

Laboratory findings of COVID-19: a systematic review and meta-analysis

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ABSTRACT

The Coronavirus Disease (COVID-19) pandemic first broke out in December 2019 in Wuhan, China, and has now spread worldwide. Laboratory findings have been only partially described in some observational studies. To date, more comprehensive systematic reviews of laboratory findings on COVID-19 are missing. We performed a systematic review with a meta-analysis to assess laboratory findings in patients with COVID-19. Observational studies from three databases were selected. We calculated pooled proportions and 95% confidence interval (95% CI) using the random-effects model meta-analysis. A total of 1106 articles were identified from PubMed, Web of Science, CNKI (China), and other sources. After screening, 28 and 7 studies were selected for a systematic review and a meta-analysis, respectively. Of the 4,663 patients included, the most prevalent laboratory finding was increased C-reactive protein (CRP; 73.6%, 95% CI 65.0–81.3%), followed by decreased albumin (62.9%, 95% CI 28.3–91.2%), increased erythrocyte sedimentation rate (61.2%, 95% CI 41.3–81.0%), decreased eosinophils (58.4%, 95% CI 46.5–69.8%), increased interleukin-6 (53.1%, 95% CI 36.0–70.0%), lymphopenia (47.9%, 95% CI 41.6–54.9%), and increased lactate dehydrogenase (LDH; 46.2%, 95% CI 37.9–54.7%). A meta-analysis of seven studies with 1905 patients showed that increased CRP (OR 3.0, 95% CI: 2.1–4.4), lymphopenia (OR 4.5, 95% CI: 3.3–6.0), and increased LDH (OR 6.7, 95% CI: 2.4–18.9) were significantly associated with severity. These results demonstrated that more attention is warranted when interpreting laboratory findings in patients with COVID-19. Patients with elevated CRP levels, lymphopenia, or elevated LDH require proper management and, if necessary, transfer to the intensive care unit.

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Introduction

In December 2019, an outbreak of a highly contagious pneumonia of unknown cause occurred in Wuhan, China; since then, it has become a pandemic. Soon the causative pathogen was isolated and identified to be a novel coronavirus later, named SARS-CoV-2 [1]. Taxonomically, it is a species of SARS-related coronaviruses that belongs to the subgenus *Sarbecovirus*, a part of the genus *Betacoronavirus* (family *Coronaviridae*; subfamily *Coronavirinae*).

SARS-CoV-2 causes respiratory infections (COVID-19), in some patients leading to acute respiratory distress syndrome [2], requiring intensive care with mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) has been used to save critically ill patients. However, many patients still die from the COVID-19. As of March 31, 2020, 81,554 cases of COVID-19 have been diagnosed, and 3,312 deaths have been reported in the Chinese Mainland (case fatality rate of 4.06%) [3]. In other countries around the world, a total of 775,785 cases and 38,687 deaths have been reported (case fatality rate of 5.00%) [4]. In addition to China, the virus is rapidly spreading worldwide, partly due to the lack of personal protective materials. It is predicted

that the morbidity of COVID-19 will drastically increase over the coming months.

In the immediate three months after the outbreak of COVID-19, many academic centres published their findings from observational studies based on clinical features, CT imaging features, and laboratory results [5–7]. Most of these studies focused on the symptoms and CT imaging features [6,8], with only limited attention paid to laboratory findings, which could be helpful in the diagnosis and in determining the severity of COVID-19. In this state of emergency, randomised controlled trials (RCTs) are not feasible, and only data from observational studies are readily available and accessible. Therefore, a systematic review is needed to summarise the laboratory findings in each study, the results of which can assist in the diagnosis and treatment of the disease.

Materials and methods

Search strategy and selection criteria

A systematic literature search was performed using PubMed, Web of Science, and CNKI (China). Records were managed

using EndNote X 9.0 software to exclude duplicates. The search terms used in PubMed were as follows: (severe acute respiratory syndrome coronavirus 2, Wuhan coronavirus, Wuhan seafood market pneumonia virus, COVID19 virus, COVID-19 virus, coronavirus disease 2019 virus, SARS-CoV-2, SARS2, 2019-nCoV, 2019 novel coronavirus) and (clinical characters, clinical features, laboratory). With consideration of the date of occurrence of COVID-19 and the final review, the searches were limited to articles published in English or Chinese in 2020. To reduce literature omissions, we checked the reference list of the included studies.

Eligible studies described the method of diagnosis of COVID-19, the number of patients, conventional laboratory indices, changes in frequency, and the cut-off value of each laboratory index. Case reports, review articles, letters, meta-analysis articles, and studies on only children were excluded. Two reviewers independently performed the literature search and screened the abstracts and full text according to these eligibility criteria. Disagreements were resolved by a third reviewer or by consensus. Then, studies in which

patients were divided into the non-severe and severe groups according to the patient's condition were selected for meta-analysis. A graphical representation of the process of literature search is shown in Figure 1.

Quality assessment and risk of bias

The two reviewers used the assessment criteria for the risk of bias from the Joanna Briggs Institute (JBI) to assess the quality of cross-sectional studies enrolled in this study. A random-effects model was applied to estimate the pooled proportion and 95% CI. The I^2 statistic, Q test, and Egger's test were used to assess statistical heterogeneity and publication bias, respectively.

Data extraction and meta-analysis

The two reviewers who performed the literature search also independently extracted the data from the selected studies.

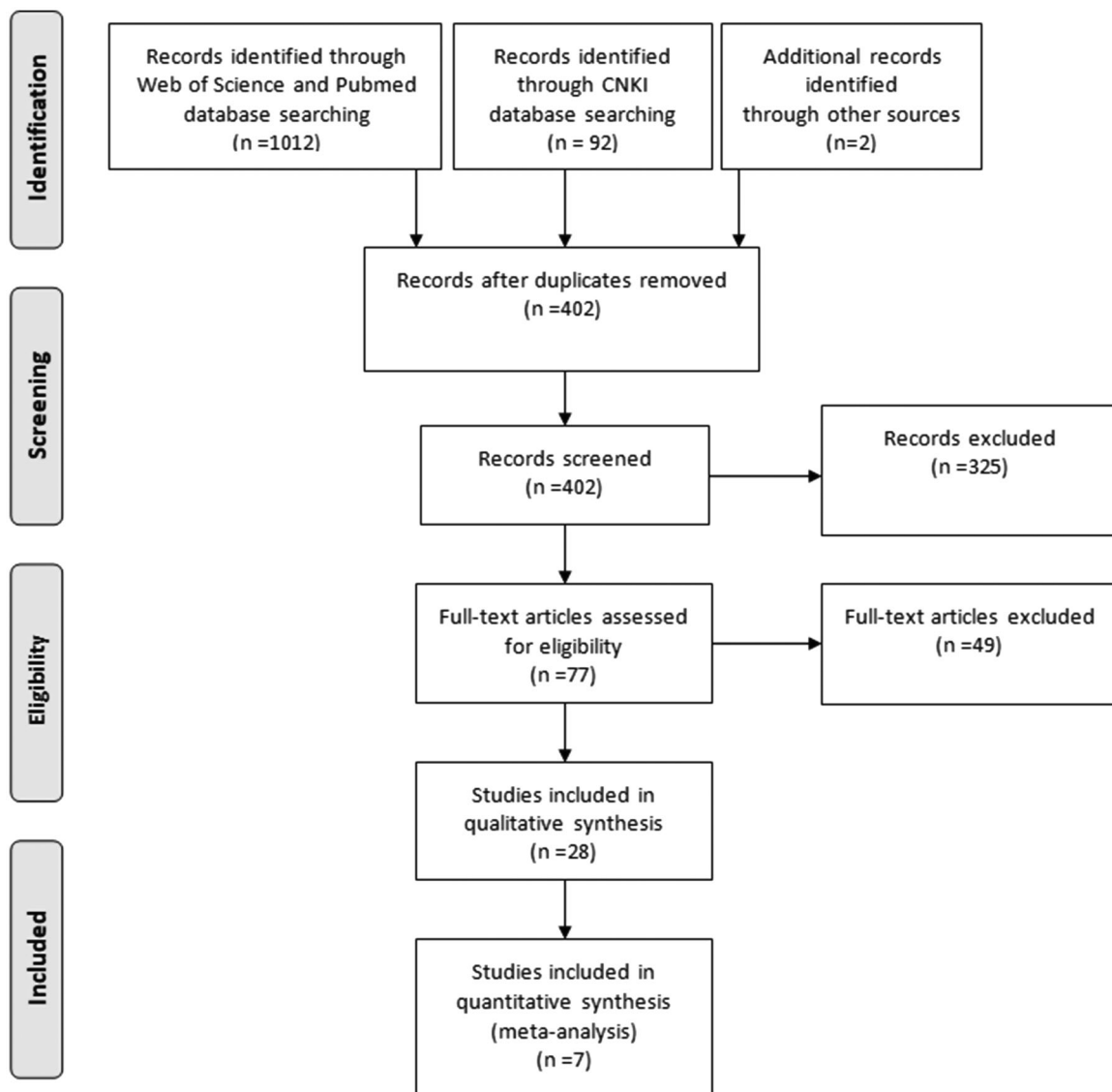


Figure 1. The process of the literature search and selection.

We extracted the following variables: author, number of patients, age, sex, number of patients classified as non-severe and versus severe, change in the frequency of laboratory indices including leukocytes, lymphocytes, eosinophils (Eos), platelets (PLT), aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), D-dimer, albumin (Alb), and interleukin-6 (IL-6). Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range.

The meta-analysis was performed using the ‘meta’ package (version 4.11-0) in R soft (version 3.6.2). The proportions and 95% confidence intervals (95% CI) were calculated to describe the ratio of increased or decreased laboratory indices of patients in the non-severe and severe groups. Due to heterogeneity within and between studies, a random-effects model was applied to estimate the pooled proportion and 95% CI.

The I^2 index was used to assess statistical heterogeneity. A meta-analysis of each variable of interest and subgroup analysis by groups (non-severe or severe) was performed. Publication bias was evaluated using a funnel plot for each variable of interest.

Results

A total of 1106 articles were identified from PubMed, Web of Science, and CNKI (China) and other sources. Finally, 28 studies [6–33] meeting the predetermined inclusion and exclusion criteria were selected in this study for a systematic review after we removed duplicates and screened all the search records. As presented in Table 1, a total of 4,663 patients were included in this meta-analysis; their mean age was 48.4 years, and 2,175 (46.7%) were female. The JBI assessment criteria were used to assess the quality of the studies, with scores ranging from 12 to 18, with a median score of 14.5.

The result of this random-effects meta-analysis showed that the most prevalent laboratory findings were increased CRP (73.6%, 95% CI 65.0–81.3%), followed by decreased Alb (62.9%, 95% CI 28.3–91.2%), increased ESR (61.2%, 95% CI 41.3–81.0%), decreased Eos (58.4%, 95% CI 46.5–69.8%), increased IL-6 (53.1%, 95% CI 36.0–70.0%), lymphopenia (47.9%, 95% CI 41.6–54.9%) and increased LDH (46.2%, 95% CI 37.9–54.7%). However, the I^2 ranging from 70.5% to 98.1% in the evaluation of the laboratory findings indicated heterogeneity in the statistical significance ($p = .000$) (Table 1).

Seven studies [12,13,15,16,23,29,30] in which 1905 patients were divided into the non-severe group and severe group according to the patient’s condition were selected for meta-analysis. CRP, lymphocytes, and LDH were selected for the subsequent meta-analysis (Supplementary Table S1). The results of this random-effects meta-analysis (Figure 2) showed the proportion of the three laboratory indices: increased CRP (73.6%, 95% CI 60.0–85.3%), lymphopenia (44.0%, 95% CI 33.2–58.3%), and increased LDH (41.7%,

95% CI 32.4–51.4%). The I^2 ranging from 86.2% to 96.0% indicated heterogeneity in the statistical significance ($p < .001$). A subgroup meta-analysis subsequently performed on each of the three indices showed that the pathogenetic condition contributes slightly to heterogeneity (Supplementary Figure S1).

As shown in Figure 3, we analysed the relationship between the three indices and patient conditions (non-severe vs severe). Patients with increased CRP, lymphopenia, and increased LDH in the severe group were found to have a higher risk than those in the non-severe group. The results showed increased CRP (OR 3.0, 95% CI: 2.1–4.4), lymphopenia (OR 4.5, 95% CI: 3.3–6.0), and increased LDH (OR 6.7, 95% CI: 2.4–18.9), respectively. Increased CRP and lymphopenia showed low heterogeneity ($I^2 < 10\%$); however, increased LDH showed high heterogeneity ($I^2 = 83.9\%$). A sensitivity analysis performed on increased LDH showed that the study of Guan W [15] contributed a lot to heterogeneity (Supplementary Figure S2).

In addition, publication bias was assessed using Egger’s test, which indicated that there was no obvious publication bias ($p > .05$) (Supplementary Figure S3).

Discussion

With COVID-19 rapidly spreading worldwide, a summary and a meta-analysis of its clinic characteristics are essential for effective patient management and treatment. This systematic review and random-effects meta-analysis were performed to summarise laboratory findings observed in COVID-19 confirmed cases published three months after the outbreak. As of 25 March 2020, 28 studies from across China, published in Chinese and English were included in this study. A total of 4662 patients confirmed with COVID-19 using RT-PCR assay were included in our meta-analysis. The median JBI score was 14.5, indicating high reliability.

This random-effects meta-analysis showed that the most common laboratory findings included increased CRP (73.6%), decreased Alb (62.9%), increased ESR (61.2%), decreased Eos (58.4%), increased IL-6 (53.1%), lymphopenia (47.9%), and increased LDH (46.2%). This analysis involved only adults in China, but it can also have implications in adult patients outside China. In another meta-analysis, with concordant results, decreased albumin (75.8%), high CRP (58.3%), high LDH (57.0%), lymphopenia (43.1%), and high ESR (41.8%) were the most prevalent laboratory results [34]. However, decreased Eos and increased IL-6 levels were not reported. Because our analysis included more studies (28 vs. 18) and patients (4662 vs. 2874), it is more accurate than previous analyses.

The pathogenesis of SARS-CoV-2 is not fully understood. However, SARS-CoV and SARS-CoV-2 have a high homology in their genome sequence (approximately 79% homologous) [35]. These laboratory findings were similar to those of patients affected by the SARS-CoV outbreak in 2003 [34]. Therefore, there may be similar mechanisms between the two viruses. The virus is known to invade

Table 1. Main Characteristics of studies included in the meta-analysis.

Authors	No. patients	Gender (M/F)	Age (median or mean years)	Leu (Decreased/total)	Lym (Decreased/total)	PLT (Decreased/total)	Eos (Decreased/total)	AST (Increased/total)	ALT (Increased/total)	LDH (Increased/total)	CRP (Increased/total)	PCT (Increased/total)	ESR (Increased/total)	D-dimer (Increased/total)	Alb (Decreased/total)	IL-6 (Increased/total)	JBI scores ^a
Wang Z	69	32/37	42.0	36/67	28/67	-	48/67	19/69	23/69	25/61	42/63	4/62	30/58	-	-	11/43	15
Wan S	135	72/63	47.0	28/135	68/135	23/135	-	30/135	-	58/135	-	3/135	-	-	-	-	18
Guan W	1099	640/459	47.0	330/978	731/890	315/869	-	168/757	158/741	277/675	481/793	35/633	-	-	-	-	18
Xu YH	50	29/21	43.9	14/50	14/50	-	-	-	-	-	26/50	-	-	-	-	-	12
Xiong Y	42	25/17	49.5	10/37	18/37	-	-	-	-	15/26	27/32	3/30	10/22	-	-	-	14
Xu XW	62	35/27	41.0	19/62	26/62	3/62	-	10/62	-	17/62	-	7/62	-	-	-	-	13
Huang, Y	34	14/20	56.2	6/34	17/34	9/34	-	7/34	8/34	-	-	13/31	13/22	5/34	25/34	-	14
Xu X	90	39/51	50.0	-	19/90	-	-	-	-	-	38/90	-	-	-	-	-	13
Qian GQ	91	37/54	50.0	14/91	28/91	10/91	47/91	9/91	7/91	-	49/91	14/91	-	22/91	43/91	-	15
Han R	108	38/70	45.0	11/108	65/108	-	-	-	-	-	107/108	-	-	-	-	-	16
Chen N	99	67/32	55.5	9/99	35/99	12/99	-	35/99	28/99	75/99	-	6/99	84/99	36/99	97/99	51/99	14
Zhang MQ	9	5/4	36.0	-	2/9	-	-	-	-	-	5/9	0/9	-	-	-	-	15
Liu M	30	10/20	35.0	8/30	12/30	-	-	7/30	7/30	5/30	-	-	-	5/30	-	-	15
Chen L	29	21/8	56.0	6/29	20/29	5/29	-	7/29	5/29	20/29	27/29	-	-	-	15/29	-	12
Zhao D	19	11/8	48.0	7/19	12/19	-	-	5/18	5/18	6/19	18/19	-	-	-	-	6/7	18
Wang D	138	75/63	56.0	-	97/138	-	-	-	-	55/138	-	-	-	-	-	-	14
Zhou F	191	119/72	56.0	32/191	77/191	11/191	-	-	59/189	123/184	-	14/164	72/172	-	-	-	17
Huang C	41	30/11	49.0	10/40	26/41	2/40	-	15/41	-	29/40	-	3/39	-	-	-	-	12
Zhang JJ	140	71/69	57.0	27/138	104/138	-	73/138	-	-	-	125/136	41/118	-	35/81	-	-	14
Liu K	137	61/76	57.0	51/137	99/137	-	-	-	-	-	115/137	-	-	-	-	-	14
Yu SM	25	16/9	37.9	3/25	8/25	0/25	-	-	-	-	-	0/25	6/25	-	-	20/25	16
Xu H	32	19/13	52.0	20/32	21/32	-	-	-	-	-	23/32	-	-	-	-	-	14
Zhao CC	189	91/98	46.5	35/189	97/189	-	-	-	-	-	130/189	-	-	-	-	-	15
Cheng KB	463	244/219	51.0	76/463	248/463	51/463	-	-	-	260/458	312/463	-	404/427	-	-	-	16
Ding Y	56	30/26	54.6	13/56	33/56	-	-	-	-	-	43/56	-	-	-	-	-	13
Dai ZH	918	478/440	44.7	213/918	351/918	-	-	-	-	-	-	-	-	-	-	-	16
Xiao KH	143	73/70	45.0	37/143	64/143	-	-	-	-	43/143	72/143	4/143	-	-	-	56/143	14
Yuan J	223	105/118	46.5	50/223	47/223	-	-	32/223	42/223	59/223	-	-	-	-	63/223	-	15
Total	4662	2487/2175	Mean 48.4														Median14.5
Proportion (%)				24.0	47.8	12.6	58.4	21.9	22.5	46.2	73.6	9.4	61.2	30.1	62.9	53.1	
95%CI (%)				20.2-28.0	41.6-54.9	7.8-21.0	46.5-69.8	17.5-26.3	17.8-28.0	37.9-54.7	65.0-81.3	5.5-16.1	41.3-81.0	20.4-39.7	28.3-91.2	36.0-69.9	
I ² (%)				86.4	96.0	93.6	75.9	70.5	73.9	92.8	94.5	91.2	96.4	82.2	98.1	86.8	
p Value of Q test				<.0001	<.0001	<.0001	.0157	.0001	.0012	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	

Leu: Leukocyte; Lym: Lymphocyte; PLT: Platelet count; Eos: Eosinophils; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactose dehydrogenase; CRP: C-reactive protein; PCT: Procalcitonin; ESR: Erythrocyte sedimentation rate; Alb: Albumin; IL-6: interleukin-6. Increased means over the upper limit of the normal range and decreased means below the lower limit of the normal range.
^aJBI scores ranged 0-20.

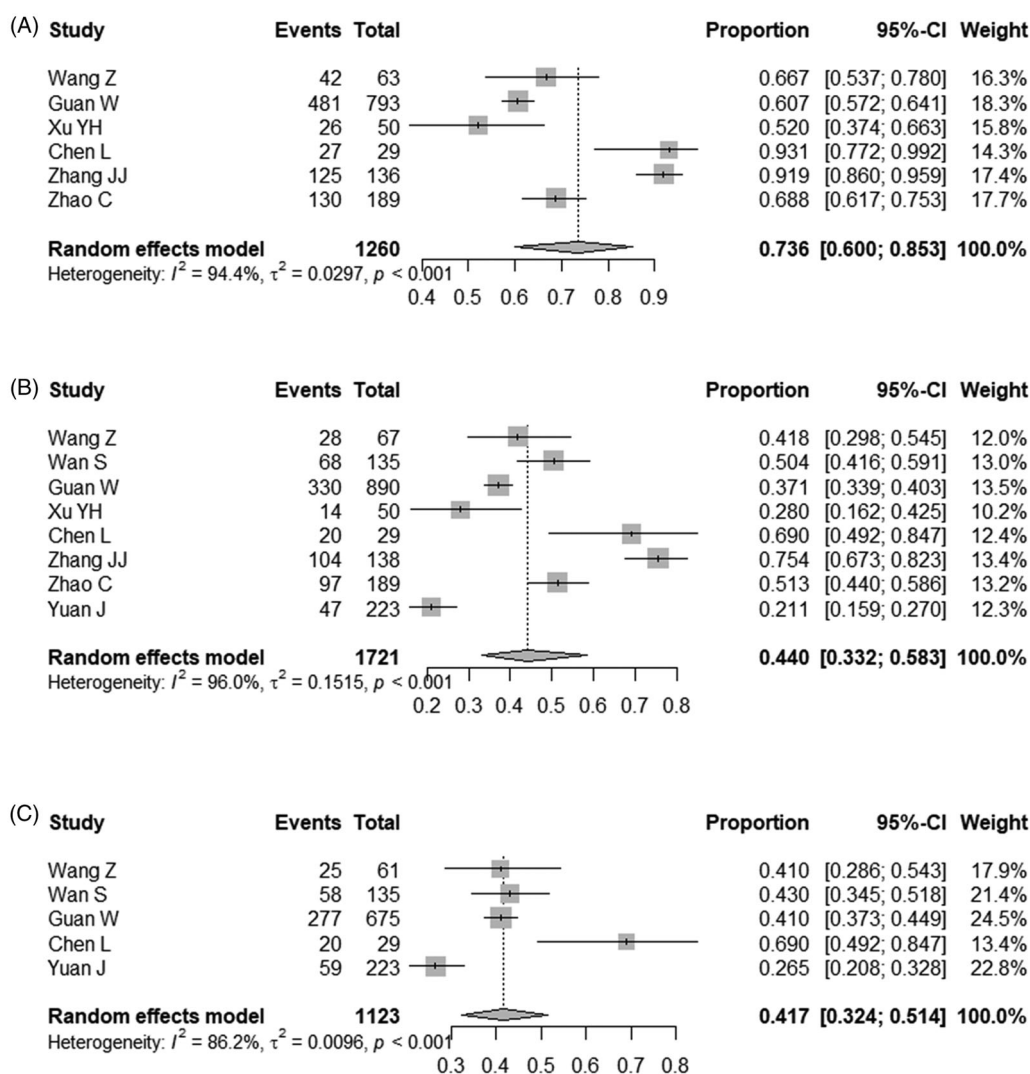


Figure 2. Meta-analysis of the proportion of increased CRP, lymphopenia, and increased LDH in patients with COVID-19. (A), (B), and (C) represent proportions of increased CRP, lymphopenia, and increased LDH, respectively.

many tissues and organs [36], especially of the respiratory and immune systems, including lymph nodes, tonsils, spleen, and bone marrow, leading to viral pneumonia, immunodeficiency, liver injury, myocardial injury, etc. These laboratory findings reflect multiple organ injuries.

Increased CRP, lymphopenia, and increased LDH were reported in seven studies [12,13,15,16,23,29,30]. These seven studies where patients were divided into the non-severe and severe groups, were selected for a subgroup meta-analysis of proportion and risk analysis between the severe and non-severe groups. The results showed that increased CRP (OR 3.0, 95% CI: 2.1–4.4), lymphopenia (OR 4.5, 95% CI: 3.3–6.0), and increased LDH (OR 6.7, 95% CI: 2.4–18.9) were highly associated with severe conditions. The numbers of CD45+ lymphocytes, CD3+ lymphocytes, CD4+ T cells, CD8+ T cells, and CD19+ B cells were significantly reduced in COVID-19 patients, and the decrease was more significant in severe patients than in non-severe patients [37]. At the same time, CRP and LDH levels were

significantly higher in severe patients than in non-severe patients. Another study [38] showed that the LDH level on admission negatively correlated with survival days ($p = .022$). Zhou *et al.* found that the ratio of lymphopenia in the non-survivor group was higher than that in the survivor group (76% vs. 26%, $p < .001$), and the proportion of increased LDH in the non-survivor group was higher than that in the survivor group (98% vs. 54%, $p < .001$) [25].

This review has several limitations. First, all the studies included in the meta-analysis were published from regions across China. The inclusion of studies from all parts of the globe will provide a more comprehensive understanding of COVID-19. Second, the confounding effects of other underlying medical conditions were not controlled in this study; therefore, the results obtained must be interpreted with caution. Lastly, the majority of the meta-analyses was highly heterogeneous. The random-effects model was applied to weaken the influence of heterogeneity, and subgroup and sensitivity analyses were performed to explore the source of heterogeneity.

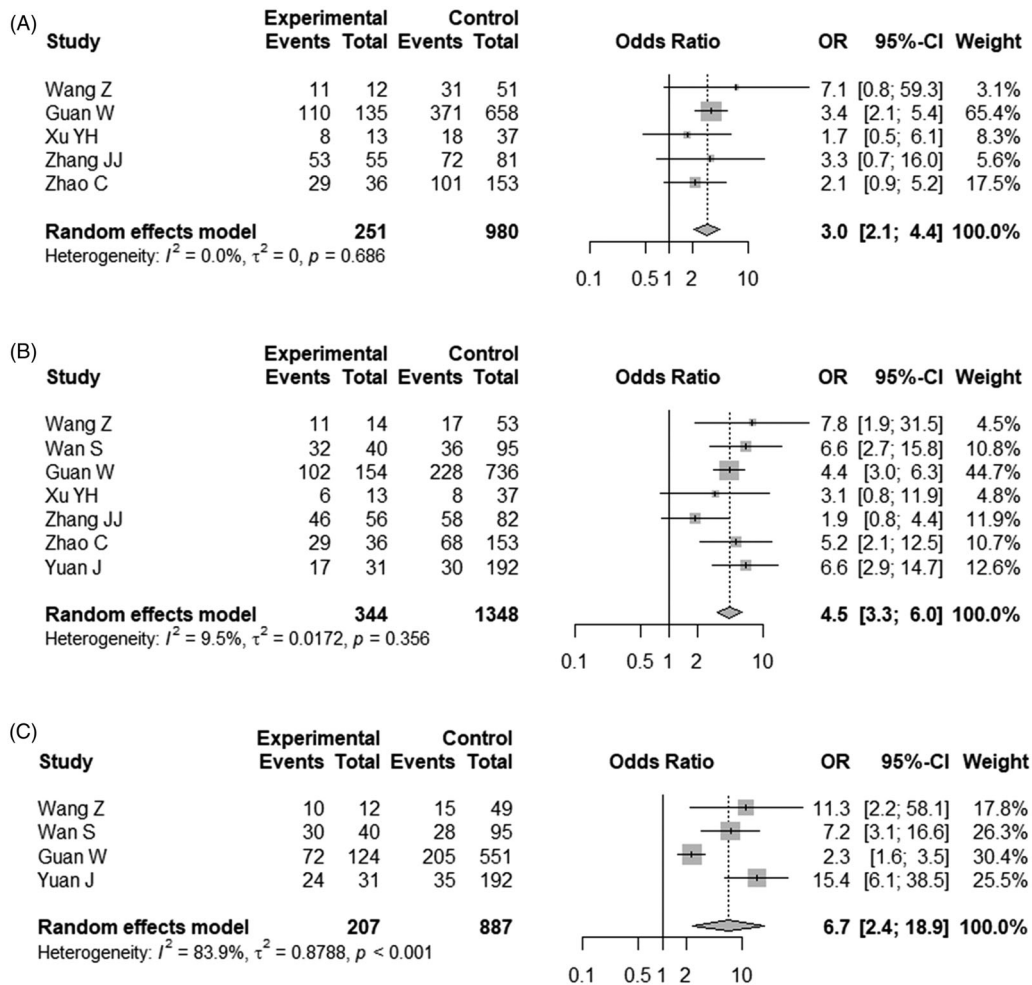


Figure 3. The risk of increased CRP, lymphopenia, increased LDH in severe patients compared to non-severe patients. (A) Increased CRP, (B) lymphopenia, and (C) increased LDH.

Conclusion

This systematic review and meta-analysis showed that the most common laboratory findings in patients with COVID-19 were increased CRP, decreased Alb, increased ESR, decreased Eos, increased IL-6, lymphopenia, and increased LDH. These results demonstrate that more attention is warranted when interpreting laboratory findings in patients with COVID-19. Patients with increased CRP, lymphopenia, and increased LDH require proper management and, if need be, should be transferred to the intensive care unit.

Disclosure statement

All authors report no potential conflicts of interest.

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Author contributions

Zhang Zuli and Li Fengzeng formulated the research questions, designed the study, developed the preliminary search strategy, and

drafted the manuscript. Hou Yulei and Li Detao refined the search strategy by conducting iterative database queries and incorporating new search terms. Li Fengzeng and Li Detao searched and collected the articles, then conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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