Prognostic Impact of Coagulopathy in Patients with COVID-19: a Meta-analysis of 35 Studies and 6427 Patients

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Abstract

Coronavirus Disease 2019 (COVID-19) is a highly contagious disease that appeared in China in December 2019. Several patients with severe COVID-19 infection can develop a coagulopathy according to the ISTH-criteria for disseminated intravascular coagulopathy (DIC). We conducted a meta-analysis of all available studies on COVID-19 to explore the impact of coagulopathy on severe illness and mortality. An electronic search was performed within PubMed, Google Scholar and Scopus electronic databases. The primary endpoint was the difference of D-dimer values between Non-Severe vs Severe disease and Survivors vs Non-Survivors. The primary analysis showed that mean d-dimer is significantly higher in COVID-19 patients with severe disease than in those without (SMD -2.15 [-2.73 to -1.56], I² 98%, P <0.0001). Additional analysis of platelet count showed lower levels of mean PLT in Severe patients than those observed in the Non-Severe patients (SMD 0.77 [0.32 to 1.22], I² 96%, P <0.001). Interestingly, longer mean PT was found in Severe group (SMD -1.34 [-2.06 to -0.62], I² 98%, P <0.0002) compared to Non-Severe group. In conclusion, the results of the present meta-analysis, the largest and most comprehensive to date, demonstrate that Severe COVID-19 infection is associated with higher D-dimer values, lower platelet count and prolonged PT.

Introduction

Coronavirus Disease 2019 (COVID–19), caused by a coronavirus named “severe acute respiratory syndrome coronavirus 2” (SARS-CoV–2) is a contagious disease that appeared in Wuhan (China) in December 2019 and spread quickly around the whole world[1].

The most common symptoms of COVID–19 are fatigue, fever, nasal congestion and cough. Nevertheless, about 1/5 people can progress rapidly and develop breathing difficulties, requiring hospitalization, septic shock, metabolic acidosis and coagulopathy[2].

Although the symptoms are usually mild, especially in young adults and children, COVID–19 can be highly deadly and lethal, especially in high-risk patients with underlying conditions such as hypertension, heart disease or diabetes. Therefore, it is mandatory to identify potential risk factors for predicting disease progression and severity. Several patients with severe COVID–19 infection can develop a coagulopathy according to the criteria for disseminated intravascular coagulopathy (DIC) with fulminant activation of coagulation[3] (Figure 1).

D-dimer is a fibrin degradation product of crosslinked fibrin and can be considered a biomarker of fibrinolysis and activation of coagulation[4]. D-Dimer has been found increased in COVID–19 patients[5], and recently Zhou et al. demonstrated that the d-dimer levels on admission greater than 1 μg/mL were associated with an increase of in-hospital death[6]. Moreover, virus-induced inflammation also may contribute to increase in blood coagulability. Thus, the data related to coagulation parameters in different stages of COVID–19 disease may be of paramount importance to consider therapeutic prophylaxis or anticoagulation.
Thus, this study aims to summarize all available data on coagulation parameters in COVID–19 patients and to perform a meta-analysis to assess the impact of coagulopathy in different stages of COVID–19 disease.

**Methods**

*Search strategy and study selection.* An electronic search was performed within PubMed, Google Scholar and Scopus electronic databases between December 2019 (first confirmed Covid–19 case) up to April 6th, 2020. The following keywords were used for the search: “laboratory” or “coagulation” and “COVID–19” or “Coronavirus” or “SARS-CoV–2”. The English language was a limiting criterium for our analysis. All reports, including the search terms, were independently screened by two investigators for relevance and eligibility (I. L. and A. P.). Additionally, references from relevant articles were also manually scanned for additional studies. Where data were not available in the published study reports, authors were contacted, whenever possible, to supply missing information by email. The authors discussed their evaluation, and any disagreement was resolved through discussion and re-reading.

*Inclusion and Exclusion Criteria.* Studies were considered eligible if the following statements were applying a) they involved a study population with COVID–19 confirmed infection; b) studies that stratify the risk of severe or fatal COVID–19; c) they reported information on the difference of D-dimer values between two groups. Exclusion criteria were (just one was sufficient for study exclusion): non-original articles or articles with the number of patients less than 10, a duplicate publication with the same endpoint, endpoint measure not specified.

*Endpoints.* The primary endpoint was the difference of D-dimer values between Non-Severe vs Severe disease and Survivors vs Non-Survivors. Moreover, results on additional coagulation parameters (platelets count, prothrombin time, activated partial thromboplastin time) were also analyzed.

*Data Abstraction and Management.* Baseline characteristics and laboratory data were abstracted from the single studies through carefully scanning of the full article by two independent reviewers (I. L. and AP). Divergences were resolved by consensus. Moreover, the following data were extracted: year of publication, location, number of study patients, source type, peer-review process, study design, study groups. Selection and data abstraction were performed according to the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) and PRISMA Checklist (Supplemental Table 1–2). The quality analysis of the selected studies was performed using the Agency for Healthcare Research and Quality (AHRQ) for cross-sectional study form (Supplemental Table 3).

*Statistical analysis.* Mean and standard deviation were calculated from median and interquartile range (IQR), according to the formula reported by Wan X. et al. The summary measure used was the Standardized mean difference (SMD) with 95% confidence. Random-effects meta-analysis was used because high variability between studies was expected. Heterogeneity was evaluated using the $I^2$ statistic. Cut-off values of 25%, 50%, and 75% indicated low, moderate, and high heterogeneity, respectively. Next, to explore potential sources of heterogeneity, we conducted a subgroup analysis between peer-reviewed/non-
peer-reviewed articles. Finally, sensitivity analyses were performed by systematically removing each study, in turn, to explore its effect on outcome as previously described \cite{8,9}. Publication bias was evaluated by the Egger test. Forest plots were used to graphically display the results of the meta-analysis, as already previously described \cite{10,11}. All Analyses were performed using R Statistical Software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Search results. Our search retrieved a total of 3439 entries, which were reduced to 3252 studies after duplicates removed. After the screening of 322 records, 290 studies were then excluded because they were not related to our research question. In the assessment of eligibility, further 20 studies were excluded because of: duplicate publication; outcome not reported; not original articles. Finally, a total of 35 studies were available for the analysis, including 6427 patients \cite{5,6,12–44}. The study selection procedure is reported in detail in figure 2.

Data on Included Studies. Since randomized trials were not currently available, only retrospective studies were included in the present meta-analysis. Table 1 summarizes the most relevant characteristics of the selected studies. Sixteen studies were peer-reviewed \cite{5,6,12–25}, nineteen were non-peer-reviewed \cite{26–44}. Not surprisingly, quality assessment revealed a non-high study quality (Supplemental Table 1). Across the studies, patients were predominantly male and approximately one-fourth of patients had a history of cardiovascular disease. More details on patients’ characteristics are provided in table 2.

Meta-analysis results

The primary analysis showed that mean d-dimer is significantly higher in COVID–19 patients with severe disease than in those without (SMD $-2.15 [-2.73 \text{ to } -1.56]$, $I^2 98\%$, $P <0.0001$) (Figure 3, panel A). Similarly, we found a much higher mean d-dimer in Non-Survivors compared to Survivors (SMD $-2.91 [-3.87 \text{ to } -1.96]$, $I^2 98\%$, $P <0.0001$) (Figure 3, panel B).

Additional analysis of platelet count showed lower levels of mean PLT in Severe patients than those observed in the Non-Severe group (SMD $0.77 [0.32 \text{ to } 1.22]$, $I^2 96\%$, $P <0.001$) (Figure 4, panel A).

Of note, a similar result was observed even when Non-Survivors were compared to Survivors (SMD $1.84 [1.16 \text{ to } 2.53]$, $I^2 97\%$, $P <0.0001$) (Figure 4, panel D).

Interestingly, longer mean PT was found in both Severe (SMD $-1.34 [-2.06 \text{ to } -0.62]$, $I^2 98\%$, $P <0.0002$) (Figure 4, panel C) and Non-Survivors groups (SMD $-1.61 [-2.69 \text{ to } -0.54]$, $I^2 98\%$, $P <0.003$) compared to Non-Severe and Survivor patients.

Whether, no statistically significant differences were found in mean aPPT in both Non-Severe/Severe (SMD $0.39 [-0.33 \text{ to } 1.12]$, $I^2 98\%$, $P = 0.28$) and Survivors/Non-Survivors (SMD
0.58 [–0.42 to 1.58], $I^2$ 97%, P = 0.26)(Figure 4, panels C-F).

**Subgroup and Sensitivity Analyses for the Primary Endpoint.**

As both peer-reviewed and non-peer-reviewed studies were included in this analysis (Table 1), we performed a subgroup analysis, revealing a similar result for both study types for the primary endpoint (peer-reviewed SMD $-1.90$ [–2.95 to –0.84], $I^2$ 98%, P <0.001; non-peer-reviewed SMD $-2.34$ [–3.0 to –1.68], $I^2$ 97%, P <0.0001)(Supplemental Figure 1, panels A-B).

Moreover, sensitivity analysis performed by the leave-one-out approach showed that no single study had a substantial contribution to the pooled mean difference (Supplemental Figure 2, panels A-B).

**Publication Bias.**

No evidence of publication bias was found by Egger’s test. The P values were: P = 0.07 for d-dimer, 0.81 for PLT, 0.13 for PT, and 0.10 for aPTT.

**Discussion**

The major finding of the present meta-analysis, the largest and most comprehensive to date, is that high levels of D-Dimer are associated with a more severe prognosis and increased mortality in patients with COVID–19. Finally, the mean platelet count is lower and mean prothrombin time more prolonged in Severe and Non-Survivor Covid–19 patients, supporting the concept that patients infected by COVID–19 may be at risk of developing disseminated intravascular coagulation (DIC). In fact, high d-dimer levels, low platelet count and prolonged PT are critical parameters of ISTH Criteria for DIC as showed in a recent study by Tang and colleagues[17]. First, they showed that most of non-survivor patients with COVID–19 disease met the criteria for DIC. Moreover, elevated D-dimer values were associated with a worse clinical outcome, reflecting coagulation activation from infection, marked inflammation and multiorgan failure[45].

Recently, Lippi et al.[46] showed in a brief letter reporting a pooled analysis of 4 studies that D-dimer is associated with the severity of COVID–19 disease. The mean difference of the four studies which reported D-dimer values showed that they are significantly higher in COVID–19 patients with severe disease than in those with mild disease.

The obvious consideration is related to therapy with heparin to limit coagulopathy. Nonetheless, it is paramount to stimulate local fibrinolysis to degrade pre-existing fibrin in the lung. Hence, a nebulizer form of tissue-type plasminogen activator to treat COVID-19 has been proposed recently[47].

Interestingly, a recent finding investigated the predictors of 28-day mortality in Severe COVID–19 patients and the association between death and low molecular weight heparin (LMWH) therapy. They showed that patients with elevated D-dimer values, prolonged PT and increased age presented a greater mortality at 28 days, while those with a higher platelet count had a lower 28-day mortality. Specifically, the use of
anticoagulant therapy resulted in lower mortality in patients with severe coagulopathy with a SIC score ≥4 (LMWH: 40.0% vs No-LMWH: 64.2%, \( p = 0.03 \)) or D-dimer >6-fold of the normal upper limit (32.8% vs 52.4%, \( p = 0.02 \)). Still, there was no overall benefit between those who use heparin and those who do not. (30.3% vs 29.7%, \( p = 0.91 \)) [17].

Although coagulopathy acknowledges various aetiological causes, our findings suggest that the worsening of coagulation parameters may indicate progressive severity of COVID–19 infection and may predict the need for more aggressive critical care and treatment. Thus, patients in the Intensive Care Unit (ICU) should have pharmacologic prophylaxis with heparin if there is not a caution. Consideration of clotting problems and antithrombotic therapy in the daily COVID–19 management process is essential, rather than focusing solely on the infection. Further, potential complications related to intravascular clotting should always be taken into consideration in the presence of worsening clinical conditions. The risk of bleeding should always be considered in individual patients when anticoagulant drugs are administered [48].

In conclusion, further studies to define whether adjunctive antithrombotic drugs may be helpful to treat patients properly with severe COVID–19 disease are still needed.

Limitations. Our study has some limitations. First, in the absence of randomized clinical trials, our analysis reported only data from retrospective and observational studies. Second, since there is significant heterogeneity, we used a random-effects model for all analyses. Third, the definition of the endpoints is variable in the different studies. Thus, we performed a subgroup analysis (Severe/Non Severe, Non Survivors/Survivors) to overcome this issue.

Conclusions

Results of the present meta-analysis, the largest and most comprehensive to date, demonstrate that Severe COVID–19 infection is associated with higher D-dimer values, lower platelet count and prolonged PT. This data suggests a possible role of disseminated intravascular coagulation in the pathogenesis of COVID–19 disease.

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Declarations

Competing interests: The author(s) declare no competing interests.

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Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request

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Tables

Table 1 - Characteristics of the selected studies
| STUDY                | YEAR | LOCATION | N   | SOURCE TYPE | PEER-REVIEWED | STUDY DESIGN       | STUDY GROUPS                          |
|---------------------|------|----------|-----|-------------|----------------|---------------------|---------------------------------------|
| Cai Q. et al.       | 2020 | China    | 298 | Journal Article | No             | Retrospective study | Non-Severe vs Severe                 |
| Chen G. et al.      | 2020 | China    | 21  | Journal Article | Yes            | Retrospective study | Moderate vs Severe                    |
| Chen T. et al.      | 2020 | China    | 799 | Journal Article | Yes            | Retrospective study | Deaths vs Recovered Patients          |
| Deng Q. et al.      | 2020 | China    | 112 | Journal Article | Yes            | Retrospective study | Non-Severe vs Severe                  |
| Gao Y. et al.       | 2020 | China    | 43  | Journal Article | Yes            | Retrospective study | Mild vs Severe                        |
| Han H. et al.       | 2020 | China    | 94  | Journal Article | Yes            | Retrospective study | Ordinary vs Severe/Critical           |
| Huang C. et al.     | 2020 | China    | 41  | Journal Article | Yes            | Retrospective study | ICU care vs Non-ICU care              |
| Huang H. et al.     | 2020 | China    | 125 | Journal Article | No             | Retrospective study | Mild vs Severe                        |
| Li J. et al.        | 2020 | China    | 134 | Journal Article | No             | Retrospective study | Non-Died Vs Died                     |
| Li K. et al.        | 2020 | China    | 102 | Journal Article | No             | Retrospective study | Non-survivor vs Survivor             |
| Li Z. et al.        | 2020 | China    | 193 | Journal Article | No             | Retrospective study | Non-Severe vs Severe                 |
| Liu Jiacheng et al. | 2020 | China    | 122 | Journal Article | No             | Retrospective study | Common vs Severe                     |
| Liu Jing et al.     | 2020 | China    | 40  | Journal Article | No             | Retrospective study | Mild vs Severe                       |
| Lu H. et al.        | 2020 | China    | 265 | Journal Article | No             | Retrospective study | Mild/Moderate vs Severe Critically Ill|
| Lu Z. et al.        | 2020 | China    | 124 | Journal Article | No             | Retrospective study | Discharged vs Death                  |
| Luo X. et al.       | 2020 | China    | 403 | Journal Article | No             | Retrospective study | Recovered vs Died, Ordinary vs Severe/Critical |
| Ma K. et al.        | 2020 | China    | 84  | Journal Article | No             | Retrospective study | Non-Severe vs Severe                 |
| Qian G. et al.      | 2020 | China    | 91  | Journal Article | No             | Retrospective study | Mild vs Severe                       |
| Tang N. et al.      | 2020 | China    | 449 | Journal Article | Yes            | Retrospective study | Non-survivor vs Survivor             |
| Wan S. et al.       | 2020 | China    | 135 | Journal Article | Yes            | Retrospective study | Mild vs Severe                       |
| Wang D. et al.      | 2020 | China    | 138 | Journal Article | Yes            | Retrospective study | ICU vs Non-ICU                       |
| Wang K. et al.      | 2020 | China    | 305 | Journal Article | No             | Retrospective study | Survivors vs Non-Survivors           |
| Wang L. et al.      | 2020 | China    | 339 | Journal Article | Yes            | Retrospective study | Survival vs Dead                     |
|                     |      |          |     |             |                |                                   | Patients with ARDS                   |
| Wu C. et al. [22] | 2020 | China | 201 | Journal Article | Yes | Retrospective study | vs Patients without ARDS, Patients Alive vs Died Patients |
|-------------------|------|-------|------|-----------------|-----|---------------------|----------------------------------------------------------|
| Wu J. et al. [21] | 2020 | China | 280  | Journal Article | Yes | Retrospective study | Mild and Moderate type Patients vs Severe and Critically ill type Patients |
| Xu Y. et al. [39] | 2020 | China | 69   | Journal Article | No  | Retrospective study | Mild cases vs Severe or Critical cases |
| Zeng J. et al. [40] | 2020 | China | 419  | Journal Article | No  | Retrospective study | ICU vs Non-ICU |
| Zhang F. et al. [41] | 2020 | China | 48   | Journal Article | No  | Retrospective study | Survivors vs Non-Survivors |
| Zhang G. et al. [42] | 2020 | China | 221  | Journal Article | No  | Retrospective study | Non-Severe vs Severe |
| Zhang J. et al. [23] | 2020 | China | 140  | Journal Article | Yes | Retrospective study | Non-Severe vs Severe |
| Zheng C. et al. [24] | 2020 | China | 55   | Journal Article | Yes | Retrospective study | Non-Severe vs Severe |
| Zheng X. et al. [43] | 2020 | China | 52   | Journal Article | No  | Retrospective study | Severe vs Common |
| Zhou F. et al. [6] | 2020 | China | 191  | Journal Article | Yes | Retrospective study | Survivors vs Non-Survivors |
| Zhou Ying et al. [44] | 2020 | China | 277  | Journal Article | No  | Retrospective Study | Non-Severe vs Severe |
| Zhou Yulong et al. [25] | 2020 | China | 17   | Journal Article | Yes | Retrospective Study | Non-Aggravation vs Aggravation Group |

**Table 2 - Baseline Patient’s Characteristics**
| STUDY            | AGE Mean±SD | MALE N (%) | HYPERTENSION N (%) | SMOKERS N (%) | DIABETES N (%) | CVD N (%) | COPD N (%) |
|------------------|-------------|------------|--------------------|---------------|---------------|-----------|------------|
| Cai Q. et al.    | 47 ± 4.6    | 149 (50.0) | 38 (12.8)          | NA            | 19 (6.4)      | 11 (3.7)  | NA         |
| Chen G. et al.   | 56 ± 3.7    | 17 (81.0)  | 5 (23.8)           | NA            | 3 (14.3)      | NA        | NA         |
| Chen T. et al.   | 62 ± 4.3    | 171 (62.0) | 97 (34.0)          | 12 (4.0)      | 47 (17.0)     | 23 (8.0)  | 18 (7.0)   |
| Deng Q. et al.   | 65 ± 3.6    | 57 (50.9)  | 36 (32.1)          | NA            | 19 (17.0)     | 15 (13.4) | 4 (3.6)    |
| Gao Y. et al.    | 43 ± 11.7   | 26 (60.0)  | 13 (30.2)          | NA            | 7 (16.3)      | 3 (69.7)  | 8 (18.6)   |
| Han H. et al.    | NA          | NA         | NA                | NA            | NA            | NA        | NA         |
| Huang C. et al.  | 49 ± 4.2    | 30 (73.0)  | 6 (15.0)           | 3 (7.0)       | 8 (20.0)      | 6 (8.0)   | 1 (2.0)    |
| Huang H. et al.  | 44 ± 18.5   | 63 (50.0)  | 20 (16.0)          | NA            | 8 (6.4)       | NA        | NA         |
| Li J. et al.     | 61 ± 3.8    | 75 (56.0)  | 44 (32.8)          | 22 (16.4)     | 34 (25.3)     | 59 (44.0) | 11 (8.2)   |
| Li K. et al.     | 57 ± 4.1    | 59 (58.0)  | 31 (30.0)          | 7 (7.0)       | 15 (15.0)     | 4 (4.0)   | 2 (2.0)    |
| Li Z. et al.     | 67 ± 3.5    | 95 (49.0)  | NA                | NA            | NA            | 70 (36.0) | NA         |
| Liu Jiacheng et al. | 62 ± 3.8 | 72 (59.0)  | 50 (41.0)          | 5 (4.1)       | 15 (12.3)     | 2 (1.6)   | 2 (1.6)    |
| Liu Jing et al.  | 48 ± 13.9   | 15 (37.5)  | 6 (15.0)           | NA            | 6 (15.0)      | NA        | NA         |
| Lu H. et al.     | NA          | NA         | 52 (19.6)          | NA            | 21 (7.9)      | 14 (5.3)  | 4 (1.5)    |
| Lu Z. et al.     | 57 ± 12.6   | 61 (49.0)  | 41 (33.0)          | 17 (10.9)     | 14 (11.2)     | 15 (12.0) | 6 (4.8)    |
| Luo X. et al.    | 56 ± 4.8    | 193 (47.9) | 113 (28.0)         | 29 (7.2)      | 57 (14.1)     | 36 (8.9)  | 28 (6.9)   |
| Ma K. et al.     | 48 ± 3.3    | 48 (57.1)  | 12 (14.3)          | 7 (8.3)       | 10 (11.9)     | 5 (6.0)   | 5 (6.0)    |
| Qian G. et al.   | 50 ± 3.4    | 37 (40.7)  | 15 (16.4)          | NA            | 8 (8.8)       | 3 (3.3)   | NA         |
| Tang N. et al.   | 65 ± 12.0   | 268 (59.7) | 177 (39.4)         | NA            | 93 (20.7)     | 41 (9.1)  | NA         |
| Wan S. et al.    | 47 ± 3.1    | 72 (53.3)  | 13 (9.6)           | 9 (6.7)       | 12 (8.9)      | 7 (5.2)   | 0 (0)      |
| Wang D. et al.   | 56 ± 4.3    | 75 (54.3)  | 43 (31.2)          | NA            | 14 (10.1)     | 20 (14.5) | 4 (2.9)    |
| Wang K. et al.   | 47 ± 15.1   | 142 (53.4) | 45 (14.8)          | NA            | 31 (10.2)     | NA        | NA         |
| Wang L. et al.   | 69 ± 1.8    | 166 (49.0) | 138 (40.8)         | NA            | 54 (16.0)     | 21 (15.7) | 21 (6.2)   |
| Wu C. et al. [22]     | 51 ± 2.8 | 128 (63.7) | 39 (19.4) | NA | 22 (10.9) | 8 (4.0) | 5 (2.5) |
|----------------------|----------|------------|-----------|----|-----------|--------|--------|
| Wu J. et al. [21]    | 43 ± 19.0| 151 (53.9) | NA        | NA | NA        | NA     | 1 (0.36) |
| Xu Y. et al. [39]    | 57 ± 6.5 | 35 (50.7)  | NA        | 5 (7.2) | NA        | NA     | NA     |
| Zeng J. et al.       | 46 ± 3.8 | 198        | 60 (14.3) | NA | 24 (5.7)  | 18 (0.36) | 5 (1.2) |

| Zhang F. et al. [41] | 70 ± 13.3| 60 (68.9)  | 32 (51.8) | NA | 10 (17.3) | 13 (14.5) | NA     |
|----------------------|----------|------------|-----------|----|-----------|--------|--------|
| Zhang G. et al. [42] | 55 ± 4.5 | 108 (48.9) | 54 (24.4) | NA | 22 (10.0) | 22 (10.0) | 6 (2.7) |
| Zhang J. et al. [23] | 55 ± 10.0| 71 (50.7)  | 42 (30.0) | NA | 17 (12.1) | 7 (5.0) | 2 (1.4) |
| Zheng C. et al. [24] | 59 ± 9.5 | 24 (43.6)  | NA        | NA | NA        | NA     | NA     |
| Zheng X. et al. [43] | 51 ± 15.9| 23 (44.2)  | 12 (23.1) | NA | 6 (11.5)  | 3 (5.8) | 2 (3.8) |
| Zhou F. et al. [6]   | 56 ± 3.5 | 119 (62.0) | 58 (30.0) | 11 (6.0) | 11 (19.0) | 15 (8.0) | 6 (3.0) |
| Zhou Ying et al. [44]| 53 ± 15.3| 170 (45.0) | 133 (35.2)| NA | 84 (22.2) | 23 (6.1) | 6 (1.6) |
| Zhou Yulong et al. [25]| 42 ± 14.0| 6 (35.0)  | NA        | NA | NA        | NA     | NA     |

**Figures**


Pathogenesis of DIC

Activation of Intravascular Coagulation

- Platelet consumption
- Coagulation Factors Consumption
- Fibrinolysis

Impaired coagulation and Bleeding

- ↓ Platelet
- ↑ PT
- ↑ aPTT
- ↑ D-Dimer

Endothelial Damage

- Microvascular thrombosis

Multi-Organ Ischemia or Failure

Figure 1

Pathogenesis of Disseminated intravascular Coagulation. DIC is characterized by systemic activation of blood coagulation, which results in generation and deposition of fibrin, leading to microvascular thrombi contributing to multi-organ dysfunction. Furthermore, consumption of clotting factors and platelets can result in life-threatening hemorrhage.
Figure 2

Flowchart Depicting Literature Review and Study Selection
Figure 3

Forest plots of the standardized mean difference in d-dimer levels. Panel A. Non severe vs Severe patients. The black squares represent the pooled standardized mean difference effect size for each analysis while the left and right extremes of the squares represent the corresponding 95% confidence intervals for the pooled standardized mean difference effect size for each analysis. All analyses are based on a random-effects model. Panel B. Survivors vs Non-Survivors. The black squares represent the pooled standardized mean difference effect size for each analysis while the left and right extremes of the squares represent the
corresponding 95% confidence intervals for the pooled standardized mean difference effect size for each analysis. All analyses are based on a random-effects model.

Figure 4

Forest plots of the standardized mean difference in platelets count (PLT), prothrombin time (PT) and activated partial thromboplastin time (aPTT). Panel A-B-C. Forest plots of the standard mean difference in PLT count, PT and aPTT between Non Severe and Severe patients. Panel D-E-F. Forest plots of the standard mean difference in PLT count, PT and aPTT between Survivors and Non-Survivors.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.pdf