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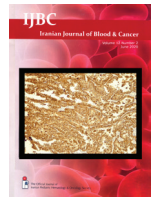

Review Article

Elevation of D-Dimer, But Not PT and aPTT, Reflects the Progression of COVID-19 Toward an Unfavorable Outcome: A Meta-Analysis

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ABSTRACT

Background: Coronavirus disease 2019 (abbreviated as COVID-19) is a mysterious respiratory syndrome symptomatically spanning from healthy carriers to patients with life-threatening complications, in some cases, leading to a mournful death. For the time being, the contributory role of hematologists is much more recognized in the management of COVID-19, since the emergence of coagulopathy has recently been the focus of many studies in SARS-CoV-2 infection.
Methods: To provide a well-conceptualized viewpoint demonstrating the prognostic value of coagulation-related laboratory tests, we planned to perform a meta-analysis of pertinent literature representing information on PT, aPTT, and D-dimer tests in patients with COVID-19.
Results: Albeit the estimated pooled means of PT and aPTT were higher in severe cases, their mean values were not significantly higher as compared with patients in a non-severe condition. On the other hand, the mean value of D-dimer in severe patients was significantly higher than non-severe cases (X^2=6.34, P=0.01), highlighting that the elevation of this parameter may be associated with the progression of the disease toward an unfavorable clinical outcome.
Conclusion: Even though at the time of writing this article the lack of adequate and appropriate studies denotes a major limitation to the current study, planning for the future research to determine the prognostic value of laboratory tests reflecting SARS-CoV-2-induced coagulopathy, mainly D-dimer, will definitively cast a flash of light on the significance of therapeutic anticoagulation at least for those with no absolute contraindication.

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Introduction

Despite endorsed and exponential research to improve diagnostic and therapeutic strategies, efforts have not yet converted into a better prospect for patients infected with the novel coronavirus (2019nCoV), first originated in late 2019 from Wuhan[1] and later designated as SARS-CoV-2 by the World Health Organization (WHO) in February, 2020.[2] In fact, this zoonotic pathogen that is currently part of the species of the SARS-related coronaviruses is apparently derived from a bat SARS-like coronavirus and transmitted to humans after the occurrence of mutations in the spike glycoprotein and nucleocapsid N protein.[3] As expected, several similarities and dissimilarities have been identified between severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) with SARS-CoV-2.[4, 5] Despite the lower mortality rate, the long incubation leading to inappropriate identification of healthy carriers

will increase the risk of contagion and facilitate the worldwide spread of SARS-CoV-2.[6] Taking a look at the number of recovered patients reveals that most of the infected cases are recuperating, however, stealing a glance at the dreadful statistics of deaths, on the other hand, recaps the fact that this deadly virus continues to infect and take its toll.[7] At the time of writing this article (May 6, 2020), over 3,700,000 cases were confirmed in more than 210 countries and territories around the world with mournful statistics of more than 250,000 related deaths (https://www.who.int/).

Keeping in mind that the results of the first four autopsies from New Orleans proposed thrombotic microangiopathy within the alveolar capillaries as a fatal mechanism in severe COVID-19 cases,[8] it might not be unrealistic to suggest that damage to the small blood vessels of vital tissues —eventually followed by intravascular coagulopathy— may probably be in charge of multi-organ failure in complicated cases of COVID-19. Since coagulopathy is among the main mechanisms that viral infections may apply to wage a full-scale war against human health,[9, 10] it comes as no surprise to assume that patients with altered coagulation may probably face with a more complicated condition in rapidly-evolving β-coronaviruses,[11, 12] and COVID-19 shall not be considered an exception to this rule.[13, 14] In the current meta-analysis, we aimed to assess whether the alteration in the prothrombin time (PT) and activated partial thromboplastin time (aPTT) together with the elevation of D-dimers could discriminate between severe and non-severe COVID-19 patients, and evaluate if there is a correlation between these parameters and disease severity.

Methods

To provide a better prospect representing the prognostic value of alteration in coagulation and fibrinolysis pathways in COVID-19, we searched national library of medicine Medline/PubMed using the keywords “coagulation” OR “coagulopathy” AND “COVID-19” OR “coronavirus 2019” OR “2019-nCoV” OR “SARS-CoV-2” between December, 2019 and the time of our analysis (i.e., May 6, 2020), without any restriction. The results of the initial search strategy were first screened by title and abstract, and then full texts of relevant articles representing information on prothrombin time (PT), activated partial thromboplastin time (aPTT), and D-dimers in COVID-19 patients with a clinically validated definition of severe disease were finally selected. To strengthen our analysis, we also scrutinized the reference list of relevant documents. Then, we performed a meta-analysis with the calculation of mean difference (MD) and 95% confidence intervals (CIs) in severe and non-severe patients. To do so, we estimated the standard deviation (SD) of selected studies based on mean and their related CIs. Since the mean and SD of the indicated parameters were not reported in several studies, we calculated them from the sample size, median and interquartile range (IQR). The statistical analysis was implemented in the R “meta” package.[15] We also applied subgroup analysis by study definition of severity. Heterogeneity between studies was estimated using the I^2 method, where I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high heterogeneity, respectively.

Results

Overall, 4221 articles were identified using the indicated criteria in our initial search and inspecting the reference lists, with a total excluding number of 4200 including letters, reviews, editorials, case reports, comments, guidelines, and book as well as those articles that did not fulfill information on prothrombin time (PT), activated partial thromboplastin time (aPTT), and D-dimers. Studies reporting cases with incomplete information were excluded, as well. The main features and values of D-dimers, PT, and aPTT of 21 selected studies were summarized in Tables 1 and 2. The number of cases ranged between 17-449, whilst severe cases, though with different definitions, varied between 5-134. The results of our meta-analysis revealed that the estimated pooled mean of D-dimers in non-severe cases was 0.55 (95% CI, 0.32–0.77) with the heterogeneity of I^2 =98% (P<0.01), whilst it was 2.24 (95% CI, 0.84–3.64) in severe patients with the heterogeneity of I^2=92% (P<0.01) (Figure 1).

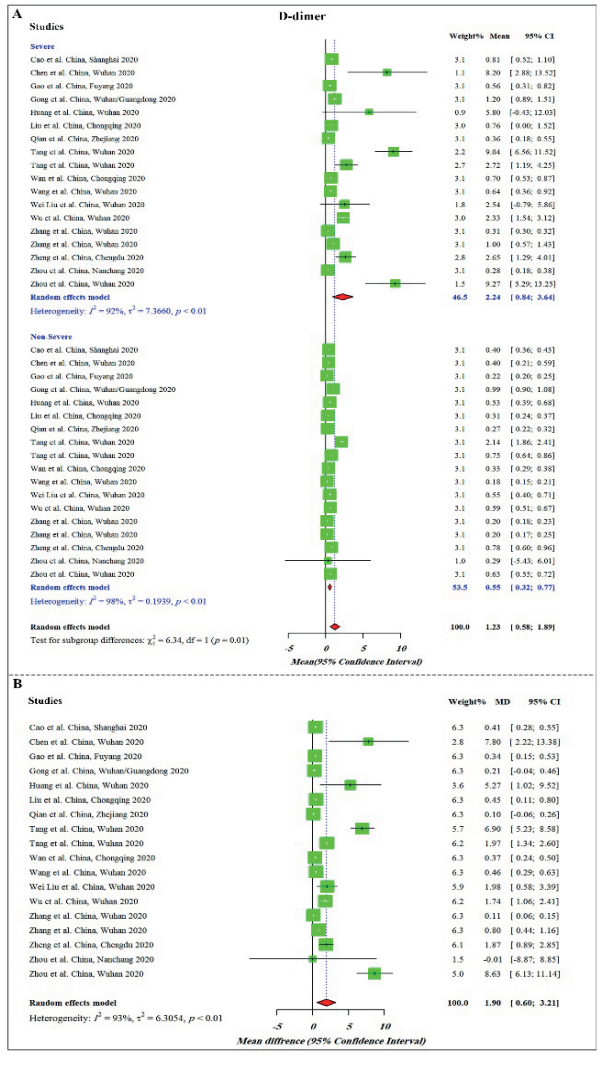

Figure 1: Forest plot of **A)** mean and **B)** mean difference in D-dimer values between severe and non-severe COVID-19 patients.

Table 1: Main features of the selected studies

Study	Country, City	Sample size	Severity definition	Severe patients			Non-severe patients		
				N (%)	Age, years	Women, %	N (%)	Age, years	Women, %
Huang et al.[21]	China, Wuhan	41	ICU admission	13 (31.7)	49.0 (41, 61)	2 (15)	28 (68.3)	49.0 (41, 57.5)	9 (32)
Chen et al.[22]	China, Wuhan	21	SpO2 < 93%	11 (52.4)	63.9 (9.6)	1 (9.1)	10 (47.6)	51.4 (13.7)	3 (30)
Tang et al.[18]	China, Wuhan	183	Death	21 (11.5)	64.0 (±20.7)	5 (23.8)	162 (88.5)	52.4 (±15.6)	80 (49.4)
Wu et al.[23]	China, Wuhan	201	ARDS	84 (41.8)	58.5 (50, 69)	24 (28.6)	117 (58.2)	48 (40, 54)	49 (41.9)
Cao et al.[24]	China, Shanghai	198	ICU admission	19 (9.6)	63.7 (16.8)	2 (10.5)	179 (90.4)	48.6 (15.6)	95 (53.1)
Zhang et al.[25]	China, Wuhan	221	WHO guideline [26]	55 (24.9)	62 (52-74)	20 (36.4)	166 (75.1)	51 (36-64.3)	93 (56)
Wan et al.[27]	China, Chongqing	135	ICU admission; M. Ventilation	40 (29.6)	56 (52-73)	19 (47.5)	95 (70.4)	44 (33-49)	43 (45.3)
Wang et al.[28]	China, Wuhan	138	ICU admission	36 (26.1)	66 (57-78)	14 (38.9)	102 (73.9)	51 (37-62)	49 (48)
Gao et al.[29]	China, Fuyang	43	NA	15 (34.9)	45.20 (±7.68)	6 (40)	28 (65.1)	42.96 (±14)	11 (73.3)
Zheng et al.[30]	China, Chengdu	99	ICU admission	32 (32.3)	63.87 (±16.51)	NA	67 (67.7)	42.51 (±15.11)	NA
Zhou et al.[20]	China, Wuhan	191	Death	54 (28.3)	69.0 (63.0, 76)	16 (30)	137 (71.7)	52.0 (45, 58)	56 (41)
Tang et al.[31]	China, Wuhan	449	Death	134 (29.8)	68.7 (±11.4)	44 (32.83)	315 (70.2)	63.7 (±12.2)	137 (43.5)
Gong et al.[32]	China, Wuhan/ Guang-dong	189	NA	28 (14.8)	45.0 (33, 62)	12 (42.9)	161 (85.2)	63.5 (54.5, 72)	89 (55.3)
Peng et al.[33]	China, Wuhan	112	ICU admission	16 (14.3)	57.5 (54, 63)	7 (43.75)	96 (85.7)	62.0 (55, 67.5)	52 (54.2)
Han et al.[13]	China, Wuhan	94	Trial version 5 [34]	45 (47.9)	NA	NA	49 (52.1)	NA	NA
Yang et al.[35]	China, Wuhan	52	Death	32 (61.5)	64·6 (11.2)	11 (34)	20 (38.5)	51·9 (12.9)	6 (30)
Liu et al.[36]	China, Chongqing	51	WHO guideline [26]	7 (13.7)	52 (44-60)	3 (42.9)	44 (86.3)	44 (33-49)	16 (36.4)
Wei Liu et al.[37]	China, Wuhan	78	Admission to ICU, Death	11 (14.1)	66 (51, 70)	4 (36.4)	67 (85.9)	37 (32, 41)	35 (52.2)
Qian et al.[38]	China, Zhejiang	91	Respiratory distress/ insufficiency	9 (9.9)	66 (54, 80)	NA	82 (90.1)	49 (35.5, 56)	NA
Zhang et al.[19]	China, Wuhan	140	Respiratory distress/ insufficiency	58 (41.4)	64 (25, 87)	25 (43.1)	82 (58.6)	52 (26, 78)	44 (53.7)
Zhou et al.[39]	China, Nanchang	17	Disease progression	5 (29.4)	42.20±14.91	5 (100)	12 (70.6)	41.50±14.31	6 (50)

On the other hand, and notwithstanding our results demonstrating that the estimated pooled means of PT and aPTT were higher in severe cases than their non-severe counterparts (13.18 vs. 12.40; 34.01 vs. 33.83, respectively), the mean values of PT and PTT in severe patients were not significantly higher as compared with non-severe patients (X^2=2.69, P=0.1; X^2=0.01, P=0.94; respectively) (Figures 2 and 3). Overall and taking advantages of our data showing that the mean value of D-dimers in severe patients was significantly higher than non-severe patients (X^2=6.34, P=0.01) with mean difference (MD) of 1.9, it is reasonable to propose that the elevation of this parameter may effectively contribute to reflect the progression of disease toward an unfavorable clinical picture. While several limitations such as low sample size, poor description of disease outcome and sampling time together with the adoption of different methods may adversely affect our analysis, we hope that the results of the present study will shed more light on the values of these parameters in COVID-19 patients.

Discussion

Coronavirus disease 2019 (abbreviated to COVID-19) is a mysterious syndrome with a wide spectrum of symptoms;

Table 2: Values of coagulation-related laboratory tests in severe and non-severe COVID-19 patients

	D-dimer		PT		aPTT	
	Non-severe	Severe	Non-severe	Severe	Non-severe	Severe
Huang et al.[21]	0.5 (0.3-0.8)	2.4 (0.6-14.4)	10.7 (9.8-12.1)	12.2 (11.2-13.4)	27.7 (24.8-34.1)	26.2 (22.5-33.9)
Chen et al.[22]	0.4 (±0.3)	8.2 (±9.0)	13.4 (±1.0)	14.1 (±0.9)	44.6 (±3.7)	36.2 (±5.8)
Tang et al.[18]	0.61 (0.35-1.29)	2.12 (0.77-5.27)	13.6 (13.0-14.3)	15.5 (14.4-16.3)	41.2 (36.9-44)	44.8 (40.2-51)
Wu et al.[23]	0.52 (0.33-0.93)	1.16 (0.46-5.37)	10.6 (10.1-11.5)	11.7 (11.1-12.45)	29.7 (25.5-32.8)	26 (22.5-35)
Cao et al.[24]	0.365 (0.26-0.56)	0.77 (0.43-1.23)	13.3 (12.9-13.7)	13.8 (13.3-14.7)	39.1 (36.7-42.15)	42.4 (38.2-49.5)
Zhang et al.[25]	0.18 (0.11-0.32)	0.31 (0.29-0.33)	12.7 (12.1-13.4)	13.4 (12.3-14.8)	31.1 (29.1-33.0)	31.1 (29-34.9)
Wan et al.[27]	0.3 (0.2-0.5)	0.6 (0.4-1.1)	10.8 (10.4-11.3)	11.3 (10.7-11.8)	26.6 (24.5-28.8)	29.7 (26.2-39.4)
Wang et al.[28]	0.16 (0.1-0.28)	0.41 (0.19-1.32)	12.9 (12.3-13.4)	13.2 (12.3-14.5)	31.7 (29.6-33.5)	30.4 (28-33.5)
Gao et al.[29]	0.21 (0.19-0.27)	0.49 (0.29-0.91)	12.03 (±1.21)	11.26 (±1.42)	30.41 (±5.31)	27.29 (±6.09)
Zheng et al.[30]	0.78 (±0.76)	2.65 (±3.93)	12.91 (±0.63)	13.49 (±0.96)		
Zhou et al.[20]	0.6 (0.3-1.0)	5.2 (1.5-21.1)	11.4 (10.4-12.6)	12.1 (11.2-13.7)		
Tang et al.[31]	1.47 (0.78-4.16)	4.70 (1.42-21)	14.6 (±2.1)	16.5 (±8.4)		
Gong et al.[32]	0.99 (0.6-1.38)	1.22 (0.66-1.72)			39.1 (±4.4)	40 (±5.4)
Peng et al.[33]			13 (12.5-14.1)	13.9 (12.6-14.7)	35.75 (31.6-40)	36.4 (33.1-44)
Han et al.[13]			12.20 (±0.88)	12.65 (±1.13)	28.56 (±2.66)	29.53 (±3.48)
Yang et al.[35]			10.9 (±2.7)	12.9 (±2.9)		
Liu et al.[36]	0.28 (0.18-0.46)	0.6 (0.28-1.4)				
Wei Liu et al.[37]	0.39 (0.2-1.07)	0.56 (0.21-6.84)				
Qian et al.[38]	0.3 (0.1-0.4))	0.45 (0.16-0.48)				
Zhang et al.[19]	0.2 (0.1-0.3)	0.4 (0.2-2.4)				
Zhou et al.[39]	0.29 (±10.11)	0.28 (±0.11)				

PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

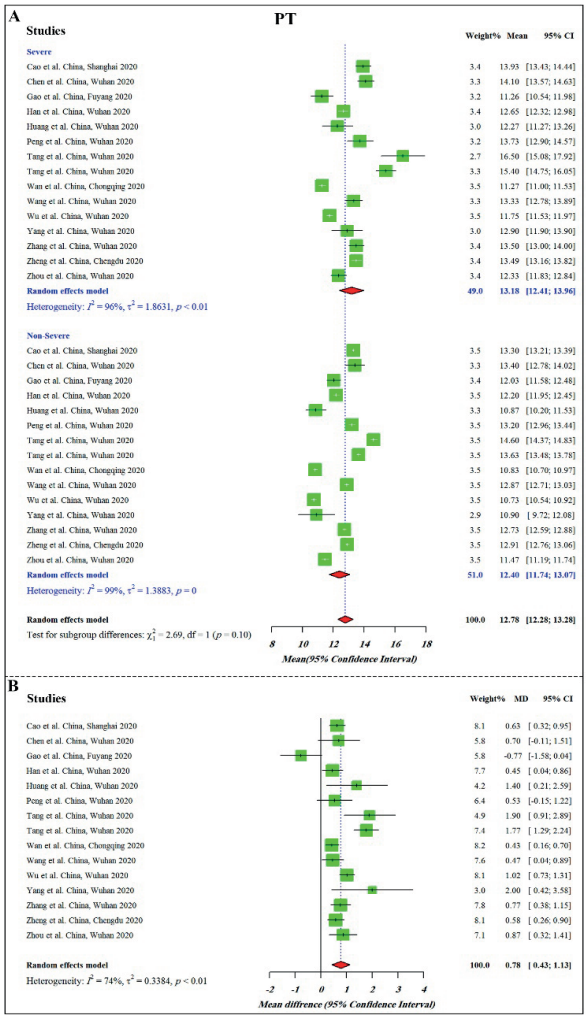

Figure 2: Forest plot of **A)** mean and **B)** mean difference in prothrombin time (PT) values between severe and non-severe COVID-19 patients.

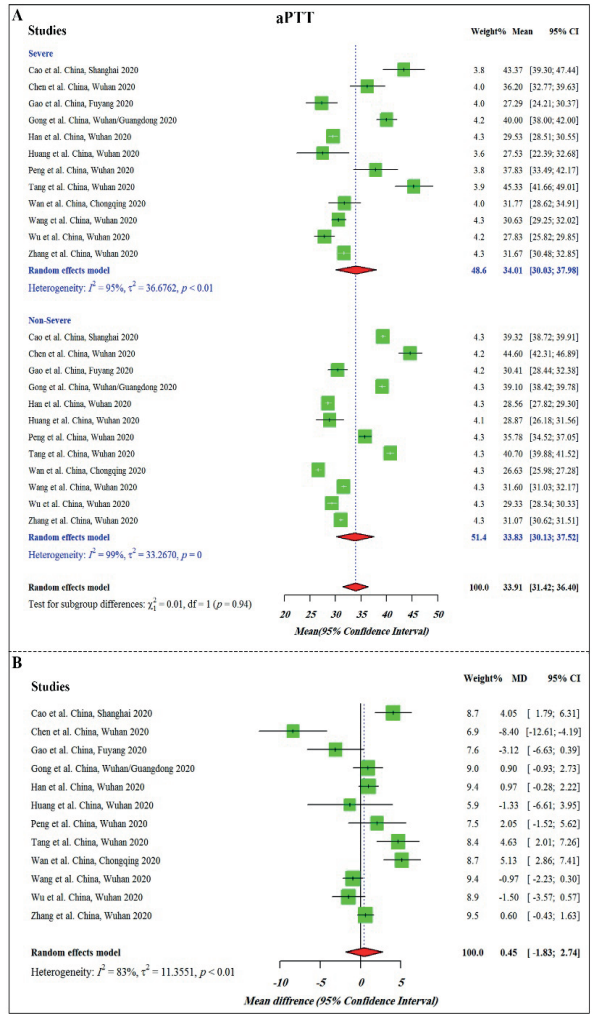

Figure 3: Forest plot of **A)** mean and **B)** mean difference in activated partial thromboplastin time (aPTT) values between severe and non-severe COVID-19 patients.

while some of the infected cases will display no or mild symptoms, others will present more serious complications leading to a critical care respiratory condition and necessitating specialized management at intensive care units (ICU).[16] Notwithstanding the fact that atypical pneumonia is the principal symptom,[17] there being evidence that the occurrence of life-threatening complications mainly resulting from the injury of non-pulmonary organs leaves no choice, in some cases, rather than a dreadful death. By considering the results of a valuable study demonstrating that thrombotic microangiopathy within the alveolar capillaries may serve as a fatal mechanism in severe COVID-19 cases,[8] it is reasonable to hypothesize that damage to the small blood vessels of vital tissues —eventually followed by intravascular coagulopathy— may probably be in charge of multi-organ failure in complicated cases of COVID-19. In this vein, a recent study proposed disseminated intravascular coagulation (DIC) as a strong predictor of mortality in COVID-19 cases. Notably, they reported that while only 0.6% of survivors met criteria for DIC, more than 70% of non-survivors experienced this fatal event.[18] In a study conducted on 140 COVID-19 patients, among which 58 cases were severe, Zhang et al. reported that increased levels of D-dimer may help clinicians to effectively discriminate between patients with severe and non-severe COVID-19 disease.[19] Although multiple lines of evidence emphasized the importance of a hypercoagulable state with micro- and macro-circulatory thrombosis, further studies are now underway to more precisely characterize the prognostic value of coagulation studies and efficiency of prophylactic doses of anticoagulation in SARS-CoV-2 infection. Albeit the results of our study revealed that the estimated pooled means of PT and aPTT were higher in severe cases, their mean values were not significantly higher as compared with non-severe patients. On the other hand, and taking advantage of our data showing that the mean value of D-dimers in severe patients was significantly higher than non-severe cases, we propose that elevation of this parameter may effectively contribute to reflect the progression of disease toward an unfavorable clinical picture. In consistent, Zhou F. et al. reported that elevated D-dimer (above 1 μg/ml) may mirror disease progression and serve as an independent risk factor for death in COVID-19 patients.[20]

Conclusion

Even though at the time of writing this article the lack of adequate and appropriate studies denotes a major limitation to the current study, planning for the future research aiming to determine the prognostic value of laboratory tests reflecting SARS-CoV-2-induced coagulopathy, foremost D-dimer, will definitively cast a flash of light on the significance of therapeutic anticoagulation at least for COVID-19 patients with no absolute contraindications.

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Conflict of Interest: None declared.

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