Severe COVID-19 and coagulopathy: A systematic review and meta-analysis

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ABSTRACT

**Introduction:** Coronavirus disease 2019 (COVID-19)-induced coagulopathy (CIC) has been widely reported in the literature. However, the spectrum of abnormalities associated with CIC has been highly variable.

**Methods:** We conducted a systematic review of the literature (until 1 June 2020) to assess CIC and disease severity during the early COVID-19 pandemic. Primary outcomes were pooled mean differences in platelet count, D-dimer level, prothrombin time, activated partial thromboplastin time (aPTT) and fibrinogen level between non-severe and severe patients, stratified by degree of hypoxaemia or those who died. The risk factors for CIC were analysed. Random-effects meta-analyses and meta-regression were performed using R version 3.6.1, and certainty of evidence was rated using the Grading of Recommendation, Assessment, Development, and Evaluation approach.

**Results:** Of the included 5,243 adult COVID-19 patients, patients with severe COVID-19 had a significantly lower platelet count, and higher D-dimer level, prothrombin time and fibrinogen level than non-severe patients. Pooled mean differences in platelet count (-19.7×10⁹/L, 95% confidence interval [CI] -31.7 to -7.6), D-dimer level (0.8μg/mL, 95% CI 0.5–1.1), prothrombin time (0.4 second, 95% CI 0.2–0.6) and fibrinogen level (0.6g/L, 95% CI 0.3–0.8) were significant between the groups. Platelet count and D-dimer level were significant predictors of disease severity on meta-regression analysis. Older men had higher risks of severe coagulopathic disease.

**Conclusion:** Significant variability in CIC exists between non-severe and severe patients, with platelet count and D-dimer level correlating with disease severity. Routine monitoring of all coagulation parameters may help to assess CIC and decide on the appropriate management.

**Keywords:** Coagulation parameters, coagulopathy, D-dimer, platelets

INTRODUCTION

Manifestations of the coronavirus disease 2019 (COVID-19) span a wide clinical spectrum, from asymptomatic carriers to critical illness with a wide range of complications.1,2 Our understanding of the pathophysiology of the disease process is still evolving. As part of the host response to viraemia, it has been postulated that coagulopathy may play a pivotal role in the pathogenesis of COVID-19.3 Autopsy reports highlighting the presence of pulmonary microemboli,3 and clinical manifestations, including massive pulmonary embolism and acute cerebrovascular stroke, have been reported.4 Systemic microthrombi formation results from the activation of dysregulated coagulation system triggered by the host response to the virus.5 Furthermore, patients with severe forms of the disease may present with consumptive coagulopathy3 and bleeding.5 This requires exploration of laboratory parameters that could help in prediction of disease progression at an early stage and contribute to improvements in outcome. Markers of the severity of coagulopathy have been investigated in some studies.6,7 We hypothesised that

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severe COVID-19 is associated with coagulopathy and therefore carried out this systematic review and meta-analysis to analyse the coagulation parameters associated with disease severity in COVID-19.

METHODS

Search strategy and selection criteria
A systematic search was conducted after registering on PROSPERO register (CRD42020181132). The literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement using PubMed, EMBASE, Cochrane and Scopus databases until 1 June 2020. The search strings included the Boolean AND, OR and NOT operators, with the following keywords and their respective variants or derivatives in any relevant combination: COVID-19 OR 2019 novel coronavirus disease OR SARS-CoV-2 OR coronavirus disease-19 AND blood coagulation disorders OR fibrin/fibrinogen degradation products OR platelet OR D-dimer OR fibrinogen OR coagulopathy OR thrombin time OR prothrombin time OR activated partial thromboplastin time [aPTT], fibrinogen) and comorbidities. Patients with severe disease were defined as those who were suffering from hypoxaemia according to the World Health Organization interim guidance,8 or Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 5, Revised),9 or Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7),10 or those who died from COVID-19. Hypoxaemia was defined as: (1) respiratory rate of ≥30/min; (2) oxygen saturation of ≤90% or ≤93%9,10 at rest as measured by pulse oximeter; or (3) ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of ≤300mmHg. Coagulopathy for this review was defined as a composite outcome of 1 or more of the following: elevated D-dimer levels, deranged coagulation parameters (PT, aPTT, fibrinogen) and deranged platelet count.

Risk of bias assessment
Two reviewers (RRL and WHP) independently assessed study eligibility using the Joanna Briggs Institute checklist for prevalence studies, and any conflicts were resolved by discussion or by the third reviewer (SM). Publication bias was assessed using the Egger's regression test.

Statistical analyses
Statistical analyses were done on R version 3.6.1 (R Foundation for Statistical Computing, Austria), using the packages meta (version 4.12-0) and dmetar (version 0.0.9000). Our primary outcome was pooled mean differences of coagulation parameters (platelet count, D-dimer, prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen) and comorbidities. Patients with severe disease were defined as those who were suffering from hypoxaemia according to the World Health Organization interim guidance,8 or Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 5, Revised),9 or Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7),10 or those who died from COVID-19. Hypoxaemia was defined as: (1) respiratory rate of ≥30/min; (2) oxygen saturation of ≤90% or ≤93%9,10 at rest as measured by pulse oximeter; or (3) ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of ≤300mmHg. Coagulopathy for this review was defined as a composite outcome of 1 or more of the following: elevated D-dimer levels, deranged coagulation parameters (PT, aPTT, fibrinogen) and deranged platelet count.
whenever applicable. Continuous variables were presented as pooled means or pooled mean differences with their corresponding 95% CIs, and the means and standard deviations for the continuous variables were pooled from the aggregate data of each study using the methods proposed by Wan et al.12

Planned subgroup analyses included the presence of comorbidities (diabetes, hypertension, cardiovascular), and sex (male versus female) in COVID-19 patients reported with coagulopathy. We used the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) guidance to assess between-study heterogeneity and rated the certainty of evidence using the GRADE approach.13-15 We used the GRADEpro Guideline Development Tool ( McMaster University and Evidence Prime Inc, Canada) to rate the evidences16 and create the GRADE evidence profiles and summary-of-findings tables using standardised terms.17,18 Leave-one-out sensitivity analysis (LOO) was performed by omitting 1 study at a time to identify outliers or influential studies. For all the outcomes, we presented the post-LOO analysis data whenever applicable. Summary-level meta-regression was conducted when at least 6 studies were available to explore potential sources of heterogeneity or prognostically relevant study-level covariates.

RESULTS

Our preliminary search identified 1,255 articles. After exclusion of duplicates and conducting initial screening, the full texts of 172 citations were obtained for eligibility (Fig. 1). In total, 24 studies19-44 that reported on adult COVID-19 patients with coagulopathy (5,243 patients) were included (Table 1) for systematic review,25,30 while 24 studies were included for meta-analysis (5,035 patients). The quality assessment performed using the Joanna Briggs Institute checklists showed that the studies were of the highest quality (score >6/9) despite their observational nature. Twenty studies were from China, while 6 were from the Netherlands, Italy, France, Ireland and the US.19,21,24,25,30,33

Demographics

The pooled mean age across the 24 studies was 53.8 years (95% CI 51.2–56.4). The pooled mean age of non-severe COVID-19 patients (5,243 patients) was 50.8 years (95% CI 47.6–53.9), while that of severe patients (5,035 patients) was 61.1 years (95% CI 58.4–63.9). The estimated proportion of men across the studies was 54.2% (95% CI 51.3–57.2). The pooled proportion of men in the non-severe and severe groups with coagulopathy were 54.1% (95% CI 51.1–57.2) and 62.0% (95% CI 56.6–67.2), respectively. Table 2A depicts the pooled prevalence of diabetes mellitus (17 studies), hypertension (15 studies) and cardiovascular diseases (12 studies) in the overall population. We found that the pooled prevalence of the different comorbidities was higher in the severe group than in the non-severe group (Table 2A). The pooled prevalence of severe coagulopathic patients from 20 studies was 30.1% (95% CI 21.8–39.1).

Primary outcomes

Table 2A illustrates the pooled estimates of different coagulation parameters between non-severe and severe patients with coagulopathy. There was a significant drop in platelet count (11 studies), while D-dimer levels (15 studies), PT (9 studies) and fibrinogen levels (5 studies) were significantly increased in severe patients (Fig. 2). However, the mean difference in D-dimer levels between severe and non-severe patients showed a significant publication bias (Egger’s test, P<0.001). No outliers were detected for D-dimer in the LOO analysis. We found a non-significant increase in aPTT (8 studies) in severe patients with coagulopathy. Our meta-regression analysis demonstrated that a fall in platelet count and a rise in D-dimer levels were significant predictors of disease severity in patients with coagulopathy (Table 2B). PT, aPTT and fibrinogen levels did not show any significant association with disease severity.

Secondary outcomes

Seventeen studies reported on the significant pooled mean difference in age between the study groups; older age was associated with severe coagulopathic disease (mean difference 10.8 years [95% CI 8.2–13.4], P<0.001). Men had higher risks of acquiring severe disease with coagulopathy (OR 1.51, 95% CI 1.28–1.79, P<0.001). We also noted that patients with diabetes mellitus (OR 3.09, 95% CI 1.59–5.99, P<0.001), hypertension (OR 2.85, 95% CI 1.77–4.58, P<0.001) and cardiovascular diseases (OR 3.79, 95% CI 2.07–6.96, P<0.001) had higher risks of suffering from severe disease with coagulopathy.

Mortality outcome

The pooled mortality estimated from 15 studies was 14.0% (95% CI 8.4–20.7) in the patients with coagulopathy.

Risk of bias

We assessed the certainty of evidence for all primary outcome measures using the GRADE classification.
The starting certainty for all outcomes was high. We found that the certainty of evidence to be high for mean differences in D-dimer level, platelet count, PT and fibrinogen level. However, the certainty of evidence for mean difference in aPTT was low owing to serious inconsistency and imprecision.

**DISCUSSION**

The presence of coagulopathy is one of the leading causes of mortality in patients with COVID-19.\(^5,45\) In the context of the current COVID-19 pandemic, we conducted this analysis to identify coagulation parameters that could aid in severity stratification and prognostication of the disease progression. Our systematic review and meta-analysis comprehensively examined the differences of coagulation parameters between non-severe and severe COVID-19 patients across 26 studies published from 6 different countries. We found significant pooled mean differences in the blood levels of coagulation parameters (platelet count, D-dimer, PT and fibrinogen) between the 2 groups of COVID-19 patients. Older men were more likely...
to be severely coagulopathic, and these patients had lower platelet counts but higher PT, D-dimer and fibrinogen levels than non-severe patients. We identified that platelet counts and D-dimer levels correlated well with disease severity. We also noted that patients with comorbidities (diabetes mellitus, hypertension or cardiovascular disease) had a higher likelihood of progression to severe disease with coagulopathy than those without comorbidities.

A recent meta-analysis demonstrated that severe COVID-19 is associated with thrombocytopenia.6,7 While single-centre observational studies have shown no significant differences in platelet count between severe and non-severe patients,46,47 our review demonstrated that the cumulative pooled mean difference of platelet count was significant between non-severe and severe patients. Deranged coagulation parameters have been correlated with poor prognosis in COVID-19 patients.48

### Table 1. Summary of studies included in the meta-analysis

| Source⁴ | Sample size | Study type | Country of study | Platelet count | D-dimer | PT | aPTT | Fibrinogen |
|---------|-------------|------------|------------------|----------------|---------|----|------|-----------|
| Bonetti,⁵⁰ 2020 | 144 | Observational | Italy | + | + | + | + | - |
| Cui,⁵¹ 2020 | 81 | Observational | China | + | + | + | + | - |
| Fogarty,⁵² 2020 | 83 | Observational | Northern Ireland | + | + | + | + | - |
| Fu,⁵³ 2020 | 75 | Observational | China | + | + | + | + | - |
| Gao,⁵⁴ 2020 | 43 | Observational | China | - | + | + | + | - |
| Helms,⁵⁵ 2020 | 150 | Observational | France | + | + | + | - | + |
| Klok,⁵⁶ 2020 | 184 | Observational | The Netherlands | - | - | + | + | - |
| Li,⁵⁷ 2020 | 74 | Observational | China | - | + | + | + | - |
| Liu J,⁵⁸ 2020 | 40 | Observational | China | + | + | + | + | - |
| Liu Y,⁵⁹ 2020 | 76 | Observational | China | - | + | + | + | - |
| Lv,⁶⁰ 2020 | 354 | Observational | China | - | + | - | - | - |
| Panigada,⁶¹ 2020 | 24 | Observational | Italy | + | + | + | + | - |
| Qu,⁶² 2020 | 30 | Observational | China | + | - | - | - | - |
| Sun,⁶³ 2020 | 116 | Observational | China | + | - | - | - | - |
| Tabatabai,⁶⁴ 2020 | 10 | Observational | US | + | + | + | + | - |
| Tang,⁶⁵ 2020 | 449 | Observational | China | + | + | + | - | - |
| Wen,⁶⁶ 2020 | 135 | Observational | China | + | + | + | + | - |
| Wu,⁶⁷ 2020 | 201 | Observational | China | + | + | + | + | - |
| Yang,⁶⁸ 2020 | 1476 | Observational | China | + | - | - | - | - |
| Yao,⁶⁹ 2020 | 108 | Observational | China | + | + | - | - | - |
| Zhang G,⁷⁰ 2020 | 221 | Observational | China | + | + | + | - | - |
| Zhang G,⁷¹ 2020 | 95 | Observational | China | + | + | - | - | - |
| Zhang J,⁷² 2020 | 140 | Observational | China | - | + | - | - | - |
| Zhao,⁷³ 2020 | 532 | Observational | China | + | - | - | - | - |
| Zheng,⁷⁴ 2020 | 99 | Observational | China | - | + | - | - | - |
| Zou,⁷⁵ 2020 | 303 | Observational | China | - | + | + | + | - |

⁴ Superscript numbers refer to reference numbers in REFERENCES
⁵ '+' indicates these data can be extracted from the studies, '–' indicates these data cannot be extracted from the studies
Fig. 2. Forest plot showing pooled mean differences of coagulation parameters between non-severe and severe patients.
Table 2. Pooled estimates and 95% confidence intervals of (2A) comorbidities and coagulation parameters, and (2B) meta-regression analysis

2A. Pooled estimates of comorbidities and coagulation parameters

| Comorbidity                  | Overall     | Severe patients | Non-severe patients | Mean difference |
|-----------------------------|-------------|-----------------|---------------------|-----------------|
| Diabetes mellitus, %        | 13.3 (9.7–17.2) | 15.0 (11.1–19.4) | 6.7 (4.3–9.4)       |
| Hypertension, %             | 24.6 (16.0–34.2) | 34.8 (28.3–41.5) | 12.3 (8.2–16.9)    |
| Cardiovascular diseases, %  | 12.9 (5.9–22.1)  | 8.5 (4.9–12.8)  | 3.0 (1.6–4.7)      |

Coagulation parameter

| Parameter                    | Overall        | Severe patients | Non-severe patients | Mean difference |
|------------------------------|----------------|-----------------|---------------------|-----------------|
| Platelets, ×10⁹/L            | 191.5 (184.0–198.9) | 177.1 (147.2–207.1) | 193.7 (183.9–203.4) | -19.7 (-31.7 to -7.6), P<0.001 |
| D-dimer (μg/mL)              | 1.0 (0.8–1.1)  | 1.6 (1.3–2.0)  | 0.6 (0.5–0.7)       | 0.8 (0.5–1.1), P<0.001 |
| PT, seconds                  | 13.0 (12.4–13.7) | 13.4 (12.5–14.3) | 12.5 (11.8–13.3)    | 0.4 (0.2–0.6), P<0.001 |
| aPTT, seconds                | 31.3 (28.7–34.0) | 32.8 (30.6–35.0) | 31.9 (28.4–35.3)    | 0.5 (-0.6 to 1.7), P=0.35 |
| Fibrinogen (g/L)             | 4.4 (3.3–5.4)  | 4.3 (2.6–6.0)  | 3.8 (1.9–5.6)       | 0.6 (0.3–0.8), P<0.001 |

2B. Meta-regression analysis

| Covariate       | Studies | Odds ratio | Lower CI | Upper CI | P value |
|-----------------|---------|------------|----------|----------|---------|
| D-dimer         | 19      | 1.014      | 1.007    | 1.020    | <0.001  |
| Platelet count  | 15      | 1.550      | 1.187    | 2.024    | 0.001   |
| PT              | 14      | 1.022      | 0.998    | 1.046    | 0.071   |
| aPTT            | 13      | 1.001      | 0.912    | 1.098    | 0.991   |
| Fibrinogen      | 9       | 0.995      | 0.998    | 1.046    | 0.772   |

aPTT: activated partial thromboplastin time in seconds; CI: confidence interval; PT: prothrombin time in seconds

Increases in PT and aPTT seen in the severe group are likely multifactorial because of consumption of coagulation factors as the disease worsens, and the presence of lupus-like anticoagulants detected in these patients. Elevated fibrinogen levels seen in COVID-19 patients might be due to an underlying high-grade inflammatory response. We also postulated that COVID-19 patients may develop hyperfibrinogenaemia as they progress from non-severe to severe disease followed by excessive fibrinolysis, elevated D-dimer and fibrin degradation products. Hyperfibrinogenaemia leads to plasma hyper-viscosity, which in turn potentiates endothelium damage and microvascular thrombosis.

Although the exact mechanism of COVID-19-associated coagulopathy is still poorly understood, the intricate interplay between inflammation and thrombosis termed as thrombo-inflammation has been implicated. It is speculated that the vascular endothelium is damaged by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus because of binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptors, leading to uninhibited and dysregulated thrombin generation with consumptive coagulopathy. Given the spectrum of coagulation disorders ranging from thrombotic complications to consumptive coagulopathy in patients with severe form of the disease, COVID-19-induced coagulopathy (CIC) might be a clinical entity that is distinct from disseminated intravascular coagulation or sepsis-induced coagulopathy. Our analysis showed that the cut-off limits for platelet count, PT and fibrinogen levels in CIC are quite different from those that define sepsis-induced coagulopathy or disseminated intravascular coagulation. Recently published guidelines endorse early anticoagulation in patients with COVID-19; however, our review demonstrated that CIC could be dynamic as the disease progresses and that anticoagulants in severe disease may be used while monitoring the coagulation profile closely. There is some evidence that full-dose anticoagulation therapy in severe COVID-19 patients may be associated with better survival. Table 4 summarises plausible theories behind coagulopathy with therapeutic interventions in COVID-19. However, the true mechanisms of coagulopathy and the pathophysiology of disease progression remain unknown, and urgent mechanistic research to determine these aspects...
Table 3. Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) summary of findings

| No. of studies | Study design | Certainty assessment | Effect | Certainty | Importance |
|----------------|--------------|----------------------|--------|-----------|------------|
|                |              | No. of events | No. of individuals | Mean difference (95% CI) |
| Mean difference in D-dimer level (μg/mL) |
| 15 Observational studies | Not serious | Not serious ¹ | Not serious | Publication bias strongly suspected ² | 2471 | 0.8 (0.5–1.1) | High | Critical |
| Mean difference in platelet count (×10⁹/mL) |
| 12 Observational studies | Not serious | Not serious | Not serious | Dose-response gradient | 3535 | -19.7 (-31.7 to -7.6) | High | Critical |
| Mean difference in fibrinogen level (g/L) |
| 6 Observational studies | Not serious | Not serious | Not serious | None | 620 | 0.6 (0.3–0.8) | High | Critical |
| Mean difference in PT (seconds) |
| 15 Observational studies | Not serious | Serious ³ | Not serious | None | 1603 | 0.4 (0.2–0.6) | Moderate | Critical |
| Mean difference in aPTT (seconds) |
| 9 Observational studies | Not serious | Serious ³ | Not serious | None | 1246 | 0.5 (0.6 to 1.7) | Low | Critical |

¹ There was considerable heterogeneity. However, meta-regression found that D-dimer was a significant indicator of disease severity, accounting for the heterogeneity.

² Publication bias was rated high as Egger’s test gave a P value of <0.001.

³ There was considerable heterogeneity. While sensitivity analysis was able to account for some of it, significant heterogeneity remained (I²>50%).

⁴ The mean difference was insignificant, and the 95% confidence interval crossed 0. Therefore, it is difficult to interpret whether severe COVID-19 will lead to a difference in aPTT or not.
is required. Concordant with our findings, recent reviews on thrombo-inflammatory and haematological biomarkers have also concluded that patients with severe COVID-19 manifest hypercoagulable conditions (e.g. elevated D-dimer and fibrinogen levels) as well as a drop in platelet count.61,62

Our systematic review has certain limitations and results should hence be interpreted with caution. The analysis was based mainly on retrospective or cohort studies with significant heterogeneity during the early pandemic. Most of the initial studies on CIC were from China. The random-effects model was used when conducting this meta-analysis for the anticipated heterogeneity, in addition to using the GRADE approach to rate the certainty of evidence. We did additional subgroup analysis to account for heterogeneity. Furthermore, the meta-regression analyses were constrained by an inherent lack of power that increased the risk of type II errors. We included the studies of non-survivors in those with severe disease; however, it is possible that some patients with severe disease might have survived. Another potential limitation is the inability to accurately determine the timing at which coagulation results were being used in the publications for this review. Finally, Egger’s test yielded non-significant results for most of our primary endpoints, except for D-dimer studies that had significant publication bias. Nonetheless, the Joanna Briggs Institute appraisal of the included studies suggested that they were of high quality, limiting the possibility of publication bias. The GRADE system showed low to high level of certainty for the results of the analysis.

CONCLUSION

This systematic review and meta-analysis demonstrated significant variability of the coagulation parameters in non-severe versus severe COVID-19. COVID-19 patients manifest a dynamic coagulation profile with the progression of disease severity. Both platelet count and D-dimer level significantly correlated with the severity
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