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Title: Crucial Laboratory Parameters in Severe COVID-19 Infection: A Systematic Review and Meta-Analysis

Running Title: Clinical Laboratory Findings and COVID-19 Severity

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Abstract

Aim: Abnormal laboratory findings have been shown to be associated with severe COVID-19. However, all aspects of this association have not been reviewed systematically. Therefore, the aim of this meta-analysis was to explore crucial laboratory parameters in severe COVID-19 infection.

Methods: We performed the literature review of scientific articles indexed in electronic databases**.** Scientific search engines were used to perform the electronic literature search. After the removal of duplicates and selection of articles of interest, 30 studies were eligible to include. If heterogeneity was high (I^2>50%), a random-effects model was applied to combine the data. Otherwise, a fixed-effects model was used.

Results: A total of 5586 individuals were assessed (1555 patients with severe COVID-19 infection and 3452 with non-severe infection). Platelets, lymphocytes and serum albumin were significantly lower in severe patients while other biochemical and immunological parameters including prothrombin time, ALT, AST, total bilirubin, LDH, procalcitonin, CRP, IL-6, and IgA were significantly higher in patients with severe infection. Neutrophil and monocyte counts as well as hemoglobin level, D-dimer, hypersensitive troponin I, IL-2R, IgG and IgM levels were different between two groups; however, the difference was not statistically significant (All P-values >0.05).

Conclusions: Lymphopenia, elevated liver enzymes, and high levels of inflammatory biomarkers are associated with severe COVID-19 infection.

Keywords: COVID-19; disease severity; laboratory findings; biochemistry findings; immunology; hematology

Introduction

The pandemic of the acute respiratory disease caused by the 2019 novel corona virus (2019-nCoV) usually presents with mild symptoms in the majority of infected individuals; however, pneumonia, multi-organ failure or even death is seen in vulnerable cases [1, 2]. Corona virus disease 19 (COVID-19) is substantially similar to severe acute respiratory syndrome regarding the virus homology, the main routes of transmission (respiratory droplets), host receptors (angiotensin converting enzyme 2), clinical signs and symptoms, disease dynamics, and even the disease progression[3]. In addition, old age and comorbidities are the common risk factors for both severe COVID-19 and severe acute respiratory syndrome [4]. However, myocardial injury and heart failure are more prevalent in patients with severe COVID-19 [2]. Laboratory findings were also different between severe and non-severe patients. Leukocytosis as well as severe lymphopenia as the indicator of cellular immune deficiency was observed in severe cases. Furthermore, high procalcitonin (>0.5 ng/mL) as a result of secondary bacterial infection strongly associated with death was detected in severe cases [1, 2, 5-8].

Impaired kidney and liver function (mild or moderate elevation of alanine aminotransferase, aspartate aminotransferase, total bilirubin, high concentrations of lactate dehydrogenase and troponin I), coagulation disorder (elevation of prothrombin time and D-dimer), raised inflammatory markers (high sensitivity C-reactive protein,), and cytokine release syndrome are other laboratory abnormalities detected in severe cases with poor prognosis [1, 2, 6, 7, 9-11].

Therefore, we were to conduct a meta-analysis to investigate the characteristics of severe COVID-19 patients regarding laboratory findings, clinical characteristics, and mortality thereby providing some insights into the treatment of the disease.

Methods

Search strategy

This systematic review and meta-analysis follows the PRISMA guidelines [12]. We searched PubMed, Embase, Scopus and web of science databases between 1 Jan 2020 and 2 April 2020. The search was performed using the following search terms: “Corona virus”, “Covid-19”, “2019-nCov”, “nCov”, “Severe acute respiratory syndrome”, “SARS-COV-2”, “Clinical Feature”, “Clinical characteristic”, “severity”, “Laboratory test”, “Biochemical test”, “ICU admission”, “Acute respiratory distress syndrome (ARDS)”, “Paraclinic”, “CT scan”, “CT finding”, “CT image”, “Radiologic”, “Erythrocyte sedimentation rate (ESR)” , “C-Reactive protein (CRP)”, “Liver function test ((LFTs or LFs), “Alanine aminotransferase (ALT)”, “Aspartate aminotransferase (AST)”, “Procalcitonin”, “White blood cell (WBC)”, “Lymphocyte”, “Neutrophil”, “D-dimer”, “Prothrombin time”, “Bilirubin”, “Haemoglobin”, “Hemoglobin”, ‘Lactate dehydrogenase”, “Hypersensitive troponin I” (see Appendix 1).

Study selection and data extraction

Inclusion and Exclusion Criteria

We included all relevant articles reporting clinical and laboratory characteristics of patients with COVID-19 infection. There was no limitation for language as well as study design. All publications from January 1, 2020 until April 2, 2020 were assessed. Case series with incomplete information as well as review articles, opinion articles and letters not presenting original data were also excluded. The criteria for the severity of COVID-19 infection include ICU admission, acute respiratory distress syndrome (ARDS), need for O2 supplement, abnormal CT imaging, cardiac decomposition, organ failure, or death.

Data extraction and Risk of bias assessment

One author (Z.E) created the systematic search strategy. Two authors (R.A and M.H) screened and evaluated the literature independently and then, third author (ME.Kh) checked the screening results. Data extraction forms including the following items were also filled out: name of the first authors, date of publication, DOI, the number of reported cases, age, and sex, laboratory findings (e.g., hematology, immunology and biochemistry). Newcastle-Ottawa Scale was used to assess all the included papers.

Statistical analysis

In most studies median were reported as a central tendency index because of skewed distribution of laboratory findings, so we used "metamedian" package in R software to estimate the pooled difference of medians across two groups and 95% confidence intervals (CIs). We also estimated standardized mean difference (SMD) and 95% confidence intervals (CIs) to present association of laboratory findings and severity of disease in some studies which presented mean as a central tendency index. We employed forest plots, Cochran's Q statistic, and I^2 statistic to evaluate heterogeneity among the primary studies. A random-effects model was used if heterogeneity was high ($I^2 > 50\%$); otherwise, a fixed-effects model was applied. In addition, the publication bias was formally tested with Egger's test to determine the asymmetry of the funnel plots, where $p<0.10$ was considered as evidence of bias. Statistical analyses were conducted using Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

Characteristics of included studies

Table 1 shows details of eligible studies included in this meta-analysis. These 30 studies were conducted on a total of 5586 patients (65% male). All studies were conducted between January and April 2020 during the novel corona virus (SARS-CoV-2) outbreak. A total of 1555 cases were defined as severe whereas 3452 were non-severe (among severe patients, 71% were female) (Figure 2).

Clinical laboratory finding

Pooled Median differences

Analysis of 24 studies reported severity assessment. The results showed substantial drop in platelets (PMD, -34.67×109/L; 95% CI, -46.5568, -22.7810× 10^9/L; I^2, 0.00%; $p^2<0.001$), Lymphocyte (PMD, -0.33×10^9 /L; 95% CI, -0.46, -0.19×10^9 /L; I^2, 92.11%; p<0.001) and Albumin (PMD, -4.5 g/L; 95% CI, -7.67, -1.337 g/L; I^2, 98.2%; p=0.0054). There was also a significant increase in biochemical or immunological factors including prothrombin time (PMD, 0.8210 s; 95% CI, 0.24, 1.40 s; I^2, 91.05%; p=0.0058), ALT (PMD, 4.71 U/L; 95% CI, 1.65, 7.76 U/L; I^2, 44.74%; p=0.0025), AST (PMD, 8.4169 U/L; 95% CI, 3.38, 13.46 U/L; I^2, 82.08%; p=0.0011), total bilirubin (PMD, 1.94 mmol/L; 95% CI, 0.40, 3.48 mmol/L; I^2, 49.46%; p=0.0136), LDH (PMD, 144.89 U/L; 95% CI, 61.52, 228.26 U/L; I^2, 93.32%; p=0.0007), procalcitonin (PMD, 0.0496 ng/mL; 95% CI, 0.00, 0.10 ng/mL; I^2, 97.16 %; p=0.0447), CRP (mg/L) (PMD, 50.95 mg/L; 95% CI, 30.04, 71.87 mg/L; I^2, 97.76 %; p<0.0001), IL-6 (pg/mL) (PMD, 26.72 pg/mL; 95% CI, 7.09, 46.36 pg/mL ; I^2, 96.27 %; p=0.0076) and IgA (g/L) (PMD, 0.2176 g/L; 95% CI, 0.03, 0.40 g/L; I^2, 0.00%; p=0.0202). Although neutrophil and monocyte counts, hemoglobin level, D-dimer, hypersensitive and troponin I concentrations as well as IL-2R, IgG and IgM levels had shown to be different in severe patients compared with non-severe individuals, they did not reach conventional levels of statistical significance (P-value>0.05) (Figure 3).

Pooled standardized mean differences

The mean difference of nine laboratory markers in COVID-19 patients with or without severe disease in ten studies was shown in figure 2. The results of the meta-analysis showed that the patients with severe COVID-19 displayed a lower lymphocyte count compared to those with milder forms (-0.18, 95% CI, -0.38, 0.02) (I^2, 0.00 %; p=0.463). The pooled results of these

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studies revealed that the albumin level (three studies) was significantly lower (SMD -0.73, 95% CI, -1.32, -0.14, I^2, 67.3 %; p=0.047) whereas CRP (four studies) (SMD0.79, 95% CI, 0.19 ,1.38, I^2, 36.5%; p=0.193) and LDH (three studies) (SMD1.22, 95% CI, 0.29, 2.15, I^2, 0.48.5%; p=0.143) were higher significantly in patients with more severe COVID-19.

Discussion

Knowing the differences between severe and non-severe patients will help to manage the disease more properly which improves patient outcomes [13]. Several studies demonstrated that serum pro-inflammatory cytokines, pulmonary infection, and the risk of extensive lung damage as well as microthrombosis were elevated in severe COVID-19 related pneumonia or ARDS which is difficult to manage and increase the rate of mortality[14].

In order to investigate factors that were associated with poor prognosis, we then compared findings in severe (N=1555) and non-severe (N=3452) COVID-19 patients and found that high levels of WBC, IL-6, IgA level and CRP and low levels of lymphocyte cell count, as well as platelet count were significantly associated with severity (Table 2, Figure 2); however, the heterogeneity of the included studies was high (I^2>90) which may be due to clinical, methodological or statistical origin. In addition, heterogeneity could be as result of different true effect of subgroups in the data. Therefore, further subgroup analyses or even meta-regression may be helpful to understand the source of heterogeneity.

Host immune response is the other contributing factor in COVID-19 pathogenesis. The level of T-lymphocyte cells could be used as an indicator for prediction of severity and prognosis of patients with COVID-19 pneumonia. In consistent with our findings, in the study by Chen et al, it was shown that lower CD4 T cells count as the indicators of compromised immune system were significantly associated with ICU admission [5]. Inflammatory biomarkers, namely IL1β, IL2, IL6, TNFα and CRP as well as monocyte-macrophage system activity were also higher in severe patients leading to cytokine storm, apoptosis, cell necrosis and progressive worsening of COVID-19 [11, 15]. Moreover, IgA response has been shown to be stronger than IgM response in COVID-19 and prevent virus colonization on the mucous membranes [16].

Gue et al found that lymphocyte counts were lower in severe cases compared to non-severe ones [17]. In the other study by Fan et al., it was shown that lymphopenia was more profound while neutrophilia was detected in the patients admitted in ICU [18]. Previously, pulmonary diseases especially ARDS have been shown to be related with aberrant neutrophil extracellular traps (NETs) formation with primed neutrophils. In COVID-19, NETs formation also occur as a result of cytokine storm [14]. Higher levels of NETs in the blood can activate small vessels occlusion and therefore end organ damage [14]. Following excessive non-effective host immune response in severe COVID-19, inflammatory monocytes also enter the pulmonary circulation leading to lung damage and higher mortality [19]. However, our finding showed that neutrophilia (P-value= 0.0745) and monocyte count reduction (P-value=0.3285) were not significantly associated with severity.

In the early stage, hypercoagulability occurs as the result of inflammation [15]. It has been shown that D-dimer was higher in severe patients which can justify the higher probability of cerebrovascular disease including acute cerebrovascular diseases and impaired consciousness or even taste and smell impairment [17]. Pooled median analysis in our study did not show any significant association between D-dimer level and COVID-19 severity may be due to high heterogeneity; however, prothrombin time as a sign of coagulopathy in non-surviving patients was significantly associated with severity (P-value=0.0058).

Moreover, hypoxia in severe patients can increase blood viscosity as well as inducing transcription factor-dependent signaling pathway and then imitating thrombosis [20]. Lung dissection in severe COVID-19 patients also confirmed the occlusion and microthrombosis in pulmonary small vessels [20]. It is claimed that platelet count cannot be a suitable marker to

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assess coagulability state in COVID patients due to increased thrombopoietin as a result of pulmonary inflammation [20]. However, our analysis showed a very significant negative association between platelet count and disease severity (P-value<0.0001).

In line with other studies, our findings revealed that increased level of procalcitonin is the other indicator of severity and its measurement will be helpful for diagnosis of more severe cases; however, a limited number of COVID-19 patients have increased procalcitonin values [21]. During bacterial infection, procalcitonin is produced from extra-thyroidal sources and is actively sustained by inflammatory markers such as IL-1β, tumor necrosis factor (TNF)-α and IL-6[21]. While interferon (INF)-γ with high concentration during viral infection subside procalcitonin synthesis; therefore, in non-severe COVID-19 patients it can be in normal range unless there is bacterial co/super infection [21].

In addition, we found a significant association between liver enzymes (ALT and AST), bilirubin, serum albumin, LDH and COVID-19 severity (Table 2, Figure 1).

In patients without the history of hepatic diseases, any liver damage during COVID-19 is interpreted as liver injury. Reduced levels of albumin as well as higher concentration of CRP, LDH, D-dimer, IL6, IL2 are indicators of severe infection and poor prognosis and may cause COVID-19-induced liver injury [22]

In a study that was conducted by Zhang et al, elevated liver enzymes mainly ALT, AST, and bilirubin were more detected in severe male COVID-19 patients ranging from 14% to 53% [22]. In addition, the pooled results of five studies showed that higher level of bilirubin was detected in severe COVID-19 patients compared to non-severe cases [23].

Moreover, Boettler et al found that higher levels of ALT and reduced levels of platelet count and albumin in hospitalized COVID-19 patients were associated with higher mortality [24]. However, these changes may happen as a result of pre-existing liver diseases in severe COVID-

19 patients [24]. Consistent with our findings, slightly elevated bilirubin levels and reduced albumin have also been documented in severe cases[25].

LDH is the other laboratory clinical marker which can be helpful in early diagnosis of pulmonary and hepatic diseases and can be a powerful predictive factor for severity in COVID-19 [26]. Notably, lymphocyte counts, which was previously mentioned to be associated with severity in COVID-19, was also relevant with serum LDH[26].

Strength and Limitation

The strengths of this study include selection of high quality studies, large sample size, and pooled median difference calculation. However, diverse laboratory parameters were measured and the heterogeneity of the included studies was high (I^2>90.

Conclusion

This meta-analysis indicates that lymphopenia, elevated liver enzymes, and high levels of inflammatory biomarkers are associated with severe COVID-19 infection; however, data provided are not inclusive enough, and various laboratory parameters were measured in different studies. Therefore, more studies are needed to confirm the results and to show whether relevant indicators can provide clinical help.

Declarations of interest

None

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Figure Legends:

Figure 1. Flowchart of literature search and article selection

Figure 2. Mean difference of nine laboratory markers in COVID-19 patients with or without severe disease in ten studies

Figure 3. Laboratory Changes in Severe Covid-19

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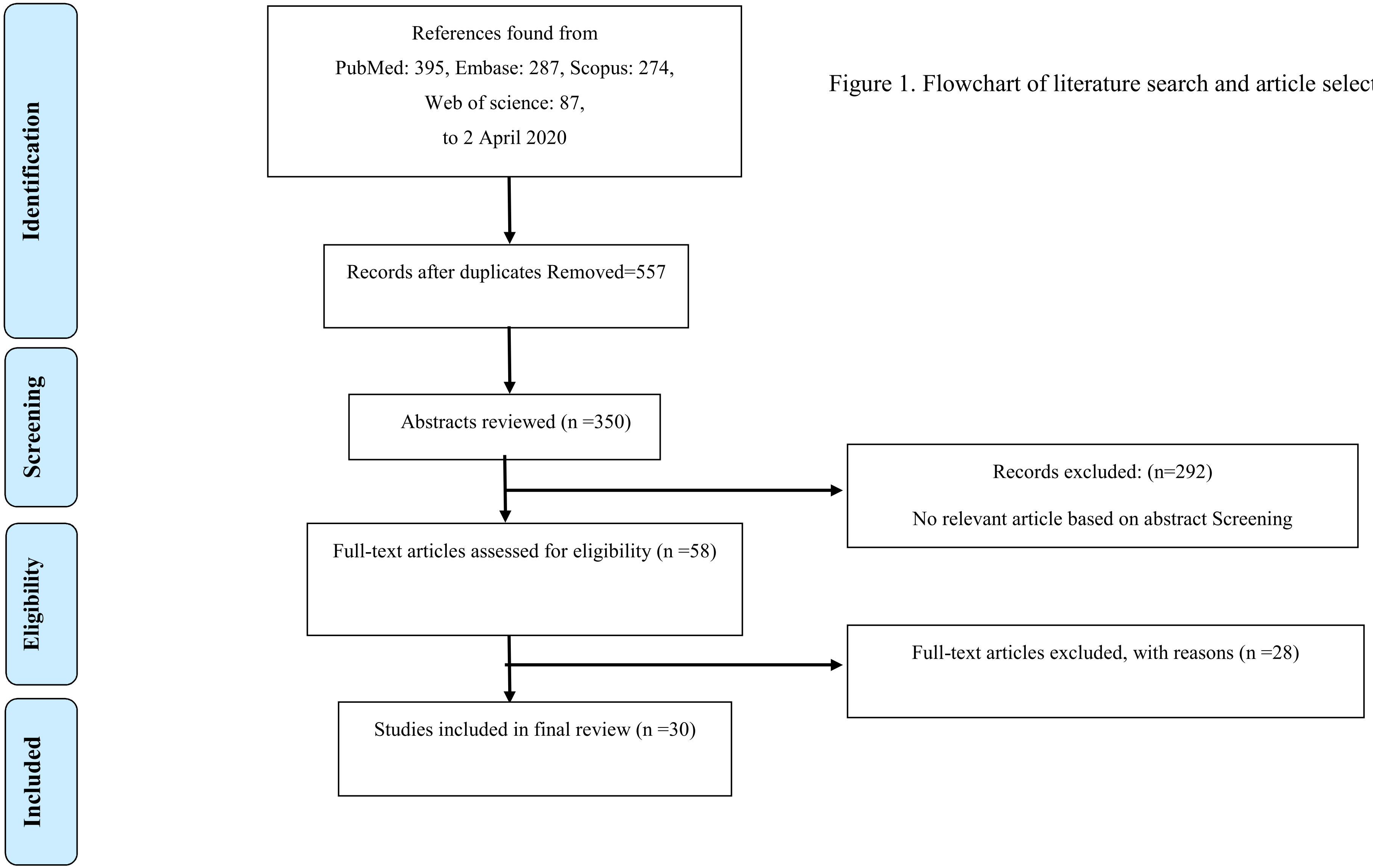

Figure 1. Flowchart of literature search and article selection

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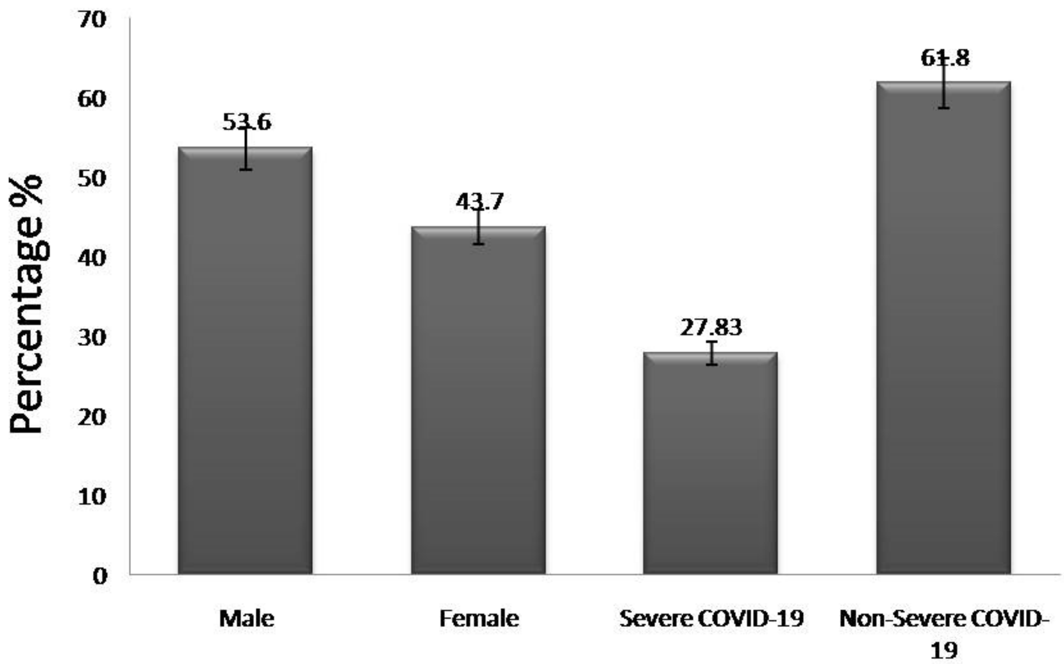

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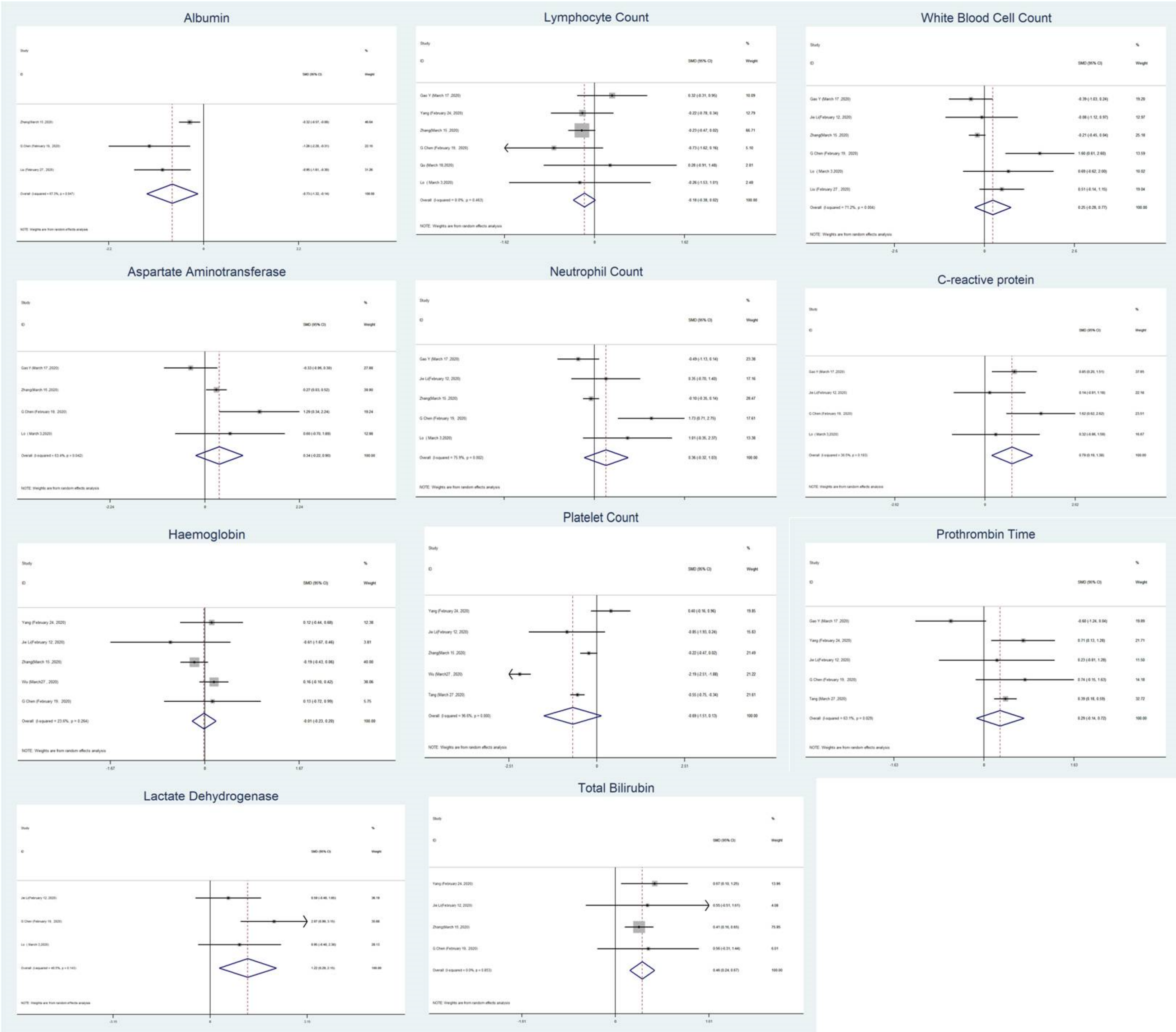

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Table 1: Demographics of the included studies

Study Author(date)	Number of patients	Age Median (Mean)	Severity		Male		Female		Ref
			Severe	**Non-Severe**	**severe**	**Non severe**	**Severe**	**Non severe**	
Mo (March 16 , 2020)	155	54	85	70	55	31	30	39	(13)
Gao Y (March 17 ,2020)	43	-	15	28	9	17	6	11	(14)
Zhou(March28, 2020)	191	56	54	131	38	81	16	56	(15)
Chen(March 17,2020)	274	62	113	161	83	88	30	73	(2)
Qin (March 12, 2020)	452	58	286	166	155	80	131	86	(16)
Zang (February 19, 2020)	140	57	58	82	33	38	25	44	(17)
Guan (February 28, 2020)	1099	47	173	926	540	100	73	386	(18)
Wang(February 7, 2020)	138	56	36	102	22	73	14	49	(19)
Huang (January 24,2020)	41	49	13	28	11	19	2	9	(20)
Liu (February 9, 2020)	12	62.5	2	10	2	6	0	4	(21)
Yang (February 24, 2020)	52	(59.7)	32	20	21	14	11	6	(22)
Jie Li(February 12, 2020)	17	(45.1)	12	5	5	4	7	1	(23)
Li(February 29, 2020)	83	(45.5)	25	58	15	29	10	29	(24)
Deng, Yan(March 20, 2020)	225	-	109	116	67	44	42	72	(1)
Wang(March, 16, 2020)	69	42	14	55	7	25	7	30	(25)
Zang (March 26, 2020)	95	49	32	63	21	32	11	31	(26)
Zhang(March 15 ,2020)	645	-	72	-	295	33	278	39	(27)
Young(March 3, 2020)	18	47	6	12	2	7	4	5	(28)
Wu (March27 , 2020)	280	(43.12)	83	197	45	106	34	91	(29)
G Chen (February 19, 2020)	21	(56.3)	11	10	10	7	1	3	(30)
Tang (February 2020)	183	(54.1)	21	162	16	82	5	80	(31)
wan (March 21 , 2020)	135	47	40	95	21	51	19	44	(32)
Qu (March 18,2020)	30	-	3	27	-	-	-	-	(8)
Lo (March 3,2020)	10	54	4	6	1	2	3	6	(33)
Liu (February 27 , 2020)	78	38	11	67	7	32	5	35	(21)
Qian (March 17, 2020)	91	50	9	82	-	-	-	-	(34)
Liu (February 20 , 2020)	32	-	4	28	-	-	-	-	(35)
Shi (March 25 , 2020)	416	64	82	334	44	63	38	173	(11)
Peng (March 20 , 2020)	112	62	16	96	7	52	9	44	(36)
Tang (March 27 ,2020)	449	(65.1)	134	315	90	178	44	137	(37)

Table 2. Clinical characteristics and laboratory results of patients infected with 2019-nCoV								
Laboratory markers (unit)	**Pooled Median difference**	**CI**	**P-value**	**I^2**	**Pooled mean difference**	**CI**	**P-value**	**I^2**
White blood cell count×10^9/L	1.489	-0.0123, 2.990	0.0519*	94.81%	0.246	-0.279, 0.770	0.004***	71.2%
Neutrophil×10^9/L	1.2360	-0.1223, 2.5943	0.0745	96.61%	0.356	-0.316 , 1.027	0.002***	75.9%
Lymphocyte×10^9/L	-0.3264	-0.4630, -0.1899	<0.0001***	92.11%	-0.183	-0.383,0.018	0.463	0.00%
Monocyte×10^9/L	-0.0555	-0.1668, 0.0558	0.3285	92.55%	-	-	-	-
PLT×10^9/L	-34.6689	-46.5568, -22.7810	<0.0001***	0.00%	-0.686	-1.506 ,0.135	<0.0001***	96.6%
Hb(g/L)	-0.9098	-4.3375, 2.5180	0.6029	49.56%	-0.014	-0.227, 0.198	0.264	23.6%
Alb (g/L)	-4.5114	-7.6897, -1.3331	0.0054**	98.20%	-0.727	-1.319,-0.136	0.047*	67.3%
D-Dimer (µg/L)	-13.3663	-42.3275, 15.5948	0.3657	100.00%	-	-	-	-
Prothrombin time(s)	0.8210	0.2382, 1.4037	0.0058**	91.05%	0.292	-0.140 ,0.725	0.029*	63.1%
ALT (U/L)	4.7059	1.6545, 7.7573	0.0025**	44.74%	-	-	-	-
AST (U/L)	8.4169	3.3782, 13.4557	0.0011**	82.08%	0.342	-0.217,0.902	0.042*	63.4%
Total Bili (mmol/L)	1.9368	0.3983, 3.4753	0.0136*	49.46%	0.459	0.245 ,0.674	0.853	0.00%
LDH (U/L)	144.8860	61.5167, 228.2553	0.0007***	93.32%	1.219	0.289,2.150	0.143	48.5%
Hypersensitive Troponin I (pg/mL)	8.1129	-1.6855, 17.9114	0.1046	93.06%	-	-	-	-
Procalcitonin (ng/mL)	0.0496	0.0012, 0.0980	0.0447*	97.16%	-	-	-	-
CRP (mg/L)	50.9536	30.0374, 71.8698	<0.0001***	97.76%	0.785	0.187, 1.384	0.193	36.5%
IL-6 (pg/mL)	26.7236	7.0922, 46.3551	0.0076**	96.27%	-	-	-	-
IL-2R (U/mL)	358.0611	-160.3494, 876.4716	0.1758	97.68%	-	-	-	-
IgA (g/L)	0.2176	0.0339, 0.4014	0.0202*	0.00%	-	-	-	-
IgG (g/L)	0.4545	-0.6710, 1.5800	0.4286	75.23%	-	-	-	-
IgM (g/L)	-0.0579	-0.1754, 0.0597	0.3345	40.68%	-	-	-	-