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RESEARCH ARTICLE

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Coagulation dysfunction is associated with severity of COVID-19: A meta-analysis

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Abstract

To systematically analyze the blood coagulation features of coronavirus disease 2019 (COVID-19) patients to provide a reference for clinical practice. An electronic search in PubMed, EMbase, Web of Science, Scopus, CNKI, WanFang Data, and VIP databases to identify studies describing the blood coagulation features of COVID-19 patients from 1 January 2020 to 21 April 2020. Three reviewers independently screened literature, extracted data, and assessed the risk of bias of included studies, then, the meta-analysis was performed by using Stata 12.0 software. Thirty-four studies involving 6492 COVID-19 patients were included. Meta-analysis showed that patients with severe disease showed significantly lower platelet count (weighted mean differences [WMD]: -16.29×10^9/L; 95% confidence interval [CI]: −25.34 to −7.23) and shorter activated partial thromboplastin time (WMD: −0.81 seconds; 95% CI: −1.94 to 0.33) but higher D-dimer levels (WMD: 0.44 μg/mL; 95% CI: 0.29-0.58), higher fibrinogen levels (WMD: 0.51 g/L; 95% CI: 0.33-0.69) and longer prothrombin time (PT; WMD: 0.65 seconds; 95% CI: 0.44-0.86). Patients who died showed significantly higher D-dimer levels (WMD: 6.58 μg/mL; 95% CI: 3.59-9.57), longer PT (WMD: 1.27 seconds; 95% CI: 0.49-2.06) and lower platelet count (WMD: -39.73×10^9/L; 95% CI: −61.99 to −17.45) than patients who survived. Coagulation dysfunction is common in severe COVID-19 patients and it is associated with severity of COVID-19.

KEYWORDS
coagulation dysfunction, coronavirus disease 2019, critically ill, meta-analysis, severe disease

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has spread rapidly around the world since its emergence in humans last December.[1,2] According to data released by World Health Organization (WHO), as of 02:00 on 24 April, there have been 2 626 321 confirmed cases of COVID-19 patients including 181 938 deaths worldwide, with a fatality rate of approximately 6.93%.[2]

According to a study conducted by Dr Chen et al,[3] 36% of the patients showed an elevated levels of D-dimer, 16% showed a reduced activated partial thromboplastin time (APTT), and 30% showed a shortened prothrombin time (PT). Besides, Wang et al[4] conducted a retrospective study of 339 COVID-19 patients, including 80 critical and 159 severe cases. Their results showed that the PT was significantly prolonged, and D-dimer levels were evidently elevated in the death group. Another study by Professor Tang, found that the nonsurvivors COVID-19 patients revealed significantly higher levels of D-dimer and FDP, longer PT, and APTT compared to survivors group on admission.[5] Elevated levels of D-dimer are an independent risk factors for acute respiratory distress syndrome and mortality in COVID-19 patients.[6]

Jieyun Zhu and Jielong Pang contributed equally to this study.

Although the above studies have shown that COVID-19 has been linked to coagulation dysfunction, most of them were single-center studies that were conducted in a specific hospital or region. Due to differences in study design and small samples, the key outcomes of these studies are complicated and unclear. A meta-analysis of nine studies suggested that COVID-19 involves longer PT and elevated D-dimer levels,[7] yet several large clinical studies of the disease have been conducted since then and have reported inconsistent findings about coagulation dysfunction.[8-10] Therefore, we meta-analyzed the blood coagulation features of COVID-19 patients to provide a reference for clinical decisions and future research.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This meta-analysis was carried out according to Preferred Reporting Items for Meta-Analyzes of Observational Studies in Epidemiology Statement.[11] The databases PubMed, Embase, Web of Science, Scopus, Chinese National Knowledge Infrastructure, WanFang, and China Science and Technology Journal Database were systematically searched for studies published from 1 January 2020 to 21 April 2020 without language limits. We also manually searched the lists of included studies to identify additional potentially eligible studies. If there were two or more studies described the same population, only the study with the largest sample size was chosen. There was no language restriction placed in the literature search, but only literature published online was included. The following keywords were used, both separately and in combination, as part of the search strategy in each database: "Coronavirus," "2019-nCoV," "COVID-19," "SARS-CoV-2," "D-dimer," "platelet," "coagulation function," "blood clotting," "coagulation," "activated partial thromboplastin time," "fibrinogen," or "prothrombin time."

2.2 | Study eligibility

Studies were included in the meta-analysis if they met the following criteria: (a) if they had cohort, case-control, or case series designs involving more than 40 patients with confirmed COVID-19; (b) if they reported sufficient details about blood coagulation parameters; (c) the diagnosis and severity classification were based on the New Coronavirus Pneumonia Prevention and Control Program

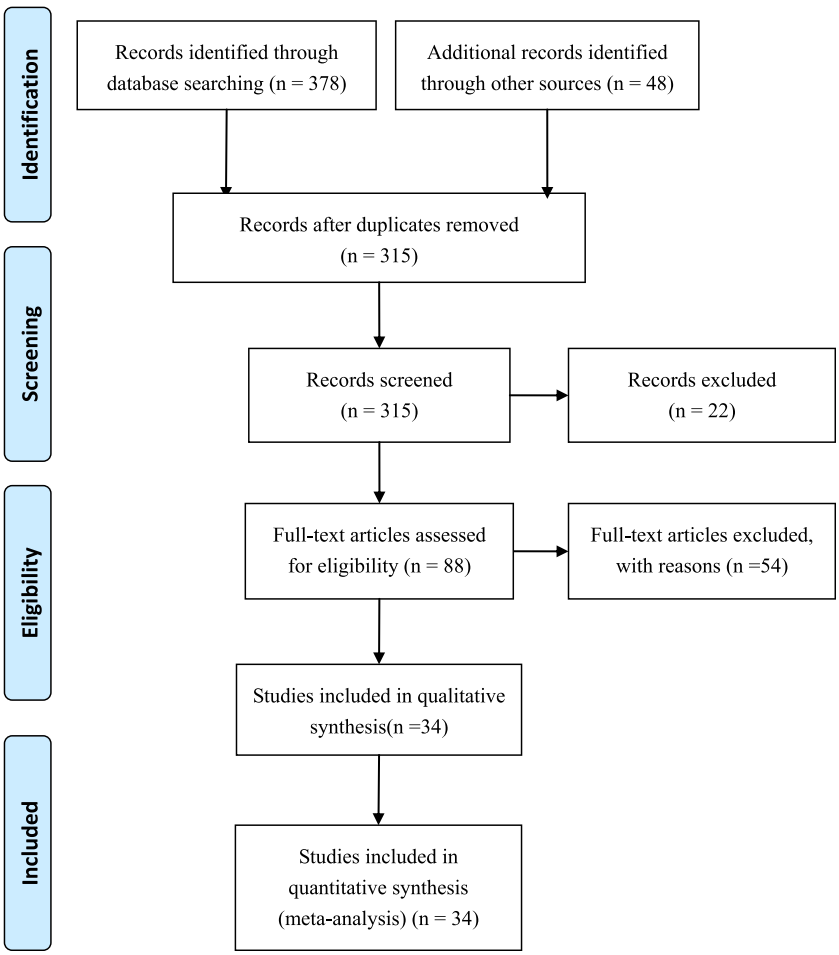

FIGURE 1 Flowchart depicting literature screening process

TABLE 1 Basic characteristics of included studies of COVID-19 patients in China

First author	Publication date in 2020	n	Single- or multicenter[a]	Patient population	Age[b], y	Diagnosis and severity criteria[c]	Outcomes[d]	Follow-up	Quality score[e]
Yang XB[14]	24 Feb	52	Single center	Survival and nonsurvival COVID-19 patients	59.7-13.3	WHO interim guideline	①	2 Dec 2019 to 9 Feb 2020	7
Zhou F[15]	11 Mar	191	Multicenter	Survival and nonsurvival COVID-19 patients	56 (46-67)	WHO interim guideline	①②③	Dec 2019 to 31 Jan 2020	8
Wang Y[16]	8 Apr	344	Single center	Survival and nonsurvival COVID-19 patients	52-72	WHO interim guideline	①②③	25 Feb to 25 Feb	7
An W[17]	16 Apr	110	Single center	Survival and nonsurvival COVID-19 patients	72.4/54.6	Current trail version	②③⑤	24 Jan to 19 Feb	6
Wang L[4]	30 Mar	339	Single center	Survival and nonsurvival COVID-19 patients	69 (65-76)	Trial sixth Edition	①②③⑤	1 Jan to 5 Mar	8
Ruan QR[18]	6 Apr	150	Multicenter	Survival and nonsurvival COVID-19 patients	67 (15-81)/50 (44-81)	Survival and nonsurvival	①	NR	7
Tu WJ[19]	6 Apr	174	Single center	Survival and nonsurvival COVID-19 patients	64-80	Survival and nonsurvival	②	3 Jan to 24 Feb	6
Liu W[20]	28 Feb	79	Multicenter	Mild and severe COVID-19 patients	38 (33, 57)	Trial fourth Edition	①②	30 Dec 2019 to 15 Jan 2020	7
Shi JH[21]	12 Mar	54	Single center	Mild, severe, and critically ill COVID-19 patients	62.5 (50.5, 68.5)	Trial sixth Edition	②	9 Feb to 29 Feb	6
Cheng KB[22]	12 Mar	463	Single center	Mild and severe COVID-19 patients	15-90	Trial fifth Edition	①	Dec 2019 to 06 Feb 2020	7
Wang D[23]	08 Feb	138	Single center	Mild and severe COVID-19 patients	56 (42-68)	WHO interim guideline	①②③⑤	1 Jan to 28 Jan	7
Yuan J[24]	06 Mar	223	Single center	Mild and severe COVID-19 patients	46.5 ± 16	Trial sixth Edition	①②	24 Jan to 23 Feb	9
Fang XW[25]	25 Feb	79	Single center	Mild and severe COVID-19 patients	45 ± 16.6	Trial sixth Edition	①②③⑤	22 Jan to 18 Feb	6
Guan W[26]	06 Feb	1099	Multicenter	Mild and severe COVID-19 patients	47.0	WHO interim guideline	①	NR	9
Qian GQ[27]	17 Mar	88	Multicenter	Mild and severe COVID-19 patients	50 (36.5-57)	WHO interim guideline	①②④	20 Jan to 11 Feb	9
Huang CL[28]	15 Feb	41	Single center	Mild and severe COVID-19 patients	49 (41-58)	WHO interim guideline	①②③⑤	Dec 2019 to 2 Jan 2020	7

TABLE 1 (Continued)

First author	Publication date in 2020	n	Single- or multicenter[a]	Patient population	Age[b], y	Diagnosis and severity criteria[c]	Outcomes[d]	Follow-up	Quality score[e]
Wan SX[29]	21 Mar	135	Retrospective	Mild and severe COVID-19 patients	47 (36-55)	WHO interim guideline	①②③⑤	23 Jan to 8 Feb	8
Gao Y[30]	17 Mar	43	Retrospective	Mild and severe COVID-19 patients	45 ± 7.7/43 ± 14	WHO interim guideline	②③⑤	23 Jan to 2 Feb	6
Zhang JJ[31]	23 Feb	140	Single center	Mild and severe COVID-19 patients	57.0	trail version 3-5	②	16 Jan to 3 Feb	7
Li D[32]	26 Mar	80	Single center	Mild and severe COVID-19 patients	47.8 ± 19.5	Trial fifth Edition	①②③	20 Jan to 27 Feb	7
Li D[33]	2 Apr	62	Single center	Mild, severe, and critically ill COVID-19 patients	49 ± 37/59 ± 31	Trial sixth Edition	①	31 Jan to 25 Feb	6
Zhang W[34]	2 Apr	74	Single center	Mild, Severe, and critically ill COVID-19 patients	52.7 ± 19	Trial sixth Edition	①③	21 Jan to 11 Feb	7
Xiong J[35]	03 Mar	89	Single center	Mild, severe, and critically ill COVID-19 patients	53 ± 16.9	Trial sixth Edition	①	17 Jan to 20 Feb	7
Xie HS[36]	2 Apr	79	Single center	Mild and severe COVID-19 patients	60 (48-66)	Trial sixth Edition	②	2 Feb to 23 Feb	7
Peng YD[37]	2 Mar	112	Single center	Mild and severe COVID-19 patients	62 (55, 67)	Trial sixth Edition	③⑤	20 Jan to 15 Feb	7
Ling Y[38]	18 Mar	292	Single center	Mild and severe COVID-19 patients	48.7 ± 16/65.5 ± 16	Trial fifth Edition	②④	20 Jan to 10 Feb	9
Zhan TT[39]	7 Apr	40	Single center	Mild, severe, and critically ill COVID-19 patients	25-90	Trial sixth Edition	①	20 Jan to 20 Feb	6
Liu SJ[40]	2 Apr	342	Single center	Mild, severe, and critically ill COVID-19 patients	1-88	Trial sixth Edition	①②④	23 Jan to 12 Feb	7
Zuo FT[41]	14 Apr	50	Single center	Mild and severe COVID-19 patients	48.2 ± 15.3	Trial fifth Edition	①③④⑤	19 Jan to 20 Mar	6
Feng Y[8]	10 Apr	476	Multicenter	Mild, severe, and critically ill COVID-19 patients	53 (40-64)	Trial fifth Edition	①②④	1 Jan to 21 Mar	8
Cai QX[42]	2 Apr	298	Single center	Mild and severe COVID-19 patients	47.5 (33-61)	WHO interim guideline	②	11 Jan to 6 Mar	7
Zheng F[43]	Mar	161	Single center	Mild and severe COVID-19 patients	45 (33.5, 57)	Trial fifth Edition	①	17 Jan to 7 Feb	6

(Continues)

TABLE 1 (Continued)

First author	Publication date in 2020	n	Single- or multicenter[a]	Patient population	Age[b], y	Diagnosis and severity criteria[c]	Outcomes[d]	Follow-up	Quality score[e]
Chen X[9]	10 Apr	296	Single center	Mild and severe COVID-19 patients	NR	Trial sixth Edition	①②	27 Jan to 15 Feb	8
Zheng YL[10]	10 Apr	99	Single center	Mild and severe COVID-19 patients	49.4 ± 18.45	Trial fifth Edition	②③	16 Jan to 23 Feb	8

Abbreviations: SD, standard deviation; WHO, World Health Organization.
[a]All studies were retrospective.
[b]Reported as range, mean ± SD, or median (interquartile range). NR, not reported.
[c]Version of New Coronavirus Pneumonia Prevention and Control Program in China, or WHO interim guideline.
[d]① Platelet count, ② D-dimer level, ③ prothrombin time,④ fibrinogen level,⑤ activated partial thromboplastin time.
[e]Score on the Newcastle-Ottawa Scale guidelines.[12]

in China or WHO interim guideline, and patients were grouped into different types such as mild, moderate, severe, and critical pneumonia; (d) the coagulation parameters of the COVID-19 patients were the findings when they were admitted to the hospital or first visited the hospital without the use of anticoagulant prophylaxis or treatment, disease severity classification was done at the end of the follow-up.

2.3 | Data extraction and quality assessment

Three reviewers independently selected literature, extracted data to an Excel database. And any disagreement was resolved by another reviewer. When required, the authors were contacted directly to obtain further information and clarifications regarding their study. Data extraction included the first author's surname and the date of publication of the article, study design, sample size, age, outcome measurement data; relevant elements of bias risk assessment.

The quality of included studies was independently evaluated by the three reviewers based on the Newcastle-Ottawa Scale[12] guidelines. Any disagreement was resolved by another reviewer. This evaluation was conducted based on a set of nine criteria, and studies with a score greater than 6 were considered to be of high quality (total score = 9).

2.4 | Statistical analyzes

Data from studies reporting continuous data as ranges or as median and interquartile ranges were converted to mean ± standard deviation.[13] The weighted mean differences (WMDs) in continuous variables between patient groups were calculated, together with the associated 95% confidence intervals (CIs). All meta-analyzes were performed using STATA 12 (StataCorp, TX). A fixed-effects model was used when the I^2 statistic was below 50% and the associated $P > .10$; otherwise, a random-effects model was used. Funnel plot together with Egger's regression asymmetry test and Begg's test was used to evaluate publication bias. A two-tailed $P < .05$ was regarded as statistically significant.

3 | RESULTS

3.1 | Literature screening and assessment

A total of 378 records were identified from the various databases examined. A total of 48 additional records were identified from the Chinese Medical Journal Network. After a detailed assessment based on the inclusion criteria, 34 studies[4,8-10,14-43] involving 6492 COVID-19 patients were included in the meta-analysis (Figure 1).

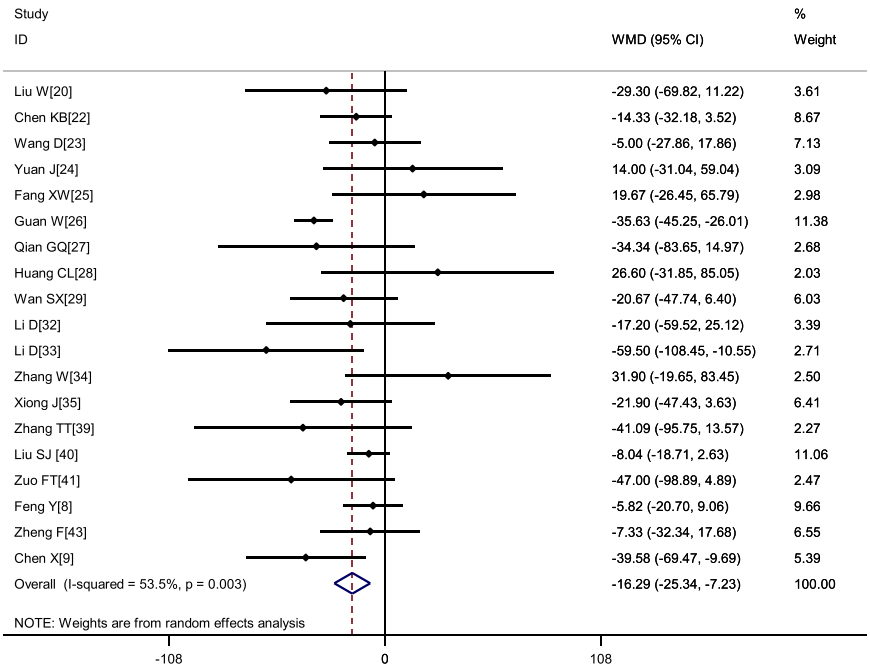

FIGURE 2 Meta-analysis of platelet count ($\times 10^9$/L) between COVID-19 patients with mild or severe disease. COVID-19, coronavirus disease 2019; WMD, weighted mean difference

3.2 | Characteristics of included studies

All studies included in the meta-analysis were conducted in China and published between 24 January 2020 and 16 April 2020. These retrospective studies examined Chinese patients distributed across 31 provinces. Follow-up data was reported for most patients. All studies received quality scores varied from 6 to 9 points, indicating high quality (Table 1).

3.3 | Meta-analysis results

3.3.1 | Coagulation parameters

Pooled results revealed that patients with severe disease showed significantly lower platelet count (WMD: -16.29×10^9/L; 95% CI: −25.34 to −7.23) and shorter APTT (WMD: −0.81 seconds; 95% CI: −1.94 to 0.33) but higher D-dimer level (WMD: 0.44 μg/mL; 95%

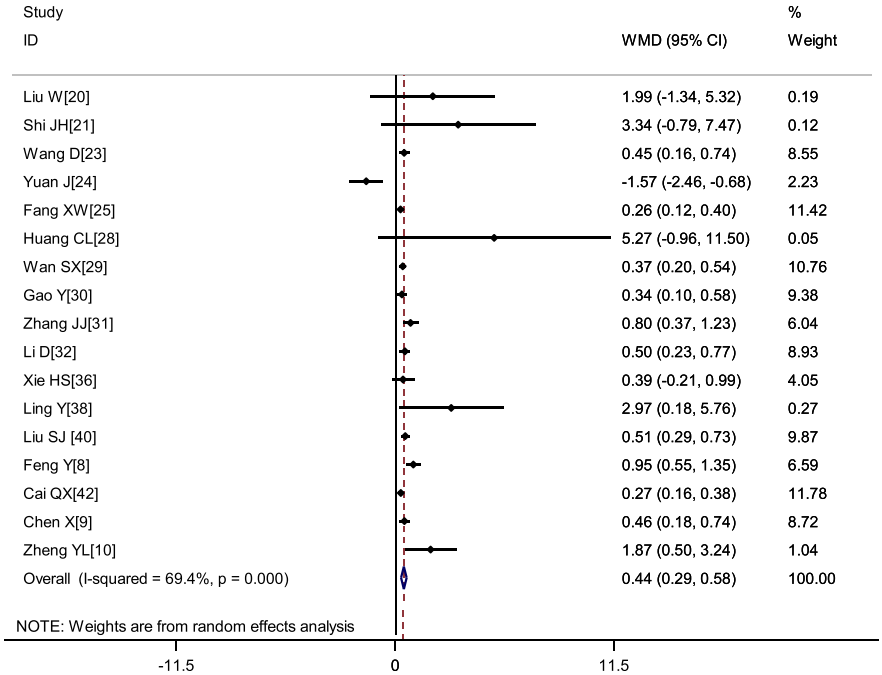

FIGURE 3 Meta-analysis of D-dimer (μg/mL) between COVID-19 patients with mild or severe disease. COVID-19, coronavirus disease 2019; WMD, weighted mean difference

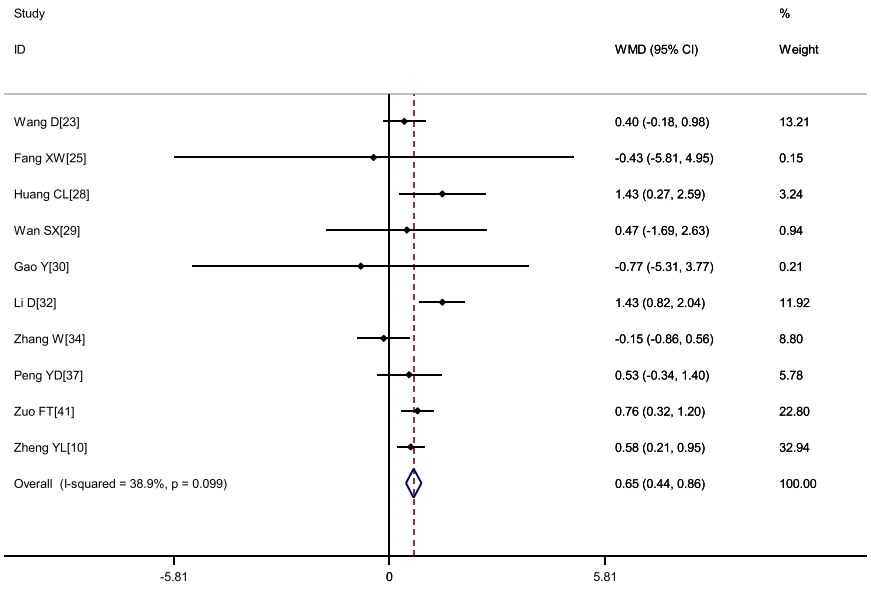

FIGURE 4 Meta-analysis of the prothrombin time (s) between COVID-19 patients with mild or severe disease. COVID-19, coronavirus disease 2019; WMD, weighted mean difference

CI: 0.29-0.58), higher fibrinogen level (WMD: 0.51 g/L; 95% CI: 0.33-0.69) and longer PT (WMD: 0.65 seconds; 95% CI: 0.44-0.86) (Figures 2-6 and Table 2).

Another analysis of seven studies[4,14-19] whose primary outcome was death. The results showed that patients who died showed significantly higher D-dimer levels (WMD: 6.58 μg/mL, 95% CI: 3.59-9.57), longer PT (WMD: 1.27 seconds; 95% CI: 0.49-2.06) and lower platelet count (WMD: -39.73×10^9/L; 95% CI: −61.99 to −17.45) (Table 2).

3.3.2 | Sensitivity analysis

There was heterogeneity in the pooled results of the platelet count and D-dimer. To determine sensitivity, the meta-analyzes of platelet count and D-dimer levels from all included studies were repeated after omitting each study in turn, and the results were similar to those obtained with the entire dataset, indicating the reliability and stability of our meta-analysis (Figure 7).

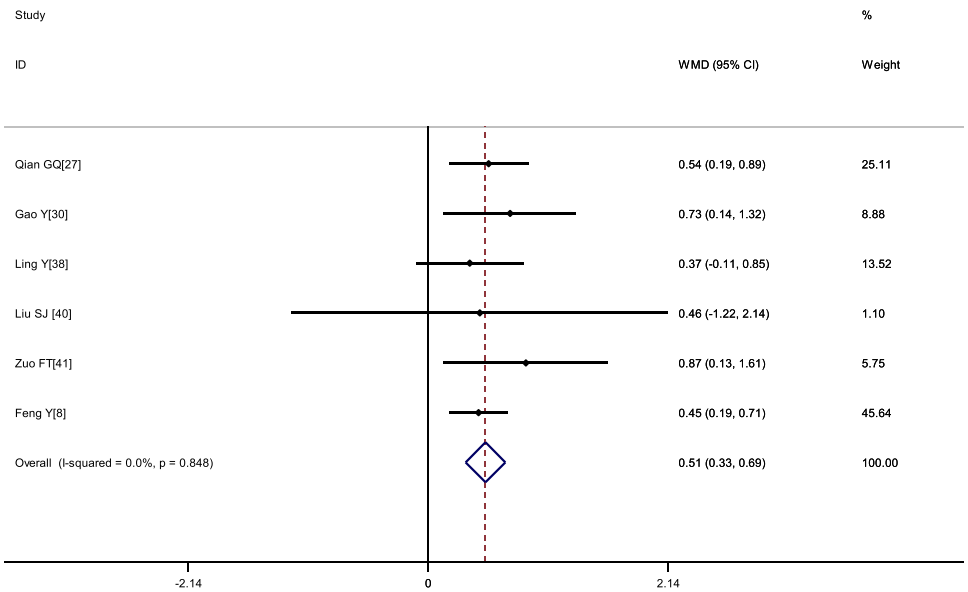

FIGURE 5 Meta-analysis of the FIB (g/L) between COVID-19 patients with mild or severe disease. COVID-19, coronavirus disease 2019; WMD, weighted mean difference

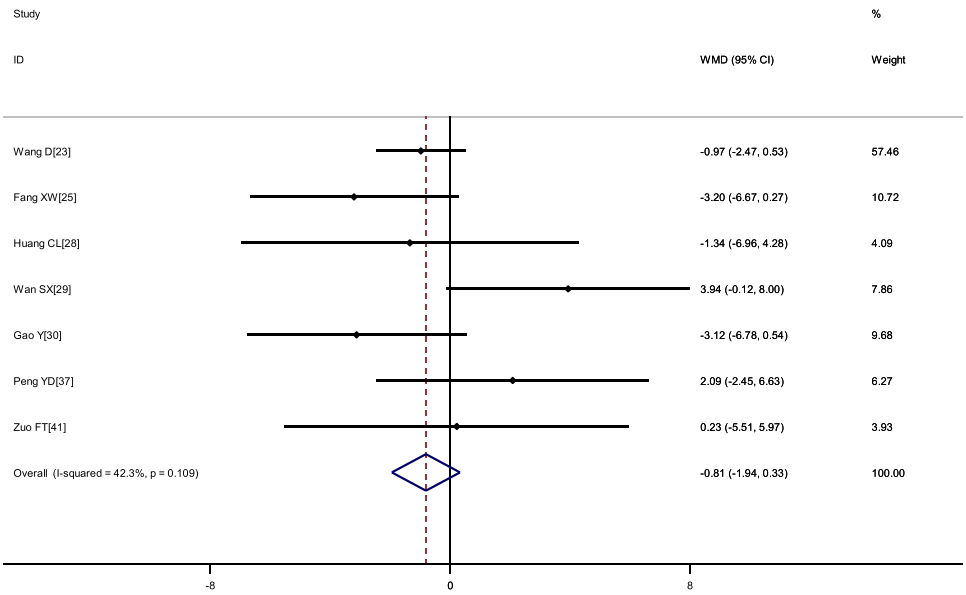

FIGURE 6 Meta-analysis of APTT (s) between COVID-19 patients with mild or severe disease. APTT, activated partial thromboplastin time; COVID-19, coronavirus disease 2019; WMD, weighted mean difference

3.4 | Publication bias

A funnel plot based on the outcome of platelet count showed the *P* values of Egger's test and Begg's test were .516 and .529 respectively, suggesting no significant risk of publication bias (Figure 8).

4 | DISCUSSION

Previous studies have shown that COVID-19 infection has been linked to coagulation dysfunction and coagulopathy appears to be related to severity of illness and resultant thromboinflammation which may increase risk of associated mortality.[23,44,45] This suggested that monitoring blood coagulation parameters during course of the disease may be helpful for the early identification of severe COVID-19 patients, which is essential for healthcare providers in their efforts to treat patients and contain the current outbreak.

Compared to the nine studies involving 1105 patients in the most recent relevant meta-analysis,[7] the present work includes 34 studies published up to 21 April 2020 and a total pooled population of 6492 COVID-19 patients. Our results indicate that low platelet count, elevated D-dimer levels, and prolonged PT occur more often in severe than mild COVID-19, and they occur more often in patients who die from the disease than in those who survive. Consistent with this, individual studies have reported that

TABLE 2 Meta-analysis of different blood coagulation parameters in COVID-19 patients

			Heterogeneity			Meta-analysis	
Parameter	No. of studies	No. of patients	*P*	I^2	Model	WMD (95%CI)	*P*
Mild vs severe disease							
Platelet count, $\times 10^9$/L	19	4027	.003	53.5%	Random	−16.29 (−25.34, −7.23)	<.001
D-dimer level, μg/mL	17	2903	<.001	69.4%	Random	0.44 (0.29, 0.58)	<.001
Prothrombin time, s	10	851	.099	38.9%	Fixed	0.65 (0.44, 0.86)	<.001
Fibrinogen level, g/L	6	1304	.848	0.0%	Fixed	0.51 (0.33, 0.69)	<.001
Activated partial thromboplastin time, s	7	598	.109	42.3%	Fixed	−0.81 (−1.94, 0.33)	<.001
Death vs survival							
Platelet count, $\times 10^9$/L	5	1076	.003	74.9%	Random	−39.73 (−61.99, −17.45)	<.001
D-dimer level, μg/mL	5	1258	.001	79.6%	Random	6.58 (3.59, 9.57)	.001
Prothrombin time, s	4	984	.012	72.7%	Random	1.27 (0.49, 2.06)	.001

Abbreviations: CI, confidence interval; WMD, weighted mean difference.

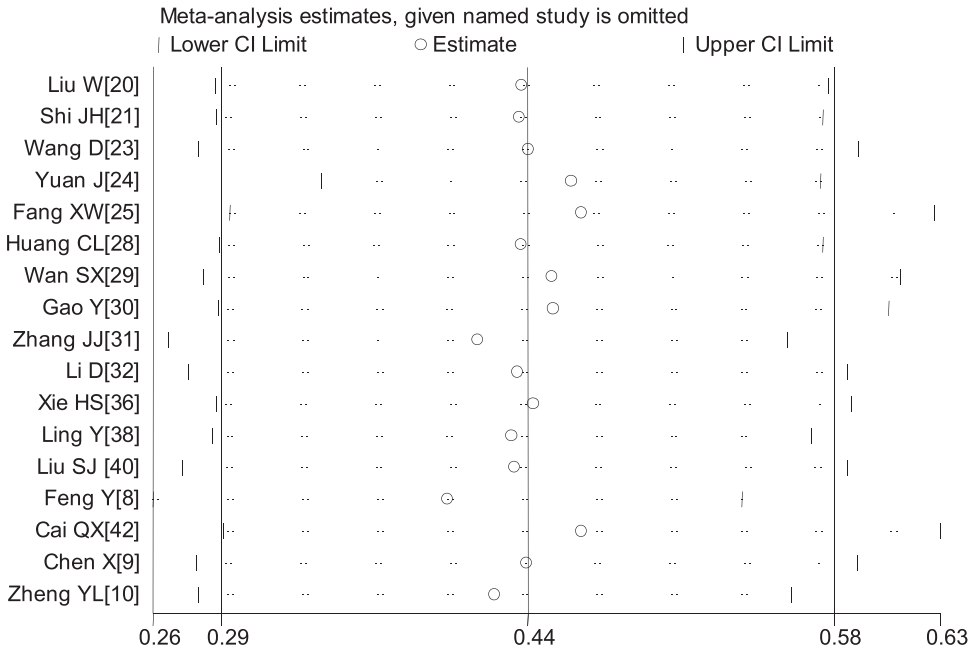

FIGURE 7 Sensitivity analysis of D-dimer levels between COVID-19 patients with mild or severe disease.COVID-19, coronavirus disease 2019

COVID-19 patients in the intensive care unit have significantly higher coagulation parameters than those of COVID-19 patients not receiving intensive care,[28] and that more than 70% of patients who die from COVID-19 meet the criteria of disseminated intravascular coagulation.[5] These findings suggest that monitoring blood coagulation parameters in COVID-19 patients may aid in early detection of severe disease.

The coronavirus causing COVID-19 may trigger coagulation dysfunction because it induces abundant release of proinflammatory cytokines in various tissues, which can lead to systemic inflammatory response syndrome that damages the microvascular system and thereby activates the coagulation system, leading to generalized small vessel vasculitis, and extensive microthrombosis.[46,47] In particular, patients with severe COVID-19 may be at high risk of venous thromboembolism, which may be present in up to 25% of such patients.[48] Indeed, a study of 1099 patients across China suggests that 40% of all COVID-19 patients may be at high risk of venous thromboembolism.[49] Risk may be exacerbated by the dehydration due to fever and diarrhea, hypotension, and prolonged bed rest characteristic of the disease, all of which are risk factors for coagulation in their own right,[50] as well as by the use of vasopressors and central venous catheters in the intensive care unit.[51] This has led to the recommendation that patients with severe COVID-19 should be carefully monitored for coagulation function and given prophylactic anticoagulant therapy in the absence of anticoagulant contraindications.[47] Dr Connors et al also reported that the use of an increased prophylactic dose of nadroparin resulted in a significant decrease in D-dimer levels.[52]

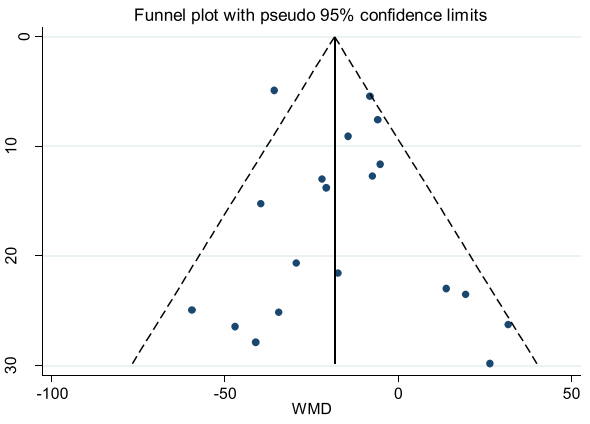

FIGURE 8 Funnel plot of platelet count data from all included studies

Although this study rigorously analyzed coagulation parameters data collected from a large sample of COVID-19 patients, we were unable to eliminate the heterogeneity observed between studies. For example, the course and the severity of the disease varied across studies. Given that most of the studies included in our meta-analysis were single-center, retrospective studies, it was difficult for us to control for the effects of several confounding factors, including bias in patient admission and selection, as well as differences in disease severity and course. Further research is needed to verify and extend our results.

5 | CONCLUSION

In summary, current evidence showed that coagulation dysfunction is common in severe COVID-19 patients, and it is associated with severity of COVID-19. And thus could be used as early warning indicators of disease progression during hospitalization.

ACKNOWLEDGMENT

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Pan Ji, Hongyuan Li, Zhimei Zhong, and Bocheng Li collected and analyzed the data. Jianfeng Zhang acquired the funding. Jieyun Zhu and Jielong Pang designed the study and wrote the first draft of the manuscript. Jianfeng Zhang and Junyu Lu designed and supervised the study and finalized the manuscript, which all authors read and approved.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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