Simple Coagulation Profile as Predictor of Mortality in Adults Admitted with COVID-19 A Meta-Analysis

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Simple Coagulation Profile as Predictor of Mortality in Adults Admitted with COVID-19: A Meta-Analysis

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Abstract

Context: COVID-19 severe manifestations must be detected as soon as possible. One of the essential poor characteristics is the involvement of coagulopathy. Simple coagulation parameters, including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and platelet, are widely accessible in many health centers.
Objectives: This meta-analysis aimed to determine the association between simple coagulation profiles and COVID-19 in-hospital mortality.
Method: We systematically searched five databases for studies measuring simple coagulation parameters in COVID-19 on admission. The random-effects and inverse-variance weighting were used in the study, which used a standardized-mean difference of coagulation profile values. The odds ratios were computed using the Mantel-Haenszel formula for dichotomous variables.
Results: This meta-analysis comprised a total of 30 studies (9,175 patients). In our meta-analysis, we found that non-survivors had a lower platelet count [SMD = -0.56 (95% CI: -0.79 to -0.33), P < 0.01; OR = 3.00 (95% CI: 1.66 to 5.41), P < 0.01], prolonged PT [SMD = 1.22 (95%CI: 0.71 to 1.72), P < 0.01; OR = 1.86 (95%CI: 1.43 to 2.43), P < 0.01], prolonged aPTT [SMD = 0.24 (95%CI: -0.04 to 0.52), P = 0.99], and increased INR [SMD = 2.21 (95%CI: 0.10 to 4.31), P = 0.04] than survivors.
Conclusions: In COVID-19 patients, abnormal simple coagulation parameters on admission, such as platelet, PT, and INR, were associated with mortality outcomes.

Keywords: COVID-19, Coagulopathy, Coagulation Profile, Platelet, Mortality

1. Context

Rapid growing numbers of COVID-19 patients and limited infrastructure resources provide significant challenges for healthcare institutions. It would be beneficial if any clinical or laboratory parameters would help us rapidly triage patients to appropriate units. The COVID-19 severe manifestations must be detected as soon as possible to predict each case's prognosis. Although the underlying pathophysiology of severe COVID-19 is poorly defined, some studies (1) reported that severe COVID-19 is related to significant coagulopathy.

A previous meta-analysis (2) demonstrated that advanced coagulation parameters such as D-dimer were associated with severity and mortality of COVID-19. However, most hospitals in peripheral areas, especially in developing countries, might not be able to test D-dimer. Simple coagulation parameters, including Prothrombin Time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and platelets, are widely accessible in many health centers (3). Based on early reports, moderate to severe COVID-19 patients were likely to have prolonged PT, elevated INR, prolonged aPTT, and decreased platelets with subsequent poorer outcomes (4-6).

2. Objectives

We aimed to identify if basic coagulation profiles have a prognostic value in COVID-19 in-hospital mortality.

3. Method

We selected observational studies or trials on adult COVID-19 patients presenting some details on coagulation profiles, including platelet (PLT), PT, aPTT, and INR, for in-hospital mortality outcomes. Any study that had incomplete required data or lacked coagulation profile information on admission was removed. This meta-analysis was written as per the Preferred Reporting Items for systematic reviews and meta-analyses (PRISMA) guidelines (7).

A systematic literature search was finalized on November 20, 2021, following the approval of the institutional review board. We searched five different databases (PubMed, Science Direct, Scopus, ProQuest, and medRxiv) using the keywords "COVID 19" OR "Sars-Cov-2" OR "Novel coronavirus" AND "Laboratory parameter" OR "Coagulation" AND "Mortality" OR "Death" OR "Survivor." We also examined reference lists of the included studies to recognize any relevant studies to be added. Before full-text retrieval, three investigators evaluated titles and abstracts. Three investigators reviewed titles and abstracts before retrieving full-text papers. Two investigators then collected the data in each comparison category from full-text studies, including the authors, publication year, location, study design, peer-reviewed publication status, study outcome, and coagulation profile data.

The coagulation profile focusing on survival and non-survival outcomes was the primary outcome in our meta-analysis. The NIH quality assessment tool for observational Cohort and cross-sectional studies was used to determine the methodological quality of the studies. The visual analysis of funnel plots and the Egger regression test were used to assess publication bias (8).

Data analysis was carried out utilizing review manager (RevMan v5.4 2020) and Stata v.16. A standardized mean difference (SMD) for coagulation profile values was used in the meta-analysis. According to Wan et al. (9), sample size, median, and interquartile range (IQR) were used to calculate the mean and standard deviation (SD). We used inverse-variance weighting and random-effects models. The pooled odds ratios (ORs) were calculated using the Mantel-Haenszel formula for dichotomous variables.

We carried out a subgroup analysis by study design. Sensitivity analysis was performed using the leave-one-out method or dependent on peer-review status to evaluate the reason for heterogeneity. We assessed the heterogeneity using the I^2 statistic. Restricted maximum likelihood random-effects meta-regression was performed for age, sex, cardiovascular disease (CVD), hypertension (HTN), and diabetes mellitus (DM) comorbidities in coagulation profiles, with a significant result and more than 10 studies included (10). In this meta-analysis, all p values less than 0.05 were statistically significant (except for heterogeneity using $P < 0.10$).

4. Results

Initial searches showed 88 PubMed records, 14 Science Direct records, 34 ProQuest records, 14 Scopus records, 262 medRxiv records, and 53 other records (Figure 1). After removing 39 duplicates and excluding 326 records, we retrieved 100 records for full-text screening. A total of 14 studies were excluded due to incorrect patient population, 13 due to unavailability of data on coagulation parameters, and 43 due to no outcome of interest. Thereby, we included the remaining 30 studies (9,175 patients) for analysis (11-40).

Tables 1 and 2 show the baseline characteristics of the included studies. There were 28 retrospective studies and two prospective observational studies. Peer review had already been completed on 21 studies. We assessed all methodologically acceptable studies (Table 1). The analyses and conclusions drawn were reliable. Nonetheless, due to their cross-sectional designs, most studies did not assess exposure before evaluating the outcome and would most likely lack adequate periods for the outcome.

Funnel plots for INR and aPTT showed an asymmetrical appearance indicating publication bias (Appendix 1). Since less than 10 studies were involved, we did not conduct Egger's regression test for INR. The publication bias for aPTT was also shown by the Egger's test ($P = 0.007$), but not for PT ($P = 0.395$) and PLT ($P = 0.896$).

4.1. Platelet

Random-effects meta-analysis revealed significantly lower platelet counts on admission in the non-survivor group than in the survivor group, as shown in Figure 2 [26 studies, SMD = -0.56 (95% CI: -0.79 to -0.33), $P < 0.01$; I2 = 94%, $P < 0.01$]. A similar result was shown in retrospective subgroup analysis. Categorical data of platelet count were found in five studies. Decreased platelet counts were associated with increased mortality [OR = 3.00 (95% CI: 1.66 to 5.41), $P < 0.01$; $I^2 = 69\%$, $P = 0.01$] (Figure 2). The sensitivity of 58% (95% CI: 38 to 76%) and specificity of 70% (95% CI: 54 to 83%) were obtained from a pooled analysis of multiple cut-off points (Appendix 2). Decreased platelet had a positive likelihood ratio (LR) of 1.9 and a negative LR of 0.6. According to a meta-regression analysis, unlike age ($P = 0.023$) and HTN ($P = 0.014$), sex ($P = 0.412$), CVD ($P = 0.580$) and DM ($P = 0.935$) had no impacts on the relationship between decreased platelet count and mortality.

4.2. Prothrombin Time

The pooled effect size demonstrated that PT was significantly higher in non-survivors than in survivors, as shown in Figure 3 [21 studies, SMD = 1.22 (95% CI: 0.71 to 1.72), P <

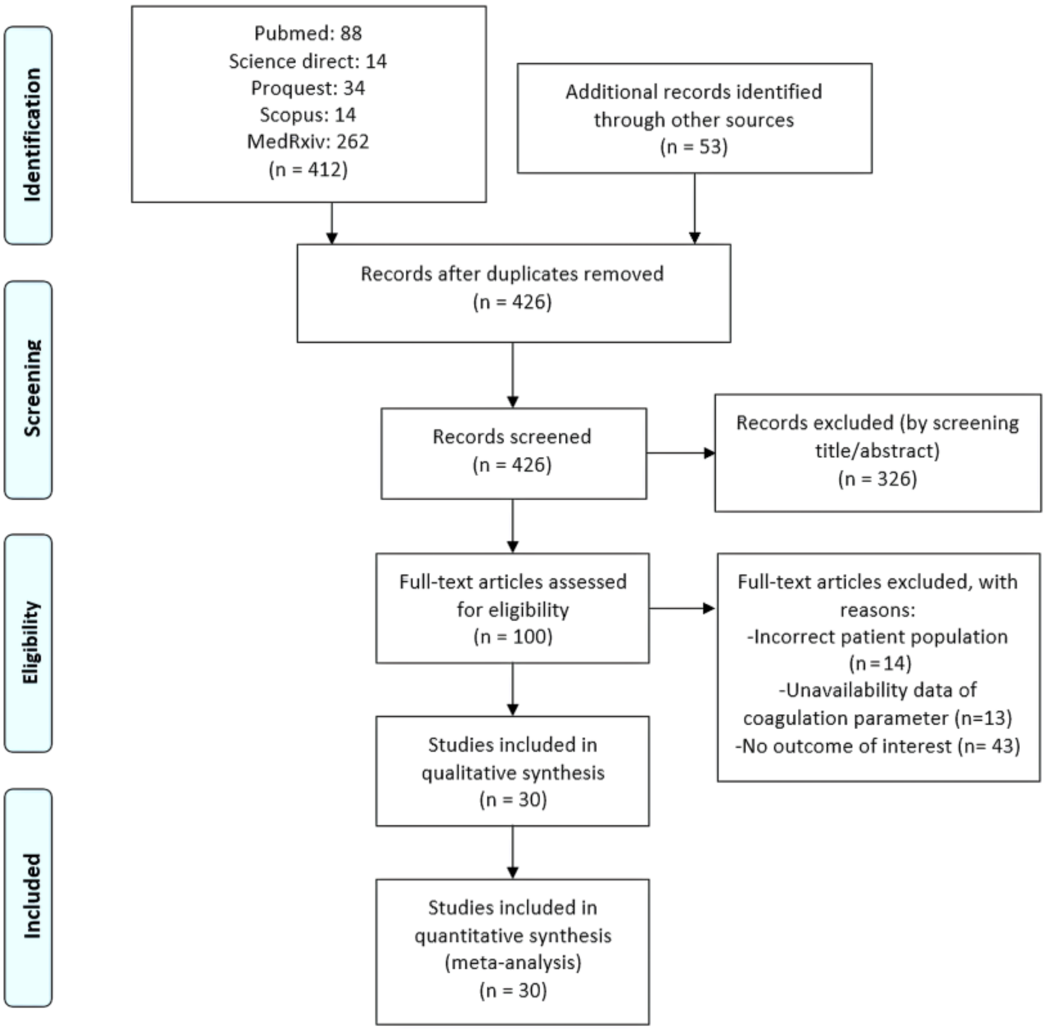

Figure 1. Study flow chart (as per PRISMA guideline)

0.01; $I^2 = 98\%$, $P < 0.01$]. A similar result was shown in retrospective subgroup analysis. Sensitivity analysis by removing Gil et al.' study (11) showed no improvement in heterogeneity. Pooled analysis of three studies with categorical data of PT demonstrated increased PT in the non-survivor group [OR = 1.86 (95% CI: 1.43 to 2.43), $P < 0.01$; $I^2 = 2\%$, P = 0.36] (Figure 3). According to a meta-regression analysis, age (P = 0.964), sex (P = 0.422), CVD (P = 0.889), DM (P = 0.955), and HTN (P = 0.910) comorbidities had no impact on the relationship between decreased platelet count and mortality.

4.3. Activated Partial Thromboplastin Time

The pooled effect size demonstrated that aPTT was non-significantly higher in non-survivors than in survivors, as shown in Figure 4 [18 studies, SMD = 0.24 (95% CI: -0.04 to 0.52), P = 0.09; $I^2 = 93\%$, $P < 0.01$]. The prospective group did not differ from the retrospective subgroup, as shown in subgroup analysis based on study design. Nevertheless, the removal of Gil et al.'s study (11) demonstrated a signifi-

Table 2. Laboratory Parameters in Included Studies[a]

No.	Author	aPTT (s)	PT (s)	PT Cut-Off	PLT (10^9/L)	PLT Cut-Off	INR
1	Zhang 2020 (14)	39.99 ± 7.12 vs. 40.25 ± 4.65	14.95 ± 1.70 vs. 13.70 ± 1.04	NR	109.42 ± 112.33 vs. 176.75 ± 54.40	NR	N/A
2	Yan 2020 (15)	40.16 ± 8.3 vs. 37.63 ± 6.77	15.47 ± 3.15 vs. 13.73 ± 0.92	NR	167 ± 88.51 vs. 202.33 ± 111,08	NR	N/A
3	Tang 2020 (16)	N/A	16.5 ± 8.4 vs. 14.6 ± 2.1	NR	178 ± 92 vs. 231 ± 99	NR	N/A
4	Wu 2020 (17)	24.9 ± 4.67 vs. 29.78 ± 9.03	11.72 ± 1.03 vs. 11.72 ± 1.15	NR	167.83 ± 92.35 vs. 201.33 ± 96.5	NR	N/A
5	Tang 2020 (13)	45.33 ± 8.59 vs. 40.7 ± 5.31	15.4 ± 1.51 vs. 13.63 ± 0.97	NR	N/A	N/A	N/A
6	Fan 2020 (18)	N/A	11.88 ± 1.55 vs. 11.13 ± 1.41	NR	168.33 ± 65 vs. 207 ± 93.33	NR	N/A
7	Li 2020 (19)	37.47 ± 7.17 vs. 35.13 ± 6.30	13.93 ± 2.80 vs. 13.33 ± 1.37	NR	N/A	N/A	1.13 ± 0.16 vs. 0.69 ± 0.76
8	Satici 2020 (20)	N/A	N/A	N/A	196 ± 47.96 vs. 198.33 ± 60.93	NR	N/A
9	Du 2020 (21)	36.7 ± 8.51 vs. 35.1 ± 6.14	14.17 ± 3.18 vs. 13.77 ± 2.09	NR	N/A	N/A	N/A
10	Pan 2020 (22)	37.45 ± 1.86 vs. 38.63 ± 1.69	14.15 ± 0.43 vs. 13.67 ± 0.29	> 13.9	187.33 ± 58.78 vs. 191.33 ± 70.34	≤ 187	N/A
11	Chen 2020 (12)	40.92 ± 1.99 vs. 40.72 ± 1.25	15.6 ± 0.56 vs. 13.85 ± 0.21	NR	160.78 ± 18.95 vs. 203 ± 16.92	NR	1.23 ± 0.05 vs. 1.08 ± 0.02
12	Gil 2020 (11)	32.63 ± 1.10 vs. 34.13 ± 1.29	13.85 ± 0.22 vs. 14.68 ± 0.45	NR	N/A	N/A	N/A
13	Alshukry 2020 (23)	45.81 ± 3.05 vs. 32.63 ± 1.3	15.87 ± 1.04 vs. 13.64 ± 0.35	NR	260.35 ± 22.89 vs. 323.92 ± 24.27	NR	N/A
14	Ayed 2020 (24)	41.5 ± 8.5 vs. 38.75 ± 6.68	N/A	N/A	216.5 ± 20.66 vs. 261.75 ± 24.9	NR	1.16 ± 0.10 vs. 1.03 ± 0.03
15	Shi 2020 (25)	30.48 ± 1.02 vs. 30.03 ± 1.10	13.32 ± 0.38 vs. 12.63 ± 0.42	NR	168 ± 26.78 vs. 159.75 ± 16.19	NR	N/A
16	Luo 2020 (26)	N/A	N/A	N/A	169.67 ± 73.72 vs. 207.33 ± 82.68	< 125	N/A
17	Zhang 2020 (26)	N/A	N/A	N/A	140 ± 100.24 vs. 182.33 ± 57.51	< 125	N/A
18	Paranjpe 2020 (28)	33.57 ± 5.54 vs. 31.63 ± 4.54	14.7 ± 2.02 vs. 13.63 ± 1.04	NR	189.33 ± 70.79 vs. 197.67 ± 69.82	NR	N/A
19	Hu 2020 (29)	N/A	15.6 ± 2.42 vs. 13.83 ± 0.98	NR	171.33 ± 78.39 vs. 211 ± 80.33	NR	N/A
20	Fu 2020 (30)	N/A	N/A	N/A	165.33 ± 50.67 vs. 226 ± 72.64	NR	N/A
21	Luo 2020 (31)	N/A	N/A	N/A	159.33 ± 76.94 vs. 202.67 ± 75.38	NR	N/A
22	Wang 2020 (32)	29.43 ± 3.26 vs. 28.37 ± 4.17	12.97 ± 1.64 vs. 12.17 ± 0.52	NR	164.67 ± 86.36 vs. 212.67 ± 81.15	NR	N/A
23	Yang 2020 (33)	N/A	12.9 ± 2.9 vs. 10.9 ± 2.7	NR	191 ± 63 vs. 164 ± 74	NR	N/A
24	Zhou 2020 (34)	N/A	12.33 ± 1.86 vs. 11.47 ± 1.65	≥ 16	167.17 ± 92.92 vs. 219.67 ± 77.17	< 100	N/A
25	Wang 2020 (35)	41.3 ± 7.32 vs. 39.3 ± 6.05	39.37 ± 6.05 vs. 14.9 ± 1.26	NR	221 ± 114.0 vs. 230.5 ± 86.5	NR	N/A
26	Sai 2021 (36)	35.87 ± 14.51 vs. 33.63 ± 9.75	13.63 ± 3.52 vs. 12.53 ± 1.77	NR	173.47 ± 107.84 vs. 225.47 ± 98.79	NR	N/A
27	Peiró 2021 (37)	N/A	N/A	N/A	226.33 ± 118.77 vs. 215.67 ± 90.52	NR	N/A
28	Velasco-Rodriguez 2021 (38)	30.07 ± 4.17 vs. 30.47 ± 3.34	13.3 ± 1.41 vs. 12.87 ± 1.19	> 14	199.17 ± 82.96 vs. 198.08 ± 128.54	< 140	N/A
29	Violi 2021 (39)	N/A	N/A	N/A	204 ± 119 vs. 211 ± 75	NR	N/A
30	Gayam 2021 (40)	31.42 ± 4.76 vs. 31.41 ± 3.95	N/A	N/A	215.33 ± 83.19 vs. 226 ± 89.43	NR	N/A

Abbreviations: aPTT, activated partial thromboplastin time; N/A, Not available; NR, not reported; PLT, Platelet; PT, prothrombin time.

[a] Data are presented as non-survivors vs. survivors in mean ± SD.

cant result of higher aPTT in non-survivors [SMD = 0.43 (95% CI: 0.06 to 0.58), P = 0.02; I^2 = 91%, P < 0.01].

4.4. International Normalized Ratio

Higher mean INR was found in non-survivors than in survivors, as shown in Figure 5 [three studies, SMD = 2.21 (95% CI: 0.10 to 4.31), P = 0.04; I^2 = 98%, P < 0.01]. Sensitivity analysis by removing Chen et al.' study (12) showed improvement in heterogeneity [SMD = 1.21 (95% CI: 0.10 to 2.32), P = 0.03; I^2 = 88%, P < 0.01].

5. Discussion

This meta-analysis found that COVID-19 patients with prolonged PT and aPTT, elevated INR, and a lower platelet level on admission had a higher mortality rate. Our results are similar to previous studies (6, 41). The prolongation of PT in the non-survivor group was consistent with another meta-analysis (4). However, the degree of PT prolongation is less prominent in COVID-19 than in bacterial sepsis-induced coagulopathy or disseminated intravascular coagulation (DIC) (42). Mild prolongation of aPTT demonstrated in COVID-19 subjects is possibly explained by the involvement of severe consumption or inhibition to specific coagulation factors (43).

Along with the emerging evidence of SARS-CoV-2, the presence of coagulopathy is one of the major factors responsible for high mortality rates other than cytokine storms (44). Severe infection activates the coagulation cascade and increases DIC risk, consequently increasing the fatality rates (13). Besides, COVID-19 increases the risk of thromboembolism in several organs, as it causes abnormal activation of coagulation and secondary hyperfibrinolysis (45). A first autopsy series to COVID-19-related deaths in New Orleans (46) reported the presence of signif-

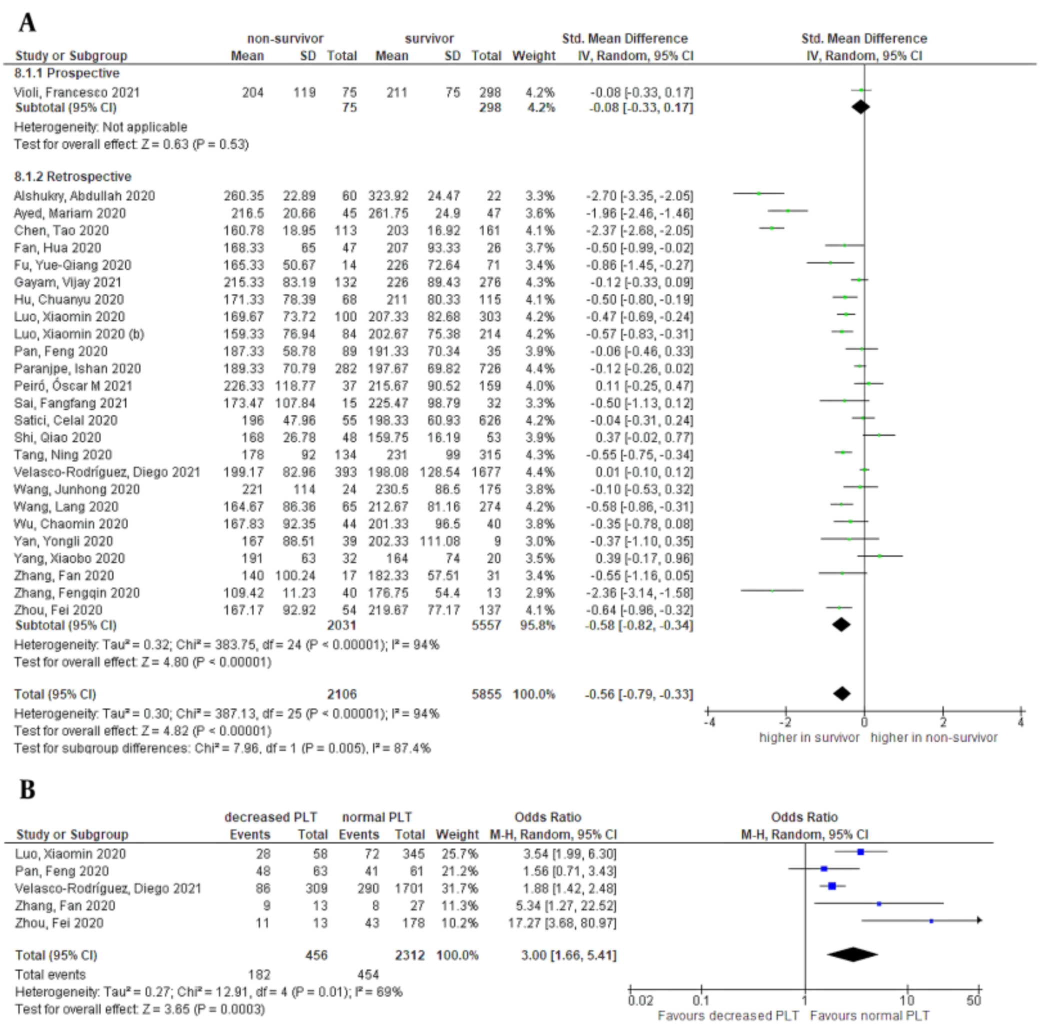

Figure 2. Forest plot of platelet level for mortality outcome. A, Non-survivors had a lower platelet level than survivors; and B, Decreased platelet was associated with increased mortality.

icant diffuse alveolar damage and pulmonary microvascular thrombosis, possibly contributing to death.

Decreased platelet counts in COVID-19 are possibly caused by hematopoiesis suppression in the bone marrow by the virus. As known, COVID-19 increases autoantibodies and immune complexes, leading to specific immune system disruption of platelets. Lung tissue and pulmonary endothelial cells damage in COVID-19 can activate platelets in the lungs, leading to microthrombi aggregation and formation and increased platelet consumption (47).

In addition, PT and aPTT are beneficial for the early detection of DIC in COVID-19-associated coagulopathy (48). Laboratory characteristics in DIC vary depending on the stage. In early DIC, hemostatic system activation is compensated. As DIC develops into the decompensated stage, which might be found in the late stage of COVID-19, decreased thrombocyte, elevated PT and aPTT, increased fibrinogen, increased fibrin degradation product, and re-

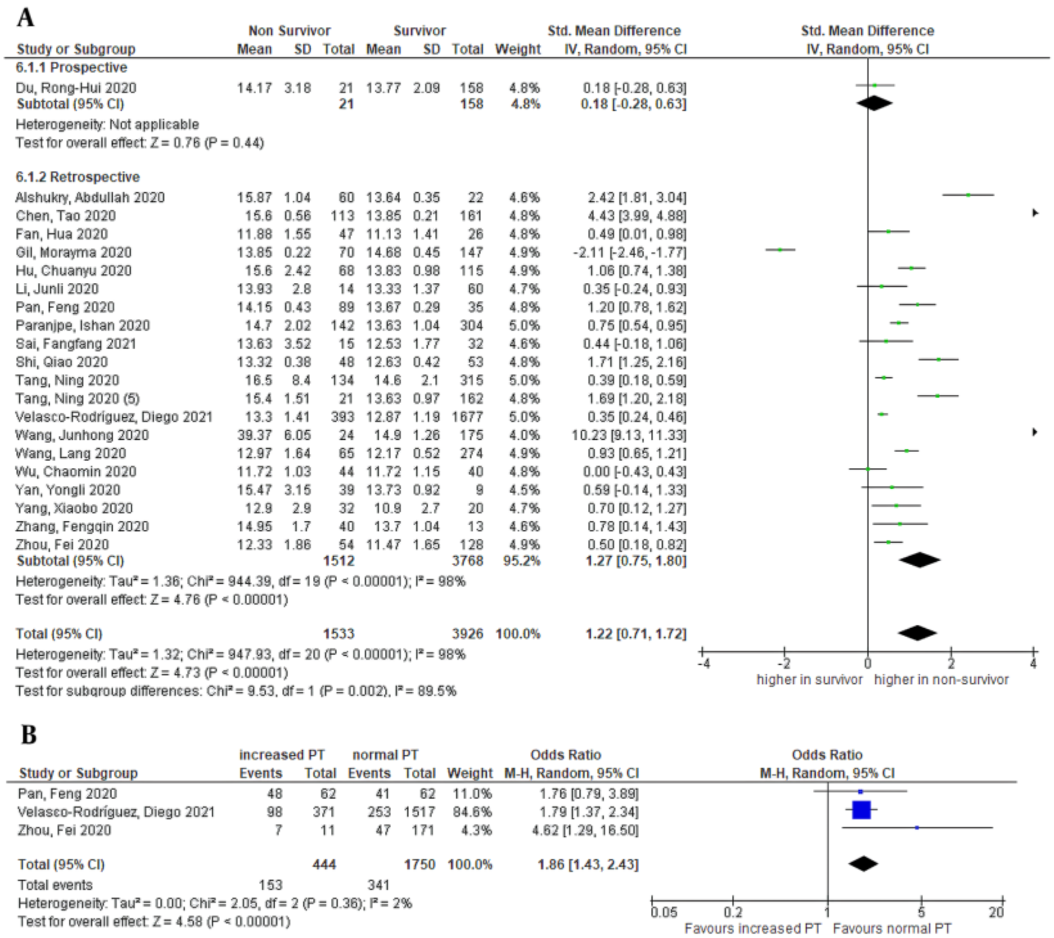

Figure 3. Forest plot of PT level for mortality outcome. A, Non-survivors had a higher PT level than survivors; and B, Increased PT and mortality (PT, prothrombin time).

duced protease inhibition are found (49). Besides, PT, aPTT, and INR are excellent parameters describing clot formation. These parameters do not provide information about fibrin crosslinking or clot dissolution and will thus be insensitive to abnormalities of fibrinolysis. On the other hand, D-dimer indicates recent or ongoing intravascular coagulation and fibrinolysis (50).

Our findings suggest that the abnormality of routine coagulation parameters on admission can be used as risk stratification tools in adult COVID-19 patients. Risk stratification in triage would help health workers allocate resources and sort the patients in the appropriate critical care or modified units, therefore maximizing the use of acute care beds (51). We encourage further studies to develop a prognostic model involving coagulation profiles in COVID-19 outcomes.

To the authors' knowledge, our review of 30 studies is the largest meta-analysis on the elaboration of coagulation profiles and in-hospital mortality of COVID-19. However, several limitations are found in our study. Publication bias was noted in several coagulation parameters. There was also substantial heterogeneity across studies. Some of the included studies in this meta-analysis were published at the preprint server. The majority of the included studies were retrospective and had limited sample sizes. Furthermore, China was the source of the majority of the studies.

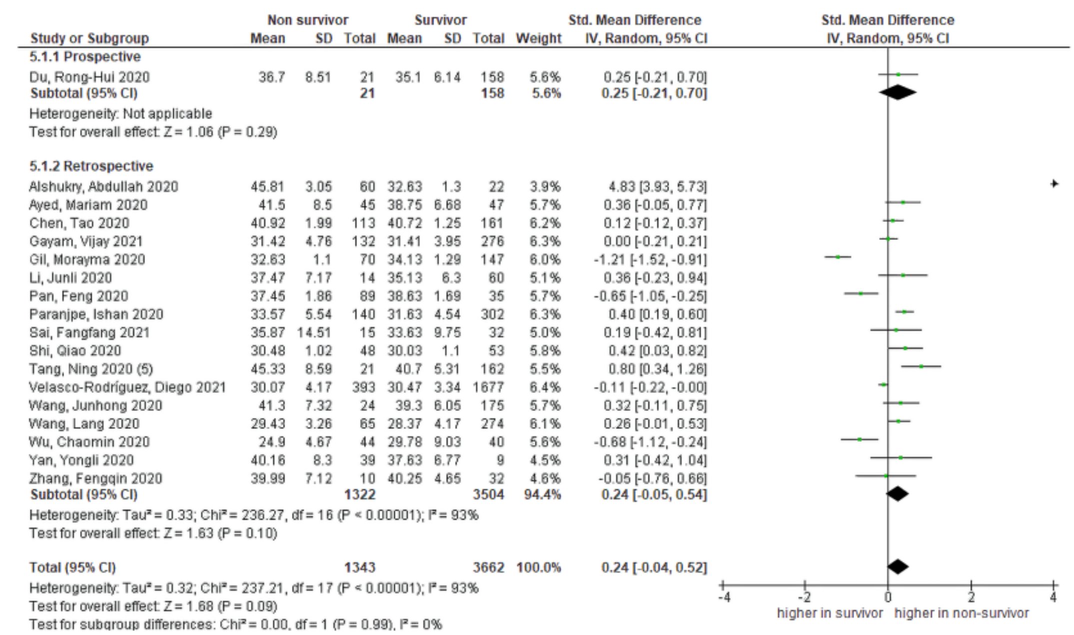

Figure 4. Forest plot of aPTT level for mortality outcome. Non-survivors had a non-significantly higher aPTT level than survivors (aPTT, activated partial thromboplastin time).

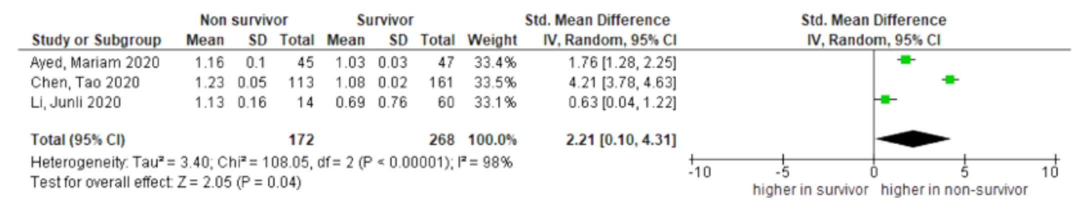

Figure 5. Forest plot of INR for mortality outcome. Non-survivors had a higher INR level than survivors (INR, international normalized ratio).

Differences in ethnicity and geography can skew the analysis results.

5.1. Conclusion

In COVID-19 patients, abnormal simple coagulation parameters on admission, such as increased PPT and INR and decreased platelets, were related to a higher risk of in-hospital mortality. We recommend clinicians closely monitor routine coagulation parameters as markers for potential progression to critical illness.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: JN, conceptualization, methodology, writing, review, editing, and supervision; AW, conceptualization, data analysis, manuscript writing, review, and editing; DR, screening, investigation, data analysis, quality assessment, and writing the original draft; EM, screening, data extraction, investigation, and writing the original draft; MA, screening, investigation, data extraction, writing the original draft, and project administration; IS, investigation, data analysis, quality assessment, and writing the original draft; IM, screening, data extraction, investigation, analysis, and writing the original draft.

Conflict of Interests: The authors declare that the research was conducted without any commercial or financial relationships that could be considered a potential conflict of interests.

Data Reproducibility: The data supporting this meta-analysis are from previously reported studies and datasets, which have been cited.

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Table 1. Characteristics of Included Studies [a]

No	Author	Study Design	Hospital	Town, Country	Period	Samples (n)	Samples with a Lab Value	Male (%)	Age (y)	HTNo. (%)	CVD (%)	DM (%)	Study Quality
1	Zhang 2020 (14)	Retro	Wuhan Pulmonary Hospital	Wuhan, China	February 7 - March 27, 2020	53 (13 vs. 40)	aPTT 42(10 vs. 32), PT 53(40 vs. 13), Platelet 53(40 vs. 13)	N/A	N/A	N/A	N/A	N/A	Fair
2	Yan 2020 (15)	Retro	Tongji Hospital	Wuhan, China	January 10 - February 24, 2020	193 (108 vs. 85)	48 (39 vs. 9)	76.9 vs. 33.3	70.5 ± 10 vs. 64.7 ± 7.3	52.8 vs. 18.8	25 vs. 4.7	36.1 vs. 10.6	Good
3	Tang 2020 (16)	Retro	Tongji Hospital	Wuhan, China	Jan 1 - Feb 3 2020	449 (134 vs. 315)	449 (134 vs. 315)	67.1 vs. 56.5	68.7 ± 11.4 vs. 63.7 ± 12.2	N/A	N/A	N/A	Good
4	Wu 2020 (17)	Retro	Jinyintan Hospital	Wuhan, China	Dec 25, 2019 - Jan 26, 2020	84 (44 vs. 40)	84 (44 vs. 40)	65.9 vs. 77.5	67.6 ± 12 vs. 49.03 ± 12.69	36.4 vs. 17.5	9.1 vs. 2.5	25 vs. 12.5	Good
5	Tang 2020 (13)	Retro	Tongji Hospital	Wuhan, China	Jan 1 - Feb 3 2020	183 (21 vs. 162)	183 (21 vs. 162)	76.19 vs. 50.61	64.0 ± 20.7 vs. 52.4 ± 15.6	N/A	N/A	N/A	Good
6	Fan 2020 (18)	Retro	Jinyintan Hospital	Wuhan, China	Dec 30, 2019 - Feb 16, 2020	73 (47 vs. 26)	73 (47 vs. 26)	68.09 vs. 65.38	65.46 ± 9.74 vs. 46.23 ± 12.01	44.68 vs. 11.54	14.89 vs. 0	21.28 vs. 7.69	Good
7	Li 2020 (19)	Retro	Wuhan Fourth Hospital	Wuhan, China	Jan 25 - Feb 26, 2020	74 (14 vs. 60)	74(14 vs. 60)	78.6 vs. 55	72.33 ± 6.59 vs. 61.67 ± 12.91	71.4 vs. 41.7	28.6 vs. 3.3	21.4 vs. 18.3	Good
8	Satici 2020 (20)	Retro	Gaziosmanpasa Research and Training Hospital	Istanbul, Turkey	April 2 - May 1, 2020	681 (55 vs. 626)	681 (55 vs. 626)	60 vs. 50.2	65.8 ± 12 vs. 56.1 ± 15.8	50.9 vs. 32.9	14.5 vs. 8.6	41.8 vs. 26.8	Good
9	Du 2020 (21)	Pros	Wuhan Pulmonary Hospital	Wuhan, China	Dec 25, 2019 - Feb 7, 2020	179 (21 vs. 158)	179 (21 vs. 158)	47.6 vs. 55.1	70.2 ± 7.7 vs. 56 ± 13.5	61.9 vs. 28.5	57.1 vs. 10.8	28.6 vs. 17.1	Good
10	Pan 2020 (22)	Retro	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Shanghai, China	Jan 27-Mar 19, 2020	124 (89 vs. 35)	124 (89 vs. 35)	75.3 vs. 51.4	69 (61-73) vs. 65 (49-77)	52.8 vs. 42.9	14.6 vs. 17.1	21.3 vs. 17.1	Good
11	Chen 2020 (12)	Retro	Tongji, Hospital	Shanghai, China	Jan 13-Feb 12, 2020	274 (113 vs. 161)	274 (113 vs. 161)	73 vs. 55	68.0 (62.0-77.0) vs. 51.0 (37.0-66.0)	48 vs. 24	14 vs. 4	21 vs. 14	Good
12	Gil 2020 (11)	Retro	Montefiore Medical Center/University Hospital for Albert Einstein College of Medicine, Moses Campus	New York, USA	Mar 20-31, 2020	217 (70 vs. 147)	217 (70 vs. 147)	67.1 vs. 53.7	68.71 ± 12.44 vs. 57.71 ± 15.56	74.3 vs. 61.2	N/A	45.7 vs. 33.3	Fair
13	Alshukry 2020 (23)	Retro	Jaber Al-Ahmad Hospital	Kuwait City, Kuwait	Feb 24-May 24, 2020	417 (60 vs. 357)	88 (60 vs. 22)	90 vs. 68.2	54.20 ± 11.09 vs. 52.32 ± 13.51	46.7 vs. 22.7	21.7 vs. 4.5	40.0 vs. 22.7	Fair
14	Ayed 2020 (24)	Retro	Jaber Al-Ahmad Al Sabah Hospital	Kuwait City, Kuwait	Mar 1-Apr 30, 2020	103 (45 vs. 47)	92 (45 vs. 47)	91 vs. 79	56 (48-63) vs. 51 (40-61)	51.1 vs. 23.4	17.8 vs. 6.5	51.1 vs. 30.4	Good
15	Shi 2020 (25)	Retro	Renmin Hospital of Wuhan University	Wuhan, China	before February 15, 2020	101 (48 vs. 53)	101 (48 vs. 53)	58.3 vs. 60.4	72.0 (59.0-78.0) vs. 71.0 (59.0-81.0)	56.3 vs. 60.4	18.8 vs. 26.4	18.8 vs. 22.6	Fair
16	Luo 2020 (26)	Retro	Renmin Hospital of Wuhan University	Wuhan, China	Jan 30-Feb 25, 2020	403 (100 vs. 303)	PLT: 403 (100 vs. 303)	57 vs. 44.9	71 (65-80) vs. 49 (37-62)	60 vs. 17.5	16 vs. 6.6 (CAD)	25 vs. 10.6	Good
17	Zhang 2020 (27)	Retro	Wuhan No.1 Hospital	Wuhan, China	Dec 25, 2019-Feb 15, 2020	48 (17 vs. 31)	PLT: 48 (17 vs. 31)	70.6 vs. 67.7	78.65 ± 8.31 vs. 66.16 ± 13.66	70.6 vs. 64.5	23.5 vs. 29.0 (CAD)	29.4 vs. 16.1	Fair
18	Paranjpe 2020 (28)	Retro	Mount Sinai Hospital	New York, USA	Feb 27-April 2, 2020	1078 (310 vs. 768)	PLT:1008 (282 vs. 726); PT: 446 (142 vs. 304); aPTT: 442 (140 vs. 302)	61.6 vs. 56.8	75 (64-85) vs. 59 (45-72)	45.2 vs. 30.3	26.8 vs. 10.9	33.9 vs. 19.7	Fair
19	Hu 2020 (29)	Retro	Tongji Hospital	Wuhan, China	Jan 28-Mar 11, 2020	183 (68 vs. 115)	183 (68 vs. 115)	73.53 vs. 49.57	68.44 ± 9.94 vs. 60.54 ± 13.19	44.12 vs. 37.39	N/A	20.59 vs. 18.26	Good
20	Fu 2020 (30)	Retro	Third Batch of Chongqing Medical Aid Team	Wuhan, China	February 4-February 16, 2020	85 (14 vs. 71)	85 (14 vs. 71)	78.57 vs. 53.52	67(50.75-74.25) vs. 62(55-70)	50 vs. 33.8	28.57 vs. 11.23	28.57 vs. 12.68	Good
21	Luo 2020 (31)	Retro	Eastern Campus of Renmin Hospital of Wuhan University	Wuhan, China	Jan 30-Feb 20, 2020	298 (84 vs. 214)	298 (84 vs. 214)	60.7 vs. 46.3	71 (64-80) vs. 51 (37-63)	58.3 vs. 17.3	15.5 vs. 6.1	21.4 vs. 12.6	Good
22	Wang 2020 (32)	Retro	Renmin Hospital	Wuhan, China	Jan 1-Feb 6, 2020	339 (65 vs. 274)	339 (65 vs. 274)	60 vs. 46.4	76 (70-83) vs. 68 (64-74)	50 vs. 38.8	32.8 vs. 11.7	17.2 vs. 15.8	Good
23	Yang 2020 (33)	Retro	Wuhan Jin Yin-tan hospital	Wuhan, China	Dec 24, 2019-Jan 26, 2020	52 (32 vs. 20)	52 (32 vs. 20)	66 vs. 70	64.6 ± 11.2 vs. 51.9 ± 12.9	N/A	9 vs. 10	22 vs. 10	Good
24	Zhou 2020 (34)	Retro	Jinyintan Hospital and Wuhan Pulmonary Hospital	Wuhan, China	December 29, 2019-Jan 31, 2020	191 (54 vs. 137)	PLT: 191 (54 vs. 137); PT: 182 (54 vs. 128)	70 vs. 59	69 (63-76) vs. 52 (45-58)	48 vs. 23	24 vs. 1	31 vs. 14	Good
25	Wang 2020 (35)	Retro	Sino-French New City Branch of Tongji Hospital	Wuhan, China	Jan 28-Mar 4, 2020	199 (24 vs. 175)	199 (24 vs. 175)	66.7 vs. 49.1	69.5 (64.5-82.75) vs. 64.0 (51.0-71.0)	50.0 vs. 37.9	8.3 vs. 12	37.5 vs. 18.9	Good

26	Sai 2021 (36)	Retro	Leishenshan Hospital	Wuhan, China	Feb 24-April 5, 2020	47 (15 vs. 32)	47 (15 vs. 32)	46.7 vs. 71.9	70.64 ± 12.33 vs. 69.67 ± 12.91	46.7 vs. 56.3	20 vs. 15.6	40 vs. 37.5	Good
27	Peiró 2021 (37)	Retro	Joan XXIII University Hospital	Tarragona, Spain	Mar 16-May 15, 2020	196 (37 vs. 159)	196 (37 vs. 159)	62.2 vs. 59.1	76.5 (68.5-82.5) vs. 61.5 (51.5-75.5)	64.9 vs. 39.6	18.9 vs. 7.6	35.1 vs. 20.8	Good
28	Velasco-Rodríguez 2021 (38)	Retro	4 hospitals in Madrid	Madrid, Spain	Feb 27-Apr 17, 2020	2070 (393 vs. 1677)	2070 (393 vs. 1677)	20.92 vs. 79.08	81 (72-87) vs. 63 (51-75)	27.75 vs. 72.25	31.49 vs. 68.51	29.1 vs. 80.9	Good
29	Violi 2021 (39)	Pros	University hospitals located in Rome (2 centers), Latina, Perugia, and Chieti	Italy	Mar 1-31, 2020	373 (75 vs. 298)	373 (75 vs. 298)	72 vs. 59	75.3 ± 13.9 vs. 65.5 ± 17.0	61 vs. 51	22 vs. 13	25 vs. 15	Good
30	Gayam 2021 (40)	Retro	inner-city teaching hospital Brooklyn	New York, USA	Mar 1-Apr 9, 2020	408 (132 vs. 276)	408 (132 vs. 276)	32.9 vs. 67.1	71 (62-80) vs. 63 (53-73)	64.9 vs. 39.6	37.04 vs. 62.92	40.91 vs. 59.09	Good

Abbreviations: CAD, coronary artery disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; Pros, prospective; Retro, retrospective; N/A, not available.
[a] Data are presented as non-survivors vs. survivors.

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