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Article type : Letters

Changes in Blood Coagulation in Patients with Severe Coronavirus Disease 2019 (COVID-19): a Meta-Analysis

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Short title: Blood Coagulation in COVID-19

Keywords: COVID-19, Coronavirus, Coagulation, laboratory, Meta-analysis

To the Editor:

Coronavirus disease 2019 (COVID-19) is widely spread and poses a critical threat to global health (Zhang et al). Prominent changes in coagulation function in severe patients of COVID-19 have been reported in a recent study (Han*, et al* 2020). Therefore, we conducted this quantitative meta-analysis to explore the difference in blood coagulation parameters between severe and mild cases of COVID-19.

Literature published from December 2019 to 30 March 2020 was searched systematically using PubMed and Embase without language limits. The keywords were as below: coronavirus, laboratory, clinical manifestations, clinical characteristics, and clinical features. All documents comparing information on coagulation parameters between mild and severe cases of COVID-19 patients were finally referred to in our meta-analysis. The pooled standardized mean difference (SMD) and 95% confidence interval (CI) were computed by applying the random-effect model using Stata software (STATA14.0, Stata Corp, College Station, TX, USA). The study quality was measured by adopting an 11-item checklist which was suggested by the Agency for Healthcare Research and Quality (AHRQ).

Table 1displayed the main characteristics of the included studies. Nine studies including one study from medRxiv, with 1105 patients, were eventually included for detailed evaluation. Platelet count (PLT), activated partial thromboplastin time (APTT), prothrombin time (PT) and D-dimer (D-D) levels were available in five, six, six and eight studies respectively. All the studies were conducted in China. Quality score varied from 3 to 7 points with a mean of 5.4 (Table 1). All the studies were of moderate quality except one was of low quality.

The main difference in coagulation function between severe and mild COVID-19 patients was shown in Fig 1. Pooled results revealed that PT and D-D levels were significantly higher in patients with severe COVID-19 (0.68, 95% CI = 0.43 to 0.93, I^2 = 53.7%; 0.53, 95% CI = 0.22 to 0.84, I^2 = 78.9% respectively). However, no significant difference in PLT and APTT values between severe and mild patients were observed (-0.08, 95% CI = -0.34 to 0.18, I^2 = 60.5%; -0.03, 95% CI = -0.40 to 0.34, I^2 =79.5% respectively). Increasing values of D-D and PT support the

notion that disseminated intravascular coagulation (DIC), maybe common in COVID-19 patients (Han*, et al* 2020). Besides, the rise of D-D level also indicates secondary fibrinolysis conditions in these patients. According to Berri et al. (Berri*, et al* 2013), fibrin clot formation favors people to fight against influenza virus infections whereas plasminogen leads the deleterious inflammation pulmonary infection. Hence fibrinolysis may potentially induce following severe 2019-nCoV infection. Future studies should aim to discover more biomarkers of severe cases of COVID-19. And studies explore the underlying mechanism of deranged coagulation function in COVID-19 are urgently needed. The hemostatic system might be explored for underlying treatment against coronavirus. In conclusion, due to the lack of sufficient studies data, we can't perform a more thorough analysis to prove beneficial of the screening parameters PLT, APTT, PT and D-D for prediction of severity of COVID-19. However, we suggest that clinical practitioners pay attention to the changes in coagulation function in COVID-19 patients on a daily basis.

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Table legends

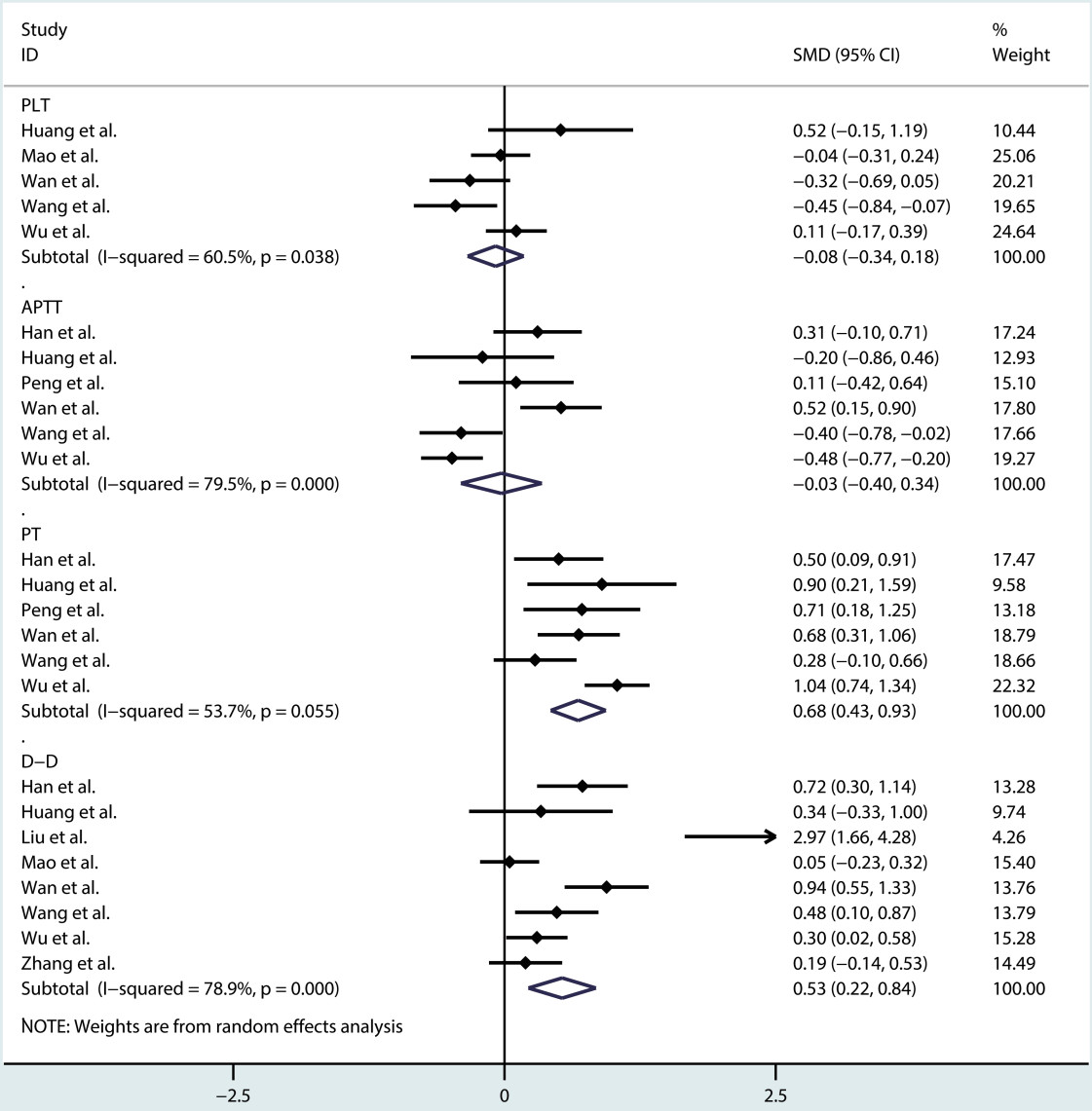
Table 1. Study characteristics

Note. *data presented as severe/mild COVID-19 patients; data given as m (SD); N, number of included patients; n, number of severe patients; QS, quality score; NA, not available; PLT, platelet, reference interval 125-350*10^9/L; APTT, activated partial thromboplastin time, reference interval 25.1-36.5s; PT, prothrombin time, reference interval 9.4-12.5s; D-D, D-dimer, reference interval 0-0.5 mg/L; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

Figure legends

Fig.1. Forest plot of PLT, APTT, PT, D-D levels in severe COVID-19 patients vs mild COVID-19 patients.

Study	N(male%)	n	Age(years)	Severity criteria	QS	Coagulation parameters*			
						PLT(10^9/L)	APTT(s)	PT(s)	D-D (mg/L)
Han et al.(Han, *et al* 2020)	94(51.0)	45	NA	trail version5	5	NA	29.5(3.2)/28.6(2.7)	12.7(1.1)/12.2(0.9)	19.3(34.5)/2.1(2.9)
Huang et al. (Huang, *et al* 2020)	41(73.0)	13	49.0(12.6)	ICU and non-ICU	6	196·0(72.6)/149·0(97.8)	26·2(8.4)/27·7(6.9)	12·2(1.6)/10·7(1.7)	2·4(10.2)/0.5(0.4)
Liu et al.(Liu, *et al* 2020)	30(33.3)	4	35.0(8.0)	trail version5	5	NA	NA	NA	1.5(1.2)/0.3(0.1)
Mao et al.(Mao, *et al* 2020)	214(40.7)	88	52.7(15.5)	WHO interim guideline	5	204.5(413.3)/219.0(400.7)	NA	NA	0.9 (14.7)/0.4 (6.3)
Peng et al(Peng, *et al* 2020)	112(47.3)	16	62.0(8.9)	standard version	6	NA	36.5(8.4)/35.8(6.2)	13.9(1.6)/13.0(1.2)	NA
Wan et al.(Wan, *et al* 2020)	135(53.3)	40	47.0(14.1)	trail version5	6	147.0(70.4)/170.0(72.6)	29.7(9.8)/26.6(3.2)	11.3(0.8)/10.8(0.7)	0.6(0.5)/0.3(0.2)
Wang et al.(Wang, *et al* 2020)	138(54.3)	36	56.0 (19.2)	ICU and non-ICU	7	142.0(61.5)/165.0(46.7)	30.4 (4.1)/31.7 (2.9)	13.2 (1.6)/12.9(0.8)	0.4 (0.8)/0.2 (0.1)
Wu et al. (Wu, *et al* 2020)	201(63.7)	84	51.0(12.3)	with and without ARDS	6	187.0(94.1)/178.0(73.7)	26.0(9.2)/29.5(5.4)	11.7(1.0)/10.6(1.1)	1.2 (3.6)/0.5 (0.4)
Zhang et al.(Zhang, *et al* 2020)	140(50.7)	58	57.0(45.9)	trail version5	3	NA	NA	NA	0.4 (1.6)/0.2 (0.1)



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