Systematic Review and Meta-Analysis

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The effect of coagulation factors in 2019 novel coronavirus patients

A systematic review and meta-analysis

Guiling Xiang, MD, Shengyu Hao, PhD, Cuiping Fu, PhD, Weiping Hu, MD, Liang Xie, MD, Qinhan Wu, MS, Shanqun Li, PhD*, Xuhui Liu, PhD*

Abstract

Background: The role of coagulation dysfunction in Severe Coronavirus Disease 2019 (COVID-19) is inconsistent. We aimed to explore the impact of coagulation dysfunction amongst patients with COVID-19.

Methods: We searched PubMed, Cochrane and Embase databases from December 1, 2019 to April 27, 2020 following Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Data about coagulation (Platelets, PT, APTT, fibrin, fibrinogen degradation products, D-dimer), prevalence of coagulation dysfunction and mortality were extracted. Meta regression was used to explore the heterogeneity.

Results: Sixteen observational studies were included, comprising 2, 139 patients with confirmed COVID-19. More severe COVID-19 cases tended to have higher mean D-dimer (SMD 0.78, 95% CI 0.53 to 1.03, $P < .001$). The similar pattern occurred with PT and fibrin, with a contrary trend for PLTs. Coagulation dysfunction was more frequent in severe cases compared to less severe (SMD 0.46, 95% CI 0.25 to 0.67, $P < .001$). Higher mortality was associated with COVID-19-related coagulopathy (RR 10.86, 2.86 to 41.24, $P < .001$). Prevalence of ARDS was increased in more severe patients than less severe cases (RR 16.52, 11.27 to 24.22, $P < .001$). PT, fibrin and D-dimer levels elevated significantly in non-survivors during hospitalization.

Conclusion: Presence of coagulation dysfunction might be associated with COVID-19 severity, and coagulopathy might be associated with mortality. Coagulation markers including PT, fibrin and D-dimer may imply the progression of COVID-19. This illuminates the necessity of effectively monitoring coagulation function for preventing COVID-19-related coagulopathy, especially in severe patients. For the obvious heterogeneity, the quality of the evidence is compromised. Future rigorous randomized controlled trials that assess the correlation between coagulation and COVID-19 are needed.

Trial registration: PROSPERO (CRD42020183514).

Abbreviations: aPL = antiphospholipid anti-bodies, APTT = activated partial thromboplastin time, ARDS = acute respiratory distress syndrome, CFR = case-fatality rate, CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, COVID-19 = coronavirus disease 2019, DIC = disseminated intravascular coagulation, ECOM = extracorporeal membrane oxygenation, FDP = fibrinogen degradation product, LA = lupus anticoagulant, MOOSE = meta-analysis of observational studies in epidemiology guidelines, NOS = Newcastle-Ottawa Scale, PAI-1 = Plasminogen Activator Inhibitor 1, PE = pulmonary embolism, PLTs = platelets, PT = prothrombin time, RRs = relative risks, SARS = severe acute respiratory syndrome, SMD = standard mean difference, WHO = World Health Organization, WMD = weighted mean difference.

Keywords: coagulation dysfunction, Coronavirus Disease 2019, mortality, severity

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Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital Fudan University, Shanghai, China.

** Correspondence: Shanqun Li, Department of Pulmonary and Critical Care Medicine, Zhongshan Hospital, Fudan University, 180 Fenglin Road, Shanghai, 200032, China (e-mail: li.shanqun@zs-hospital.sh.cn).*

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1. Introduction

As of May 5, 2020, 3, 525, 116 laboratory-confirmed COVID-19 cases and 243, 540 deaths were reported to World Health Organization (WHO) from 215 countries, areas or territories across the globe.[1] Tang et al[2] first reported 15 (71.4%) of non-survivors developed disseminated intravascular coagulation (DIC), while only one (0.6%) survivor did during hospital stay. In 383 French patients, Helms et al[3] also reported 51.3% of patients with COVID-19-related acute respiratory distress syndrome (ARDS) developed thrombotic complications, mainly life-threatening pulmonary embolisms (PE).

ARDS is one of the leading complication in COVID-19 patients.[2] The mechanisms regarding to ARDS secondary to COVID-19 remain unclear. Due to lung inflammation in patients with ARDS, fibrinolytic dysfunction and increased pro-coagulant activity cause excessive deposition of fibrin in alveolar spaces. Accordingly, weakened fibrinolytic activity is attributed to fibrin deposition and increased levels of the plasminogen activator inhibitor 1 (PAI-1).[3–6] During the severe acute respiratory syndrome (SARS) epidemic in 2003, elevated PAI-1 levels were measured in SARS patients, and compared with the healthy controls and other pneumonias patients.[7] Up to now, whether coagulation dysfunction is frequent in severe COVID-19 patients and whether it contributes to ARDS and further death are still unclear. To obtain a more compelling evidence, we pooled data from all available original studies in the area. We aimed to answer the following question: Does the presence of coagulation dysfunction are associated with COVID-19 severity? Furthermore, we sought to assess whether coagulopathy and ARDS are associated with mortality.

2. Methods

2.1. Study selection and inclusion criteria

Current systematic review is performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[8] The electronic databases (PubMed, Cochrane and Embase) were searched through the keywords "(novel coronavirus OR SARS-CoV-2 OR HCoV OR nCoV OR COVID* OR NCP* OR pneumonia). Searches were limited to: those published from Dec 1 2019 to April 27 2020; original articles; human; written in English and Chinese. As a complement to this search strategy, we searched medRxiv (https://www.medrxiv.org), the references of included studies and relevant reviews.

Cohort studies of COVID-19 patients exploring potential clinical risk factors of severity or mortality was included. We required that studies reported coagulation index (Platelets, PLTs; prothrombin time, PT; activated partial thromboplastin time, APTT; fibrin; fibrinogen degradation products, FDP; D-dimer) or coagulation dysfunction. Studies which enrolled the same patients were evaluated by two reviewers and only one was included.

2.2. Data collection and quality assessment

XGL and HSY independently reviewed the titles and abstracts of the records (n = 3, 491) identified, excluded duplicate (n = 685) and irrelevant studies (2,340). The rest of 466 studies were read in full and the data in the included 16 studies were extracted by the same two researchers (XGL and HSY) (see Figure S1, Supplemental Content, http://links.lww.com/MD/F613, which illustrates the search strategy and screening process). The following data were extracted: first authors, sample size, city of study, age, sex, symptoms (Fever, Cough, Dyspnea), underlying disease (hypertension; diabetes; cardiovascular; chronic obstructive pulmonary disease, COPD; malignancy; chronic kidney disease, CKD), disease severity (severe or non-severe), mortality (non-survivors or survivors), coagulation indexes (Platelets, PT, APTT, fibrin, FDP, D-dimer) and coagulation dysfunction. Quality assessments of included studies was performed by Newcastle-Ottawa Scale (NOS). Any discrepancies were addressed though consultation by all authors.

2.3. Ethics

In this study, ethical approval is not required because the included data are based on previously reported articles, and identifying information of participants will not be revealed.

2.4. Data analysis

Statistical analysis in this study was carried out using Stata version 15.1 (Stata Corp., College Station, TX). For continuous variable, we estimated the weighted mean difference (WMD) or standard mean differences (SMD) with 95% confidence intervals (CI), appropriately; while for categorical variable, we estimated the pooled relative risks (RRs) with 95% CI. I2-index was estimated and reported to measure heterogeneity. For results with significant heterogeneity ($I2 \geq 50\%$ or $P \leq .10$), random effects models were used; otherwise ($I2 < 50\%$ and $P > .10$), fixed effect models were utilized. Through meta regression, we explored the source of heterogeneity. In addition, funnel plots and Egger's tests were performed to evaluate publication bias.

3. Result

3.1. Search result and study characteristics

16 included studies were all retrospective and cohort design, with a maximum of 339 patients and minimum of 30, and 144 deceased.[2,9–23] Eleven[9–19] compared values between severe cases and non-severe cases, and the remainder[2,20–23] compared non-survivors with survivors. Three[2,20,22] reported the association of coagulopathy with death, 3 reported dynamic changes of coagulation parameters from admission to discharge or death.[2,20,23] Additionally, eight studies enrolled patients from designated hospitals in Wuhan, epicenter of the epidemic. Patients with more severe disease (severe or non-survivors) were older, more likely to be men, and had higher morbidity of underlying disease (eg. hypertension; diabetes; cardiovascular; CKD). The main characteristics of all eligible studies were presented in Table 1. NOS scores of all studies were more than 6 (Table 1 and see Table S1, Supplemental Content, http://links.lww.com/MD/F614, which illustrates the risk of bias of included studies). No publication bias was detected by Egger test ($P = .565$) (see Supplementary Digital Content, Fig. 2, Supplemental Content, http://links.lww.com/MD/F613, which illustrated the Egger funnel plot showing publication bias regarding severity of COVID-19 on coagulation indexes).

3.2. The association of disease severity with coagulation dysfunction

On the whole, coagulation indexes were worse in severe cases compared to less severe patients (SMD 0.46, 95% CI 0.25 to

Table 1

Characteristics of included studies comparing more severe and less severe cases.

Author	No.	Period	Consecutive Patients	Age (y)	Female	Concomitant diseases				Quality
						Hypertension	Diabetes	Cardio-vascular	CKD	
Wuhan										
Mao et al[9]	214	1.16–2.19	Yes	58.2, 48.9	50, 65.9	36.4, 15.1	17.1, 11.9	NA	2.3, 3.2	8
Zhang et al[10]	221	1.2–2.10	Not clear	62, 51	36.4, 56	47.3, 16.9	12.7, 9	23.6, 5.4	9.1, 0.6	7
Xie et al[11]	79	2.2–2.23	Yes	62.5, 59	35.7, 49	14.3, 19.6	7.1, 11.8	7.1, 9.8	NA	7
Zhang et al[12]	140	1.16–2.3	Yes	64, 51.5	44.6, 53.7	39.3, 24.4	14.3, 11	7.1, 3.7	3.6, 0	9
Zhou et al[20]	191	12.1–1.31	Yes	69, 52	29.6, 40.9	48.2, 23.4	31.5, 13.9	24.1, 1.5	3.7, 0	7
Wang et al[21]	339	1.1–2.6	Yes	76, 68	40, 53.7	49.2, 38.7	16.9, 15.7	32.3, 11.7	6.2, 3.3	8
Tang et al[6]	183	1.1–2.3	Yes	64, 52.4	23.8, 49.4	NA	NA	NA	NA	7
Zhang et al[22]	48	12.25–2.15	Yes	78.7, 66.2	29.4, 32.3	70.6, 64.5	29.4, 16.1	23.5, 29	29.4, 0	7
Outside Wuhan										
Zheng et al[13]	96	1.19–3.20	Yes	57, 47.5	33.8, 59.1	41.9, 18.2	13.5, 4.6	9.5, 0	1.4, 0	8
Qu et al[14]	30	1–2	Not clear	60, 49.4	NA	NA	NA	NA	NA	7
Zheng et al[15]	99	1.16–2.20	Yes	63, 42	NA	NA	NA	NA	NA	8
Gao et al[16]	43	1.23–2.2	Not clear	45, 42	40, 39.3	40, 25	40, 3.6	6.7, 7.1	NA	7
Wan et al[17]	135	1.23–2.8	Not clear	56, 44	47.5, 45.3	10, 9.5	22.5, 3.2	15, 1.1	NA	7
Zheng et al[18]	161	1.17–2.7	Not clear	57, 40	53.3, 49.6	40, 7.6	6.7, 3.8	6.7, 1.5	NA	8
Ma et al[19]	84	1.21–3.2	Yes	58, 46.5	40, 43.8	20, 12.5	16.9, 15.7	10, 4.7	0, 1.6	7
Fogarty et al[23]	83	3.13–4.10	Yes	68, 60.5	33.3, 34	NA	NA	NA	NA	9

CKD = chronic kidney disease, NA = not available, No. = number of included patients.

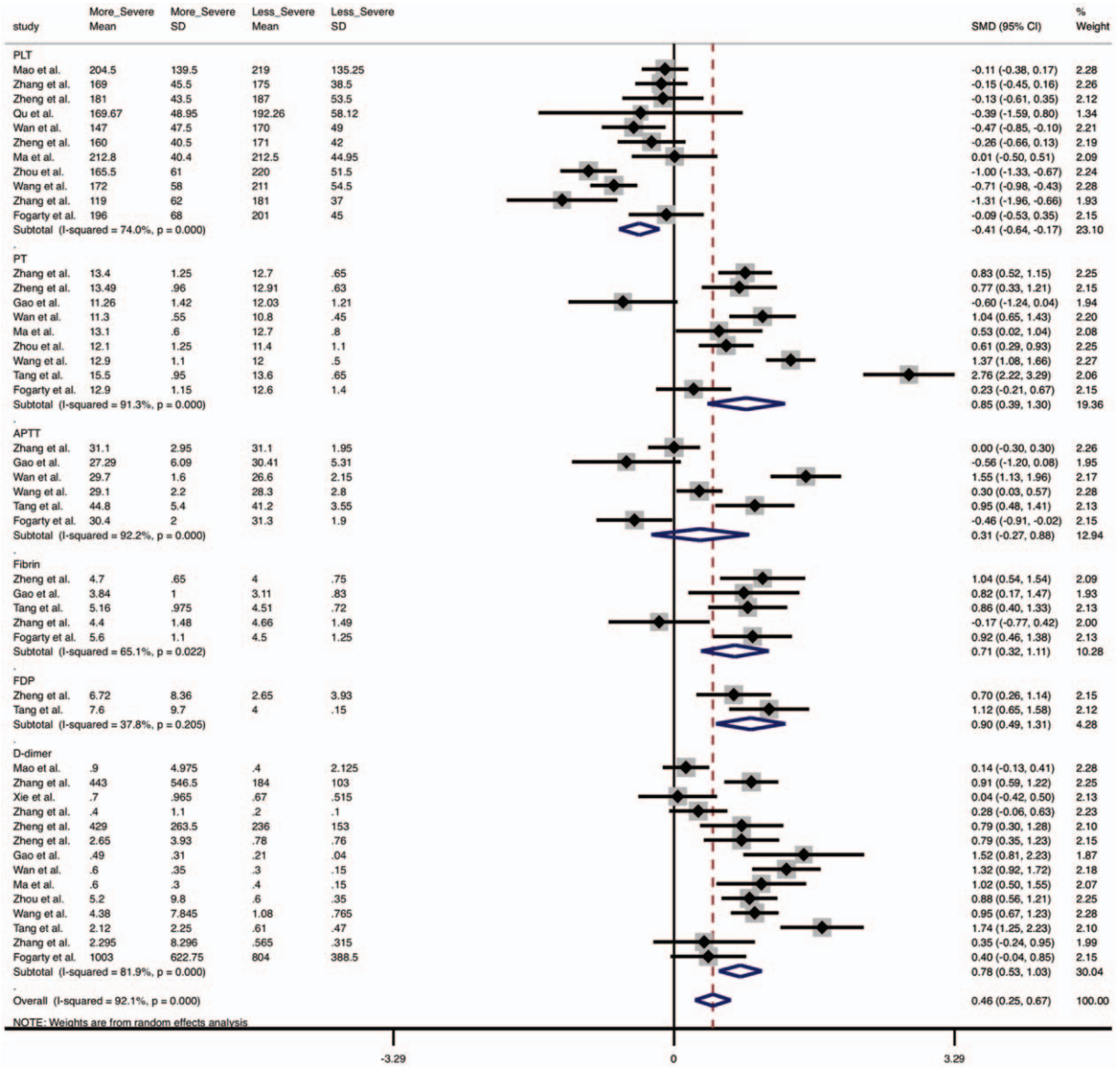

Figure 1. Forest plots of coagulation markers change between more severe and less patients with COVID-19.

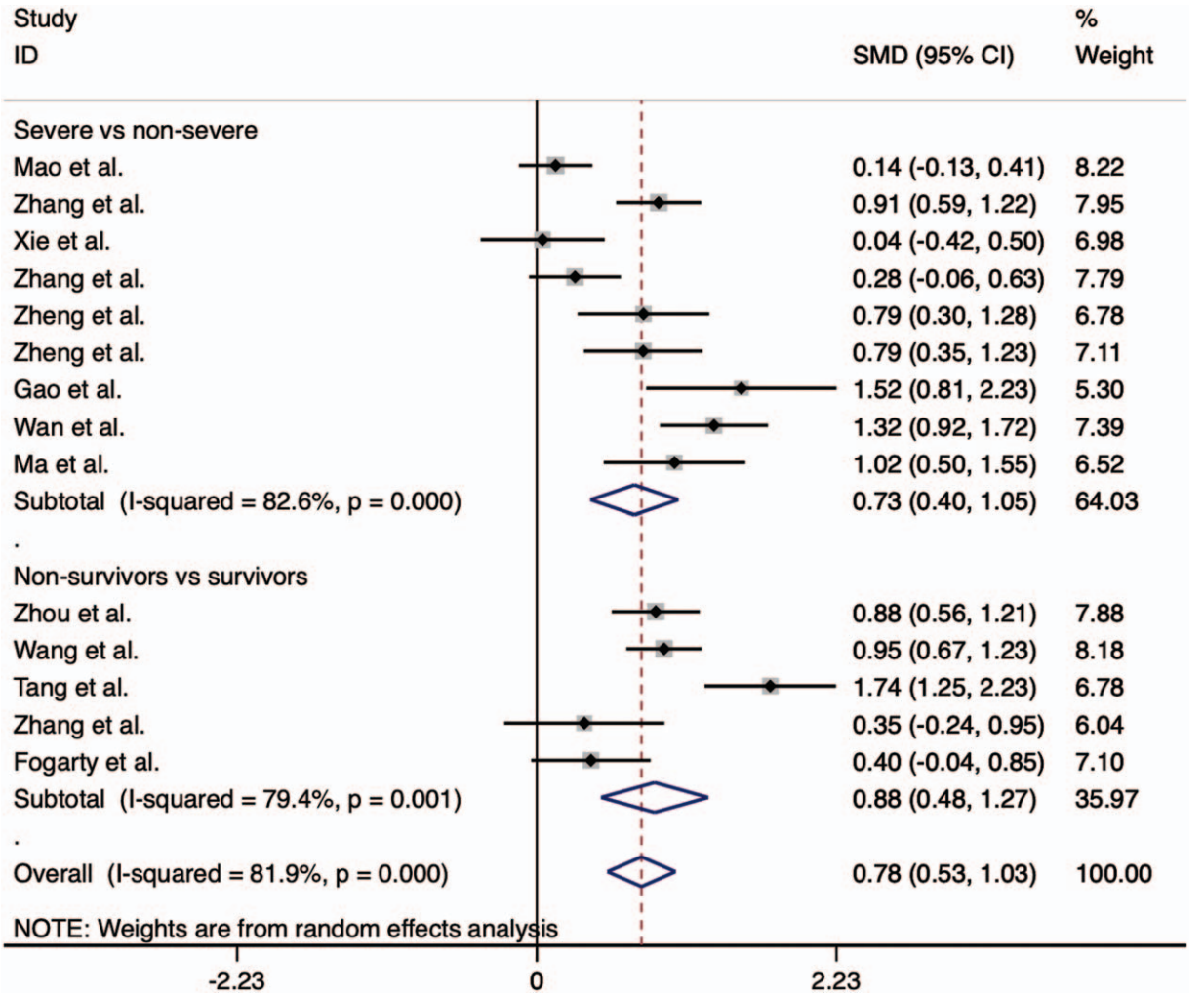

Figure 2. Forest plots of D-dimer change between more severe and less patients with COVID-19.

0.67, $P < .001$) (Fig. 1). Similar results were observed by subgroup analysis. Mean D-dimer in severe cases was higher than those in less severe cases (SMD 0.78, 95% CI 0.53 to 1.03; $P < .001$), as was mean PT (WMD 0.66, 95% CI 0.55 to 0.78 s, $P < .001$) and fibrin (WMD 0.68 g/L, 95% CI 0.38 to 0.98, $P < .001$) (Figs. 2–4). Besides, mean PLTs in patients with severe conditions was lower compared to less severe patients (WMD -21.68, 95% CI -34.28 to -9.07, $P = .001$) (Fig. 5). A higher incidence of DIC in non-survivors was also reported compared to survivors (71.4% vs 0.6%, $P < .001$).[2] There was no difference in mean APTT between patients with severe conditions and less severe conditions (WMD 0.79, 95% CI -0.74 to 2.31, $P = .314$) (Fig. 6). Meta regression showed that SMD of coagulation indexes in each included study were not associated with increasing age, male sex, underlying diseases, clinical type of COVID-19, symptoms on admission and sites of studies (Table 2).

3.3. The association of mortality with coagulopathy

Mortality was higher in patients with coagulopathy than those without (RR 10.86, 2.86 to 41.24, $P < .001$) (Fig. 7). Mortality was also increased in patients with more severe COVID-19 than those who were less severe (RR 16.87, 4.25 to 67.03, $P = .001$) (Fig. 8). Prevalence of ARDS was elevated in more severe patients than less severe cases (RR 16.52, 11.27 to 24.22, $P < .001$) (Fig. 9).

3.4. Dynamic changes in coagulation parameters during hospitalization

Three studies showed clearly dynamic elevation of PT, fibrin and D-dimer levels among non-survivors compared with survivors. The pooled outcomes of PT, fibrin and D-dimer levels elevated significantly in non-survivors during the clinical course, on the contrary, the rise of those in survivors were not remarkable (Fig. 10A–C). However, clearly dynamic decreased APTT levels in both non-survivors and survivors was displayed in Figure 10D.

4. Discussion

In this meta-analysis of 2, 139 COVID-19 patients from 16 studies, the pooled results revealed that an increased risk of coagulation dysfunction might associate with severity of COVID-19 and coagulopathy might be associated with mortali-

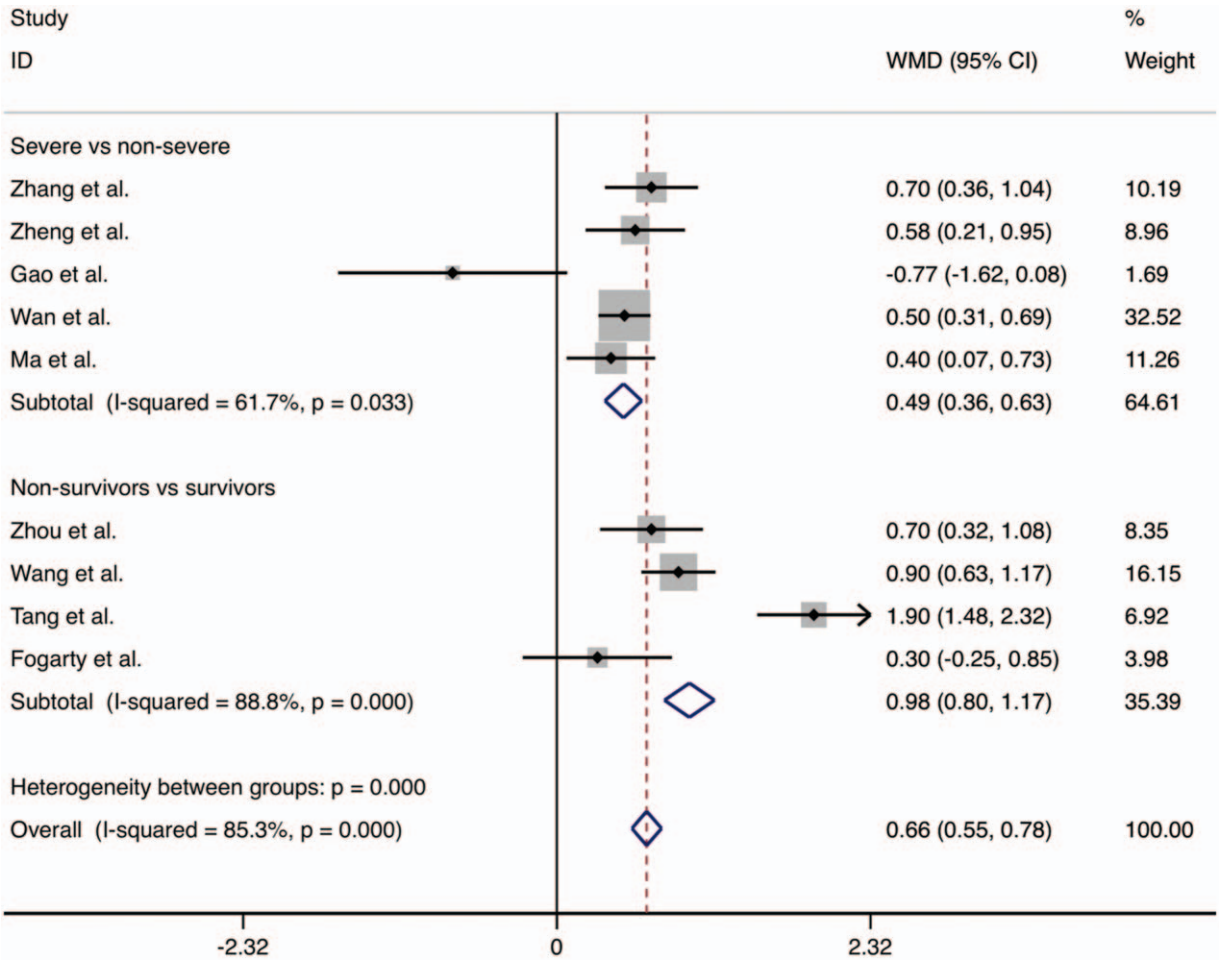

Figure 3. Forest plots showing PT change according to severity of COVID-19.

ty. Our findings are concomitant with a previous COVID-19 meta-analysis on PLTs count, which reported platelet count was significantly decreased in patients with severe COVID-19 or non-survivors.[24] Another previous meta-analysis demonstrated that PT and D-dimer levels were significantly higher in severe COVID-19 patients which was consistent with our results, but no difference of PLTs and APTT was observed.[25] The divergence may be due to less included literatures and confounding factors in their review.

The increase of PT, fibrin, FDP and D-dimer levels is indicators of possible coagulation dysfunction due to COVID-19 infection. Evaluation of the dynamic change in PT, fibrin and D-dimer show that coagulation markers rise rapidly above normal range before death. The fibrin and D-dimer level of non-survivors were beyond normal even on admission which suggests that coagulation dysfunction may already exist before ARDS. Two case reports[26,27] have observed acute PE, and a French report[28] by experience with extracorporeal membrane oxygenation (ECOM) in ARDS revealed 20% of PE event during COVID-19 infection. We guess severe compromised ability of gas exchange may due to thrombosis within the pulmonary vasculature in patients with COVID-19.

Zhang et al[29] described three COVID-19 cases with significant coagulopathy and multiple infarcts. Antiphospholipid anti-bodies (aPL) were also detected in all the patients, but not lupus anticoagulant (LA) which contributes to thrombosis. In a multicenter study, positive LA was detected in 50 (87.7%) COVID-19 patients and LA/aPL elevations were measured in majority of patients.[3] Strikingly, rare increase of LA/aPL was observed in other pathologies. LA/aPL may indicate remarkable cellular destruction. Presence of LA has a strong association with high D-dimers level and early thrombosis in the COVID-19 course.[3]

Wu et al[30] found the overall case-fatality rate (CFR) from COVID-19 was 2.3% (1, 023 deaths/ 44, 672 confirmed cases). No death occurred among milder cases, but CFR in critical cases was 49.0%. We report mortality risk of severe COVID-19 increased 34-fold compared to milder infection, and coagulopathy mostly indicated by abnormal levels of coagulation marker, is associated with 11-fold increase of mortality risk (see Supplementary Digital Content, Fig. 3, Supplemental Content, http://links.lww.com/MD/F613, which illustrates the schematic diagram about COVID-19 on coagulation dysfunction). Based on reported findings, we suggest clinical practitioners closely monitor dynamic changes of coagulation markers, especially severe COVID-19 infection, which may contribute to risk stratification early, and then give corresponding treatment to prevent poor outcomes. Moreover, rigorous randomized controlled trials should be conducted to determine whether the use of anticoagulant therapy are beneficial in COVID-19.

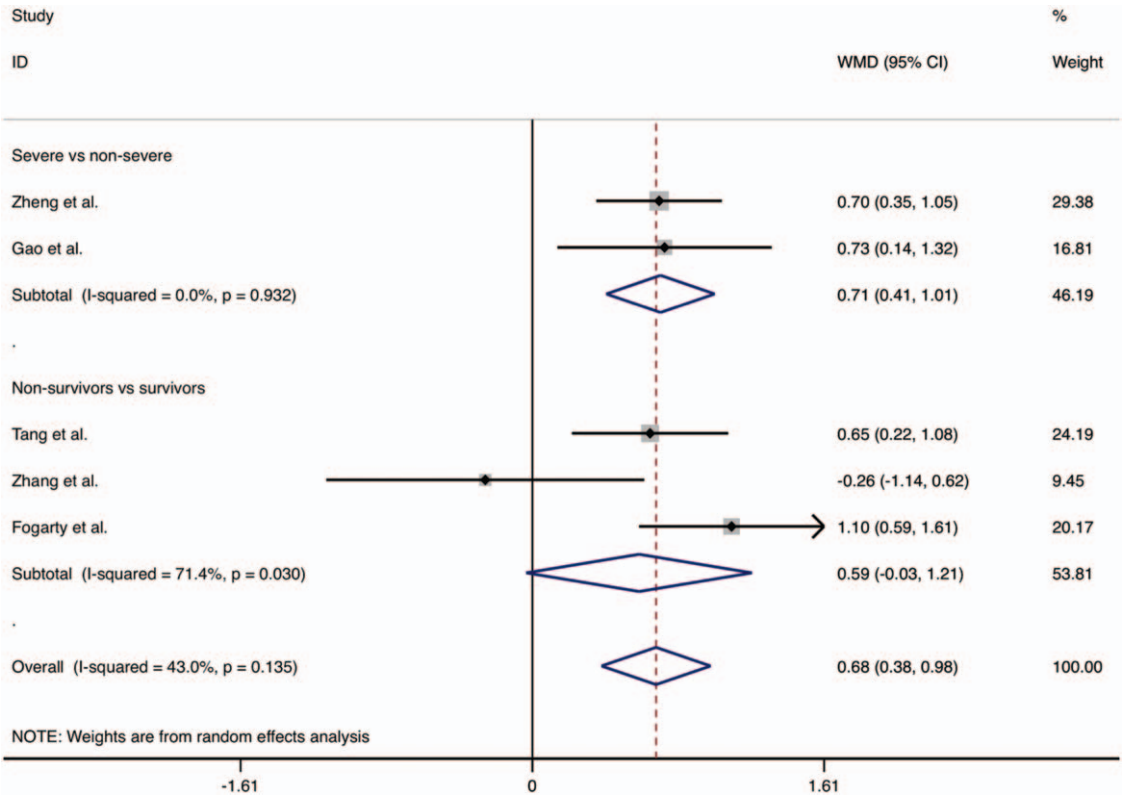

Figure 4. Forest plots showing fibrin change according to severity of COVID-19.

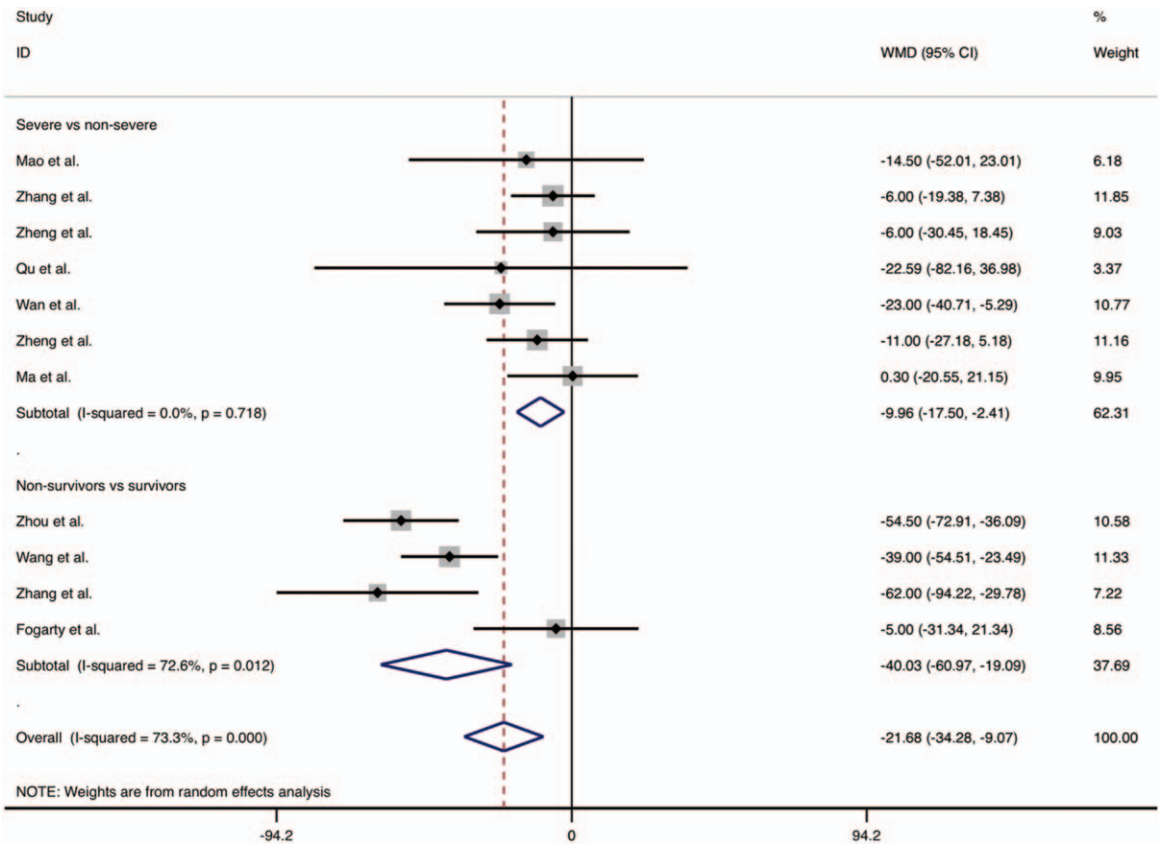

Figure 5. Forest plots showing PLT change according to severity of COVID-19.

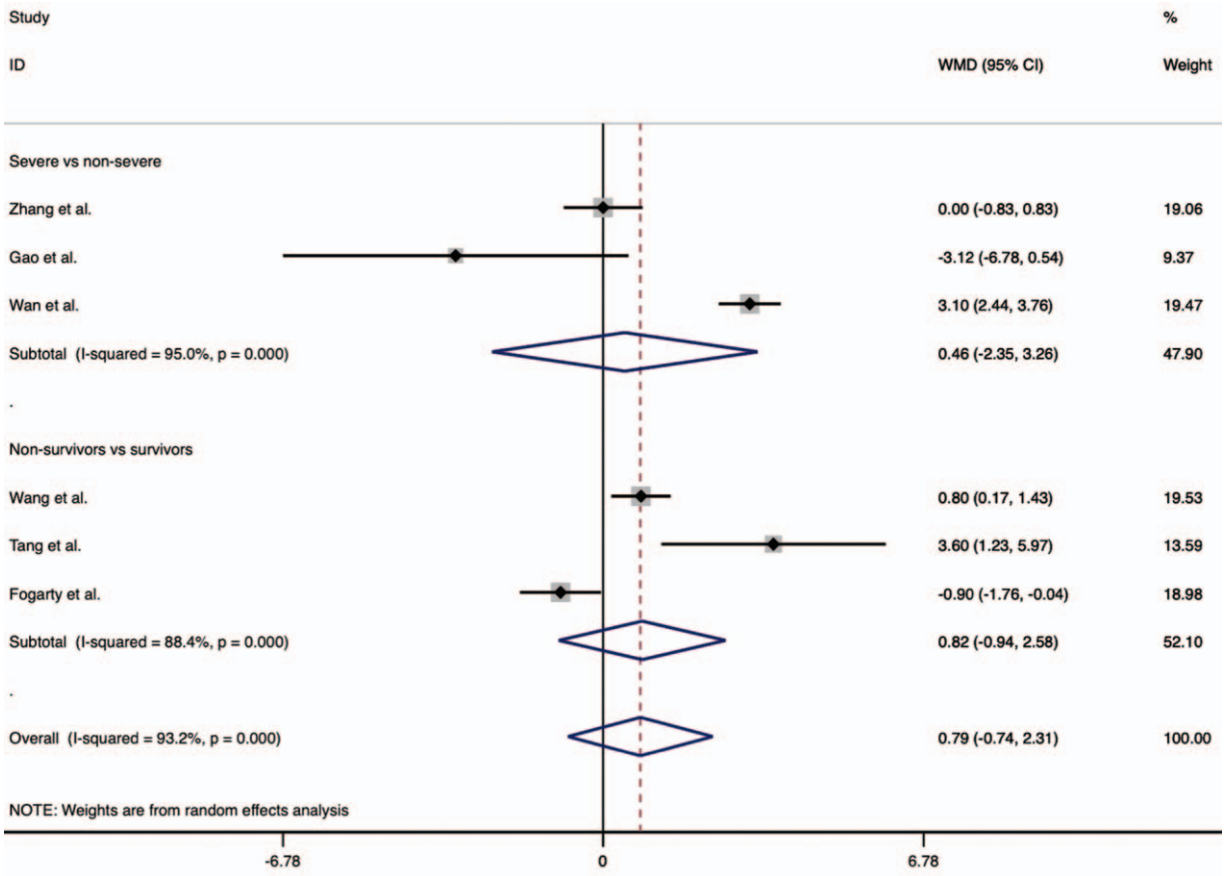

Figure 6. Forest plots showing APTT change according to severity of COVID-19.

As far as we know, this is the first comprehensive meta-analysis on the associations of coagulation dysfunction with the severity and mortality of COVID-19. The strengths of our meta-analysis lies in the number of included studies and large sample size. In addition, the literature search strategy, study selection form and data extraction form were determined and registered before starting the study. Our meta-analysis has several limitations. Firstly, although without publication bias, obvious heterogeneity exists among studies regarding definitions of severity type, coagulopathy and markers to detect coagulation dysfunction. Secondly, some included studies were limited by small sample size, few available data, or poor methodologic quality, thus the results should be cautiously interpreted within that context. Finally, majority of the included studies were from China. Indeed, ethnicity is potential risk factor of thrombosis. Further meta-analysis including studies from other countries are urgently needed.

Table 2

Meta-regression results for baseline characteristics difference on coagulation indexes.

	No. of study	Coef (exp)	95% CI	*P* value
Age	16	0.98	0.95, 1.03	.992
Female	14	0.99	0.94, 1.04	.612
Hypertension	12	1.00	0.97, 1.03	.999
Diabetes	12	1.04	0.96, 1.12	.342
Cardiovascular	11	1.01	0.99, 1.03	.190
COPD	9	1.04	0.96, 1.14	.292
Malignancy	7	0.90	0.79, 1.08	.199
CKD	8	0.95	0.83, 1.08	.359
Clinical Types	16	1.13	0.67, 1.93	.617
Fever	11	1.02	0.99, 1.05	.117
Cough	10	1.00	0.97, 1.04	.875
Dyspnea	7	1.00	0.97, 1.04	.875
Site of study	16	1.03	0.54, 1.97	.921

CI = confidence interval, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease.

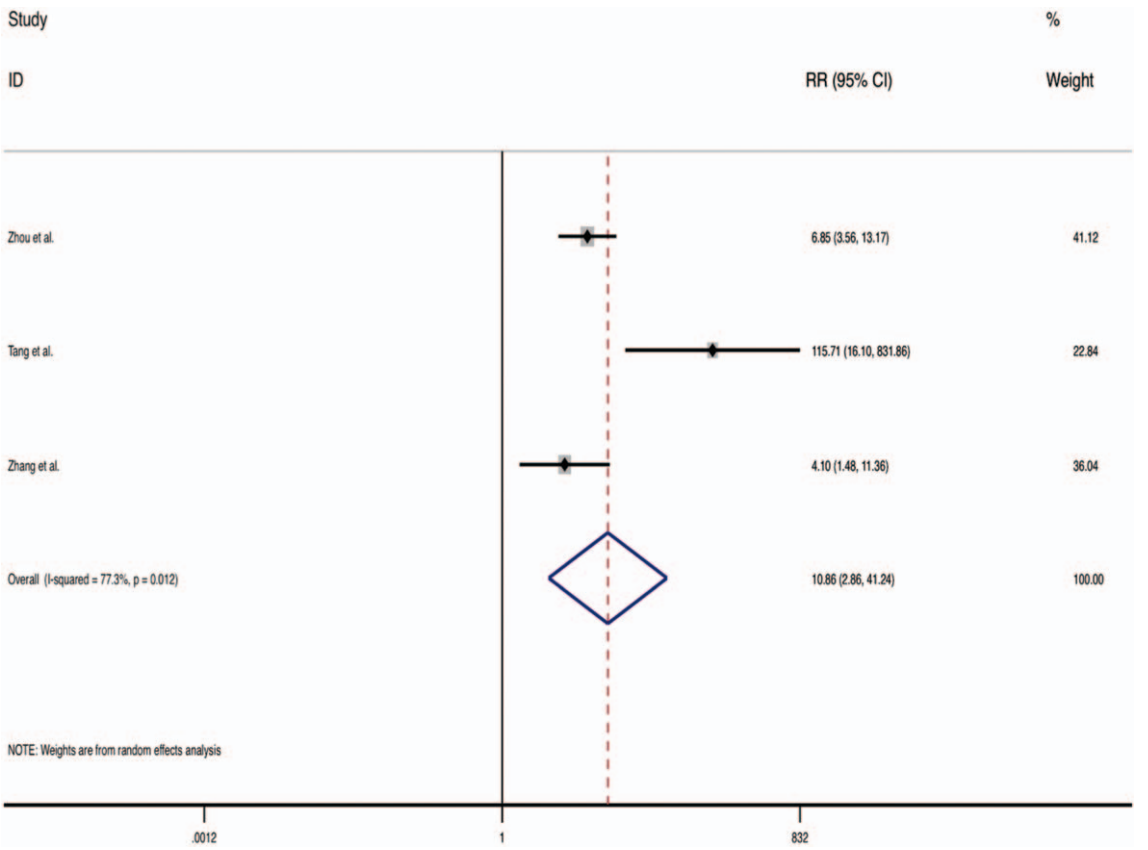

Figure 7. Forest plots showing risk ratio (RR) for decease according to coagulopathy (Yes vs No).

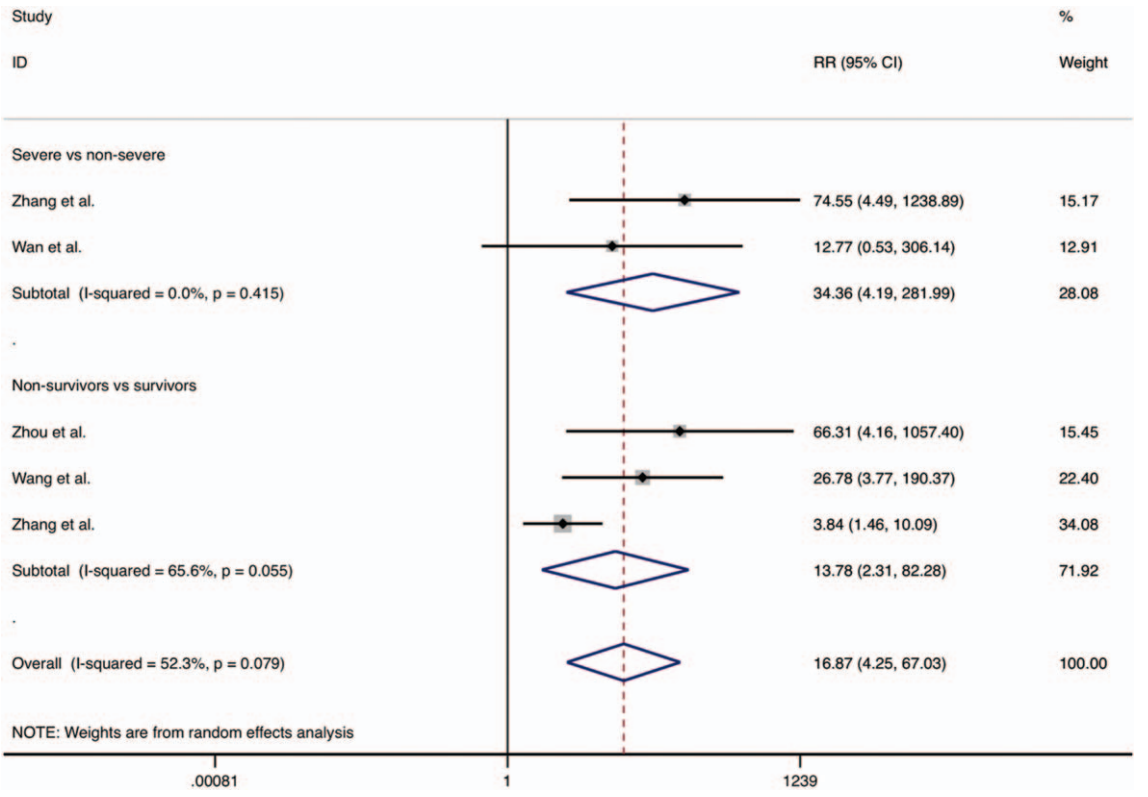

Figure 8. Forest plots showing risk ratio (RR) for decease according to severity of COVID-19 (Yes vs No).

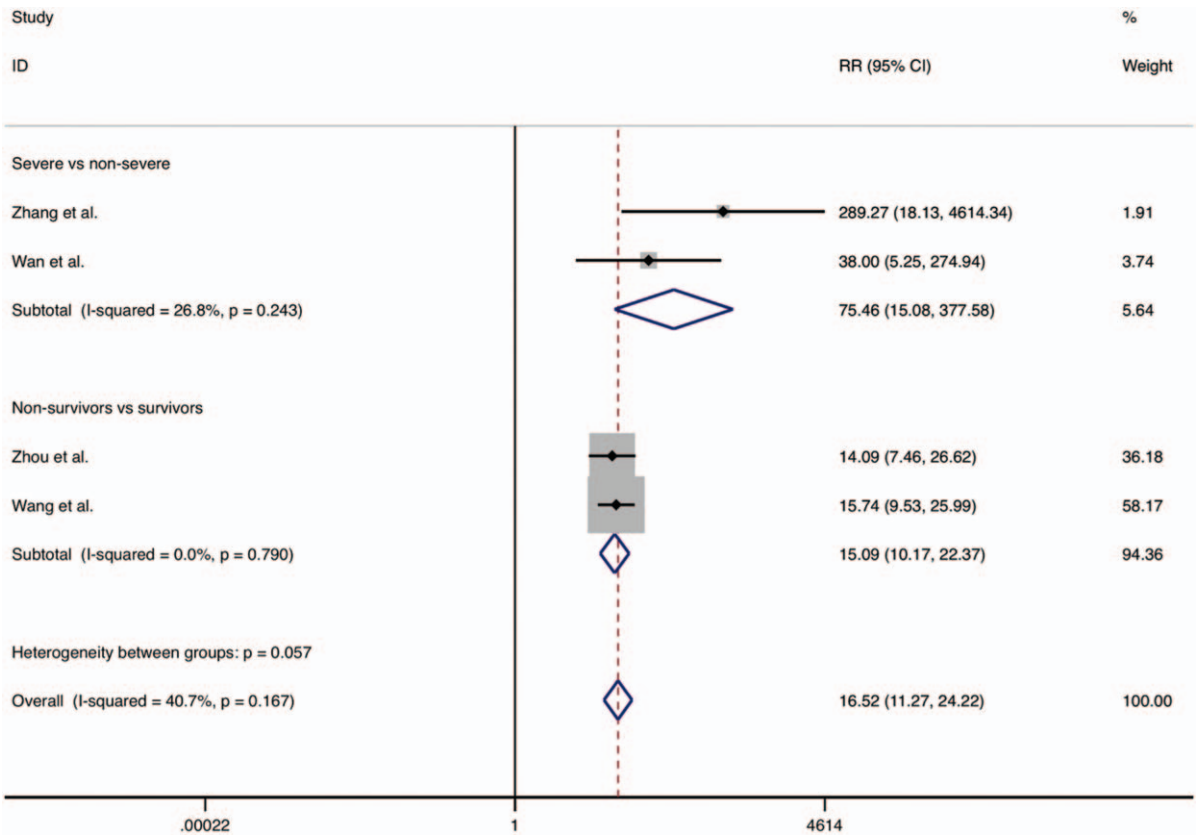

Figure 9. Forest plots showing risk ratio (RR) for ARDS according to severity of COVID-19 (More vs Less).

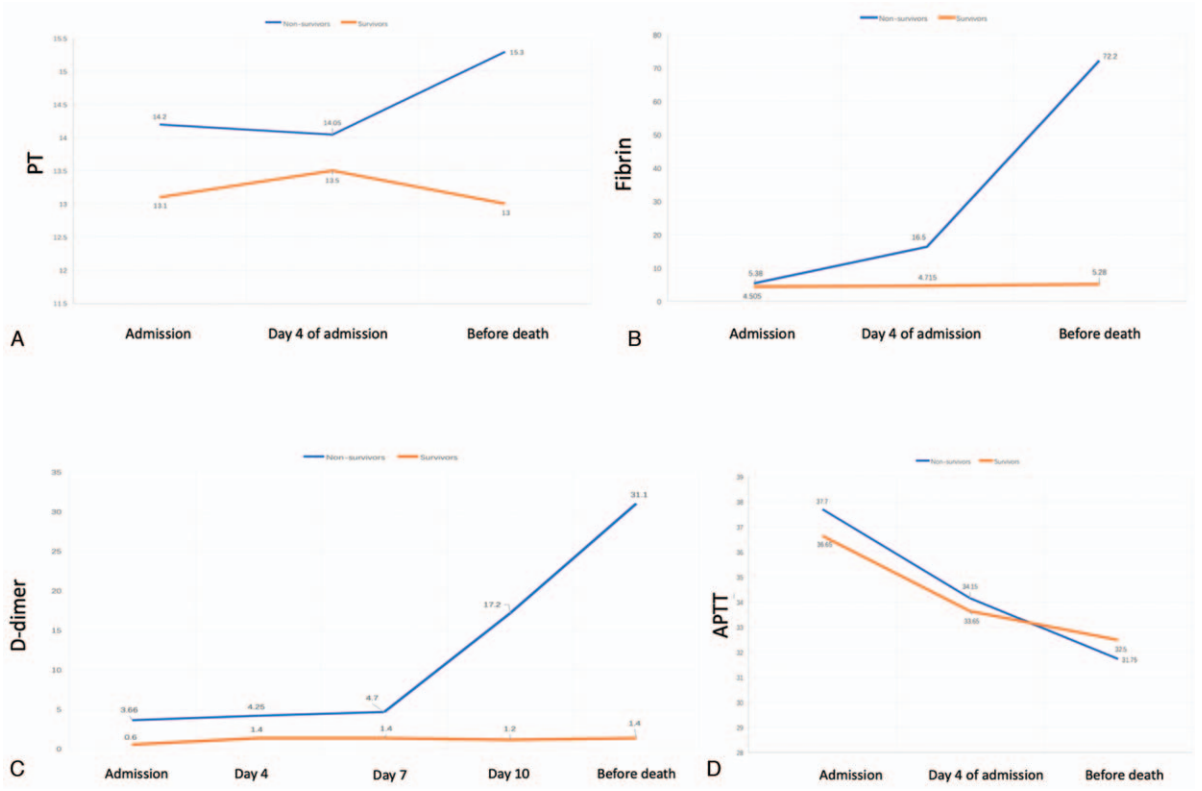

Figure 10. Dynamic changes in PT (A), fibrin (B), D-dimer (C) and APTT (D) during hospitalization.

5. Conclusions

This review of available retrospective studies provides insight into impact of COVID-19 on coagulation dysfunction. Presence of coagulation dysfunction and ARDS might be associated with COVID-19 severity and mortality. Coagulation markers such as PT, fibrin and D-dimer could imply the progression of COVID-19. For the obvious heterogeneity, the quality of the evidence is compromised. High quality of the evidence that assesses the correlation between coagulation and COVID-19, investigates underlying mechanisms are warranted. Future studies are also needed to determine whether anticoagulant therapy is beneficial in patients with severe COVID-19.

Author contributions

LSQ and LXH designed the study. XGL and HSY screened the studies, extracted the data and evaluated the study quality. XGL performed the statistical analyses and drafted the manuscript. XGL and FCP were responsible for data presentation. HWP, XL and WQH participated in the interpretation of data and writing of the manuscript. All authors approved the final version of manuscript.

Conceptualization: Guiling Xiang, Xuhui Liu, Shanqun Li.
Data curation: Guiling Xiang, Shengyu Hao, Cuiping Fu, Xuhui Liu, Shanqun Li.
Formal analysis: Guiling Xiang, Cuiping Fu, Xuhui Liu, Shanqun Li.
Funding acquisition: Cuiping Fu, Xuhui Liu, Shanqun Li.
Investigation: Guiling Xiang, Shengyu Hao, Cuiping Fu, Weiping Hu, Xuhui Liu, Shanqun Li.
Methodology: Guiling Xiang, Shengyu Hao, Cuiping Fu, Weiping Hu, Liang Xie, Qinhan Wu, Shanqun Li.
Project administration: Guiling Xiang, Qinhan Wu, Xuhui Liu, Shanqun Li.
Resources: Shengyu Hao, Cuiping Fu, Weiping Hu, Liang Xie, Shanqun Li.
Software: Guiling Xiang, Weiping Hu, Liang Xie, Qinhan Wu.
Supervision: Guiling Xiang, Weiping Hu, Qinhan Wu.
Validation: Guiling Xiang, Liang Xie, Qinhan Wu.
Visualization: Guiling Xiang, Liang Xie, Qinhan Wu.
Writing – original draft: Guiling Xiang.
Writing – review & editing: Guiling Xiang, Shengyu Hao, Weiping Hu, Liang Xie, Qinhan Wu.

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