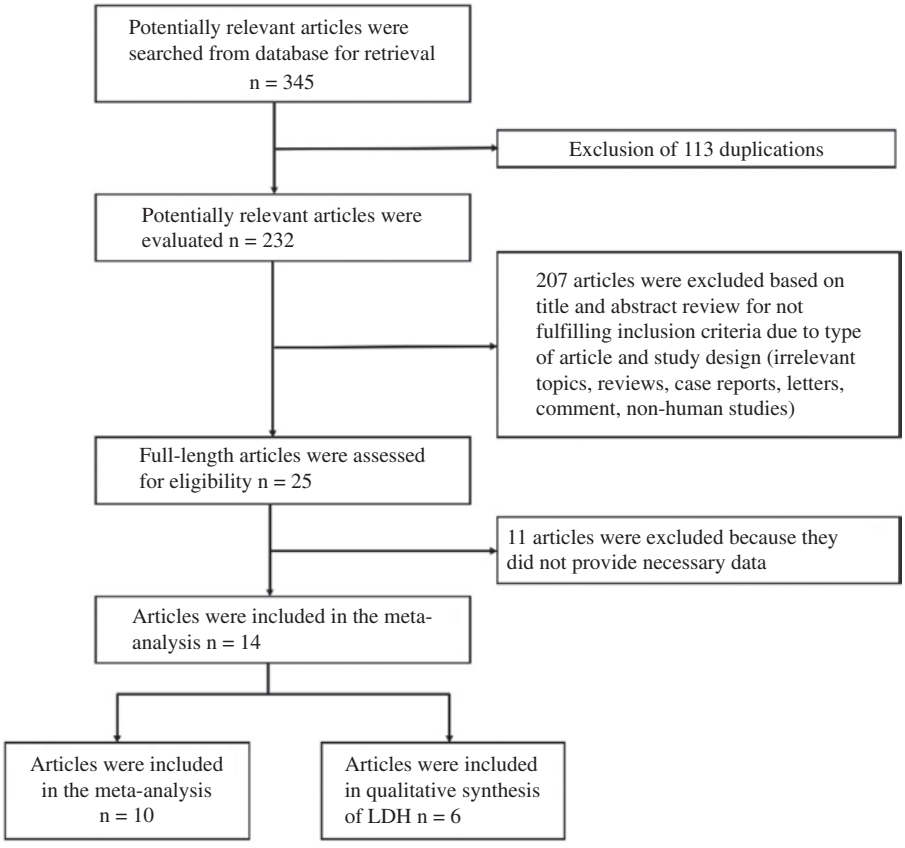

Figure 1: Flow diagram for the inclusion of studies in the meta-analysis and qualitative synthesis of LDH.

Quantitative synthesis of ALT and AST abnormalities

Seven studies and 1144 patients with COVID-19 were included in the meta-analysis, and 222 patients showed ALT abnormalities. The overall proportion of ALT abnormalities in patients with COVID-19 was 0.16 (95% CI: 0.10–0.24). As the heterogeneity among studies was high ($I^2 = 81.0\%$, $p < 0.01$), a random-effect model was selected for the analysis (Figure 2).

A total of 1263 patients with COVID-19 were included from nine studies, and 274 patients showed AST abnormalities in the meta-analysis. The overall proportion of AST abnormalities among patients was 0.20 (95% CI: 0.14–0.27). As the heterogeneity was high ($I^2 = 80.0\%$, $p < 0.01$), a random-effect model was chosen (Figure 3).

Quantitative synthesis of albumin abnormalities

To evaluate ALB abnormalities in patients with COVID-19, six studies and 403 patients were included, and 151 patients presented a decrease in ALB. The overall proportion of ALB abnormalities was 0.34 (95% CI: 0.19–0.59). As the heterogeneity test indicated high heterogeneity ($I^2 = 96.0\%$, $p < 0.01$), a random-effect model was used (Figure 4).

Quantitative synthesis of total bilirubin abnormalities

A total of 1125 patients with COVID-19 from seven studies were included in the meta-analysis, and 103 cases showed an increase in TBil. The overall proportion of TBil abnormalities was 0.06 (95% CI: 0.02–0.11). Because the heterogeneity among studies was high ($I^2 = 81.0\%$, $p < 0.01$), a random-effect model was adopted for the analysis (Figure 5).

Quantitative synthesis of urea nitrogen and creatinine abnormalities

To assess renal function in patients with COVID-19, BUN and serum CRE abnormalities were analyzed. Four studies and 357 patients were included, and 13 patients from three

Table 1: Main characteristics of the included studies.

Characteristics	Chen [10]	Chen [11]	Huang [12]	Yang [13]	Wu [14]	Huang [15]	Liu [16]	Xu [17]	Guan [18]	Zhang [19]
Location	**Wuhan, China**	**Wuhan, China**	**Wuhan, China**	**Wenzhou, China**	**Jiangsu, China**	**Wuhan, China**	**Shenzhen, China**	**Zhejiang, China**	**Wuhan, China**	**Wuhan, China**
Cases	29	99	34	149	80	41	12	62	1099	140
Age, years (median)	56	56	56	45	46	49	54	41	47	57
Women (%)	8 (28%)	32 (32%)	20 (59%)	68 (46%)	41 (51%)	11 (27%)	4 (33%)	27 (44%)	459 (41.9%)	69 (49%)
Blood biochemistry										
ALT	5 (17%)	28 (28%)	8 (23.5%)	18 (12.1%)	3 (3.8%)	N/R	2 (16.7%)	N/R	158/741 (21.3%)	N/R
AST	7 (24%)	35 (35%)	7 (20.6%)	27 (18.1%)	3 (3.8%)	15 (37%)	2 (16.7%)	10 (16.1%)	168/757 (22.2%)	N/R
ALB	15 (52%)	97 (98%)	25 (73.5%)	9 (6.0%)	2 (2.5%)	N/R	6 (50%)	N/R	N/R	N/R
TBil	1 (3%)	18 (18%)	3 (8.8%)	4 (2.7%)	1 (1.3%)	N/R	0 (0%)	N/R	76/722 (10.5%)	N/R
BUN	5 (17%)[a]	6 (6%)[a] 17 (17%)[b]	N/R	17 (11.4%)[b]	2 (2.5%)[a]	N/R	N/R	N/R	N/R	N/R
CRE	2 (7%)[a]	3 (3%)[a] 21 (21%)[b]	6 (17.6%)[a] 7 (20.6%)[b]	43 (28.9%)[a] 1 (0.67%)[b]	2 (2.5%)[a]	4 (10%)[a]	2 (16.7%)[a]	3 (5%)[a]	12/752 (1.6%)[a]	N/R
CK	N/R	13 (13%)	1/12 (8.3%)	12 (8.1%)	18 (22.5%)	13/40 (33%)	N/R	5 (8%)	90/657 (13.7%)	4/60 (6.7%)
LDH	20 (69%)	75 (76%)	N/R	45 (30.2%)	17 (21.3%)	29/40 (73%)	11 (91.7%)	17 (27%)	277/675 (41.0%)	N/R
Quality (NOS)	6	6	6	7	6	7	5	6	8	5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TBil, total bilirubin; BUN, blood urea nitrogen; CRE, creatinine; CK, creatine kinase; LDH, lactate dehydrogenase; NOS, Newcastle-Ottawa Scale; N/R, not (clearly) reported. [a]Increased percentage; [b]Decreased percentage. Biochemistry data are presented as percent according to the local reference ranges.

Table 2: The trend of blood biochemistry abnormalities in patients with COVID-19.

– Increased alanine aminotransferase (ALT)
– Increased aspartate aminotransferase (AST)
– Decreased albumin (ALB)
– Increased total bilirubin (TBil)
– Increased or decreased blood urea nitrogen (BUN)
– Increased or decreased creatinine (CRE)
– Increased creatine kinase (CK)
– Increased lactate dehydrogenase (LDH)

studies of a total of 208 patients showed an increased level of BUN; however, in two studies, 34 of 248 patients showed a decreased level. The meta-analysis was not carried out on account of the limited quantity of included studies.

Nine studies and 1258 patients with COVID-19 were included, and 77 patients showed CRE elevation; however, three studies and 282 patients were included, and 29 patients showed CRE reduction. The overall proportion of CRE elevation in patients with COVID-19 was 0.08 (95% CI: 0.02–0.17). As the heterogeneity among studies was high ($I^2 = 93.0\%$, $p < 0.01$), a random-effect model was selected for the analysis (Figure 6).

Quantitative synthesis of creatine kinase abnormalities

The meta-analysis included 1159 patients with COVID-19 from eight studies, and 156 patients showed abnormalities in CK. The overall proportion of CK abnormalities in patients with COVID-19 was 0.13 (95% CI: 0.09–0.18). Based on moderate heterogeneity among studies ($I^2 = 68.0\%$, $p < 0.01$), a random-effect model was selected for the analysis (Figure 7).

Quantitative synthesis of LDH abnormalities

In total, eight studies and 1146 patients with COVID-19 were included in the meta-analysis, and 491 subjects showed increased LDH. The overall proportion of increased LDH was 0.52 (95% CI: 0.37–0.66). As there was high heterogeneity among studies ($I^2 = 94.0\%$, $p < 0.01$), a random-effect model was used for the analysis (Figure 8).

Qualitative synthesis of LDH abnormalities

All six studies showed that the value of LDH was significantly higher in severe patients than in non-severe

Table 3: Main data of the included studies in the meta-analysis.

Study (first author, location)	All patients				Non-severe patients				Severe patients			
	Cases, n	Age, years Median (IQR)	Women, n (%)	LDH, U/L Median (IQR)	Cases, n	Age, years Median (IQR)	Women, n (%)	LDH, U/L Median (IQR)	Cases, n	Age, years Median (IQR)	Women, n (%)	LDH, U/L Median (IQR)
Huang, Wuhan, China [15]	41	49 (41.0–58.0)	11 (27)	286.0 (242.0–408.0)	28	49 (41.0–57.5)	9 (32)	281.0 (233.0–357.0)	13	49 (41.0–61.0)	2 (15%)	400.0 (323 · 0–578 · 0)
Fan, Singapore [20]	67	42 (35.0–54.0)	30 (44.8)	446.0 (364.0–595.0)	58	41 (32.0–53.0)	27 (48.6)	401.0 (352.0–513.0)	9	54 (47.0–62.0)	3 (33.3)	1684.0 (1053.0–2051.0)
Young, Singapore [21]	18	47 (31.0–73.0)	9 (50)	512.0 (285.0–796.0)	12	37 (31.0–56.0)	5 (41.7)	424.0 (285.0–748.0)	6	56 (47.0–73.0)	4 (66.7)	550.0 (512.0–796.0)
Liu, Shenzhen, China [16]	12	62.5 (40.0–65.0)	4 (33.3)	575.5 (479.8–687.5)	6	43.5 (28.8–60.0)	1 (16.7)	500.5 (475.8–580.5)	6	64 (62.8–65.3)	3 (50.0)	679.0 (487.0–856.5)
Wang, Wuhan, China [22]	138	56 (42.0–68.0)	63 (45.7)	261.0 (182.0–403.0)	102	51 (37.0–62.0)	49 (48.0)	212.0 (171.0–291.0)	36	66 (57.0–78.0)	14 (38.9)	435.0 (302.0–596.0)
Huang, Jiangsu, China [23]	221	45 (33.5–56.0)	95 (43.0)	236.0 (175.5–360.5)	196	44 (33.0–54.0)	88 (44.9)	227.0 (173.8–342.8)	25	51 (36.5–64.5)	7 (28.0)	332.0 (239.5–630.0)

LDH, lactate dehydrogenase; IQR, interquartile range.

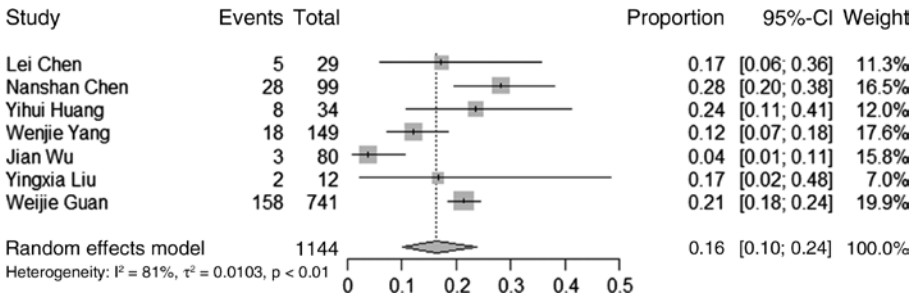

Figure 2: The forest plot of the proportion of ALT abnormality in COVID-19 patients.

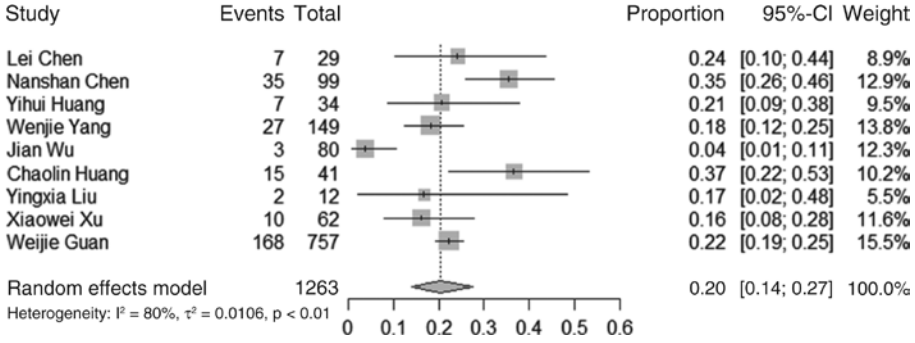

Figure 3: The forest plot of the proportion of AST abnormality in COVID-19 patients.

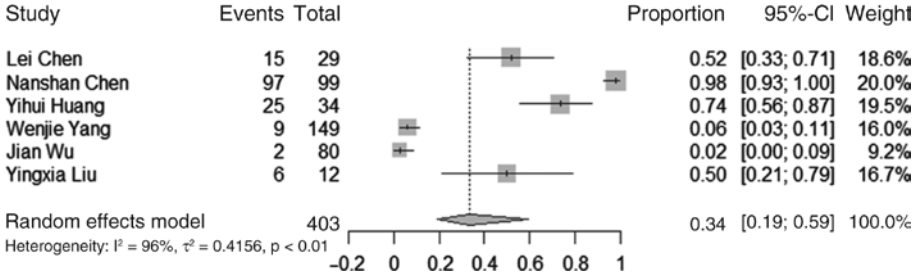

Figure 4: The forest plot of the proportion of ALB abnormality in COVID-19 patients.

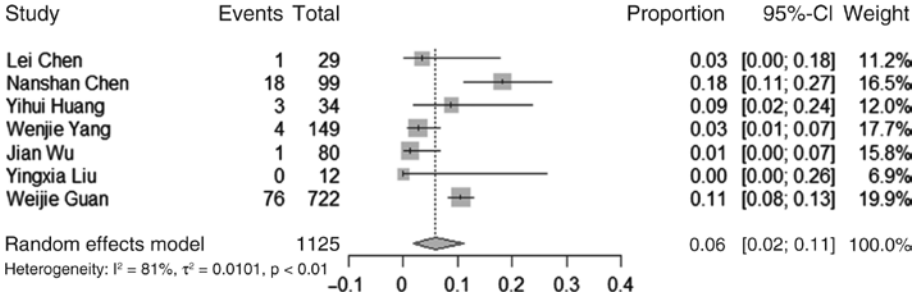

Figure 5: The forest plot of the proportion of TBil abnormality in COVID-19 patients.

patients. Huang et al. reported that LDH levels were increased in 29 (73%) of 40 patients, including 12 (92%) of 13 intensive care unit (ICU) patients and 17 (63%) of 27 non-ICU patients, and LDH levels were higher in ICU patients (median 400.0 U/L [interquartile range (IQR) 323.0–578.0]) than in non-ICU patients (median 281.0 U/L [IQR 233.0–357.0]), p = 0.0044) [15]. Fan et al. showed that LDH levels were dramatically higher in ICU patients

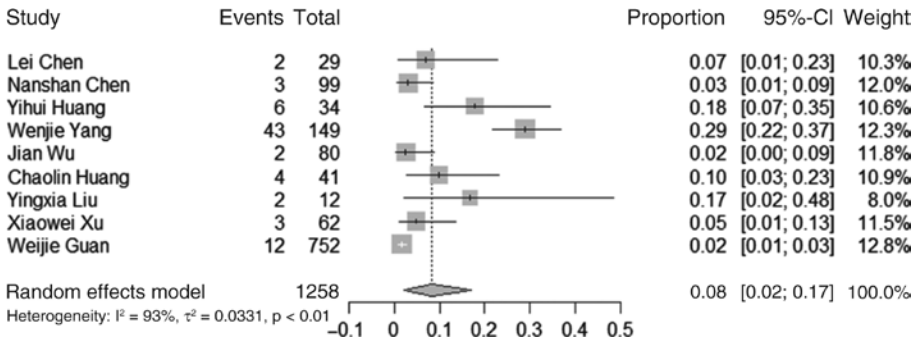

Figure 6: The forest plot of the proportion of CRE abnormality in COVID-19 patients.

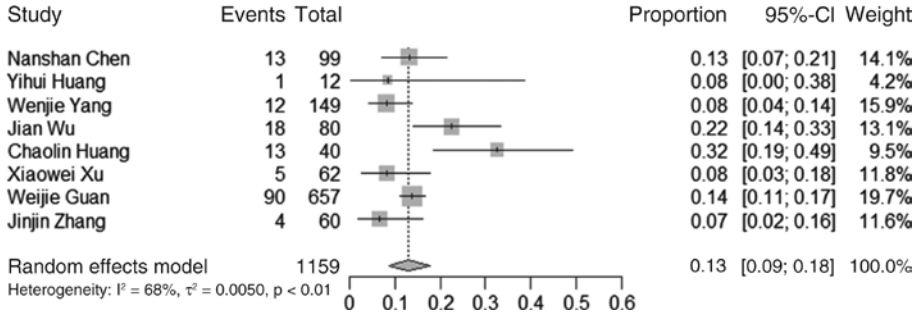

Figure 7: The forest plot of the proportion of CK abnormality in COVID-19 patients.

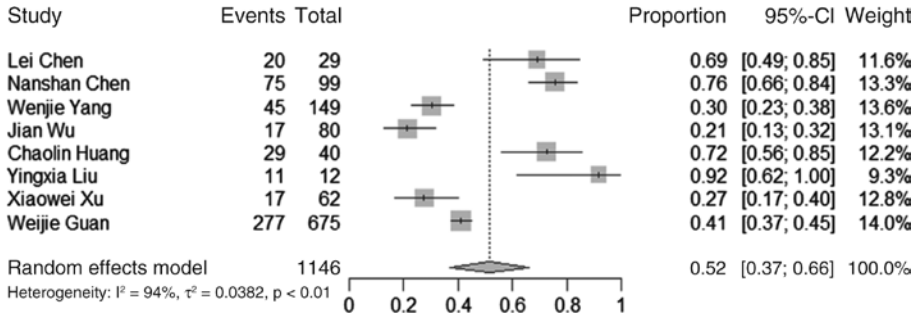

Figure 8: The forest plot of the proportion of LDH abnormality in COVID-19 patients.

(median 1684.0 U/L [IQR 1053.0–2051.0]) than in non-ICU patients (median 401.0 U/L [IQR 352.0–513.0]), p = 0.003) [20]. Young et al. and Liu et al. also observed a significant increase in LDH levels in severe patients, but they did not list p-values [16, 21]. Wang and colleagues indicated that there were prominent differences in LDH levels between patients admitted to the ICU (median 435.0 U/L [IQR 302.0–596.0]) and those not admitted to the ICU (median 211.0 U/L [IQR 171.0–291.0], p < 0.001) [22]. Similarly, in Huang et al.'s study, severe patients had higher LDH levels (median 332.0 U/L [IQR 239.5–630.0]) than non-severe patients (median 227.0 U/L [IQR 173.8–342.8], p < 0.001) [23].

In addition, of the six studies, three reported that severe patients were older than non-severe patients (p < 0.05), and the other three studies showed that there was no significant difference in age (p > 0.05) [20, 22, 23]. In addition, all six studies showed that the severity of the disease was independent of sex (p > 0.05).

Meta-regression analysis

In the meta-regression, we found that the proportion of abnormalities in biochemical indexes, except ALB and LDH, was not associated with the factors including female

proportion, age, and sample size. For the proportion of ALB abnormalities, the age of cases partly demonstrated the heterogeneity (coefficient = 0.0649, p = 0.012), and for the proportion of LDH abnormalities, both female proportion (coefficient = – 2.6475, p = 0.003) and the number of cases (coefficient = 0.0407, p = 0.008) were the potential causes of heterogeneity (Supplementary Table 1).

Evaluation of publication bias

There was publication bias in the meta-analysis of ALB and LDH levels according to visual inspection of funnel plots. The results of publication bias analysis are shown in Supplementary Figure 1.

Discussion

2019-nCOV belongs to the β-coronavirus cluster. As the third most highly pathogenic coronavirus, the clinical presentations of 2019-nCoV infection resemble those of the other two coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) [24, 25]. The number of 2019-nCOV infections is increasing rapidly because of the existence of the following features: person-to-person transmission through respiratory droplets, with possible transmission through aerosols under specific circumstances; the high affinity of the spike glycoprotein of 2019-nCOV for angiotensin-converting enzyme 2 (ACE2) receptors in human host cells; infectivity in a latent period; asymptomatic infection with atypical clinical symptoms; and insufficient attention in the early stages [26–29]. On March 11, 2020, the WHO made the assessment that COVID-19 should be characterized as a pandemic, with an emerging trend of outbreaks in European countries. It is urgent to curb the spread of the coronavirus by taking measures such as restricting citizen movement and screening, isolating, testing and treating each case and tracking each close contact, using a fit-tested N95 respirator, and avoiding gatherings.

Similarities in clinical characteristics between COVID-19 and previous coronavirus infections have been noticed. The most common symptoms of COVID-19 are fever, dry cough, and bilateral ground-glass opacities on chest CT scans. Some patients have muscle soreness, fatigue, diarrhea, headache, sore throat, and hemoptysis; the symptoms of few patients advance dyspnea, acute respiratory distress syndrome (ARDS), and even fatality [30, 31]. Through March 11, 2020, the proportion of severe cases was consistently over 20.0% in China. The case fatality rate of patients with COVID-19 is 3.91% in China, the case fatality rate was 3.02% in 113 countries outside of China, and the case fatality rate was 3.63% globally. Although the mortality rates of COVID-19 are lower than those of SARS and MERS (9.6% and 35%, respectively), the numbers of infected persons and involved countries are vastly greater than those of SARS and MERS [2].

In addition to focusing on epidemiology and clinical symptoms, recent studies have been concerned about laboratory abnormalities, such as depressed lymphocyte count, prolonged prothrombin time, increased C-reactive protein (CRP) and elevated LDH [22]. Studies have suggested that some hospitalized patients with COVID-19 have acute kidney injury, acute cardiac injury, and liver function damage [15, 32]. The abnormalities in laboratory indexes, particularly blood biochemical parameters, may be associated with the severity of multiple organ dysfunction.

According to the results of the meta-analysis, we found that approximately one-fifth of patients with 2019-nCoV infection had elevated transaminase, and 6% of patients had a TBil increase. Huang et al. indicated that AST levels of ICU patients were significantly higher than those of non-ICU patients (62% vs. 25%); TBil levels of ICU patients (median 14.0 mmol/L [IQR 11.9–32.9]) were slightly higher than those of non-ICU patients (median 10.8 mmol/L [IQR 9.4–12.3], p = 0.011). Their study also mentioned that there was only one patient with chronic liver disease in the non-ICU care group [15]. Another study showed that the AST levels of severe patients were higher than those of non-severe patients (39.4% vs. 18.2%); severe patients had higher rates of TBil increase than non-severe patients (13.3% vs. 9.9%). There were 22 patients with hepatitis B infection in the non-severe group and only one patient with hepatitis B infection in the severe group [18]. These studies suggest that a subset of patients had acute liver injury, and patients with severe disease had more prominent hepatic dysfunction.

Our meta-analysis showed that the overall proportion of ALB abnormalities was 34%, and we found that there were substantial differences among different studies. Chen et al. showed a reduction in ALB in 98% of patients with COVID-19 [11]; Wu et al. showed that only 2% of patients had decreased ALB levels. The possible explanations are differences in sample size, the age of cases, the proportion of severe cases, and the number of patients with comorbidities. Moreover, of six studies included in this analysis, researchers did not suggest a potential correlation between ALB level and the severity of COVID-19.

However, another study revealed that ALB was significantly lower in the progression group (36.62 ± 6.60 g/L) than in the improvement/stabilization group (41.27 ± 4.55 g/L, p = 0.006) [33]. These results suggest that we should consider changes in ALB as a risk factor for COVID-19 progression.

In addition, our results showed that 8% of patients presented an increased level of CRE. Of nine studies included in this analysis, two studies indicated that the proportion of CRE elevation in severe patients was marginally higher than that in non-severe patients, while one of two studies noted that both few severe and non-severe patients had chronic renal disease [15, 18]. Furthermore, we found that 13% of patients had elevated levels of CK, and three studies showed that the rates of CK abnormalities were higher among severe patients than among non-severe patients, whereas both severe and non-severe patients had concomitant coronary heart disease, hypertension, and stroke [15, 18, 19]. These studies suggest that 2019-nCoV infection may, to some extent, cause acute renal function damage; nonetheless, we should also pay attention to whether the patients with COVID-19 have underlying diseases. Notably, some studies found that some patients had different degrees of decreased BUN or serum CRE [11–13]. These presentations may be associated with the lack of nutrition due to pathogenic conditions.

Next, our results revealed that more than half of patients with COVID-19 had increased LDH levels in the meta-analysis, and the LDH levels of severe patients were higher than those of non-severe patients. LDH, as a cytoplasmic cellular enzyme, is present in all major organ systems. Studies have demonstrated that a high level of LDH is associated with the severity of adenovirus respiratory infection and is a biomarker for the prognosis of severe infection [34, 35]. Hence, it is plausible to suggest that the LDH value could help physicians identify patients with COVID-19 who are likely to develop severe illness and provide better supportive treatment.

To the best of our knowledge, this is the first meta-analysis and systematic review of published studies assessing the abnormalities in biochemical parameters and analyzing the association between laboratory examinations and the severity of COVID-19. Our systemic review and meta-analysis provided promising results to guide the clinical treatment and prognosis of COVID-19.

However, there are some limitations in our meta-analysis and systematic review. First, all studies included in the meta-analysis were retrospective studies with high heterogeneity. Second, there was a publication bias in the quantitative synthesis. Third, most studies included in the meta-analysis were from China, and differences in biochemical indices may exist among countries and races. Finally, all eligible studies were retrospective and observational studies and provided percentages and insufficient data, which made it difficult to estimate the causal relationships between biochemical parameters and COVID-19 severity.

Therefore, based on the limitations listed above, further studies with more careful designs and larger sample sizes are warranted to establish the association between biochemical indexes and COVID-19.

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Competing interests: Authors state no conflict of interest.

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