

LETTER TO EDITOR

Predicted value of coagulation function for prognosis and admission time to negative RT-PCR detection in non-critical COVID-19 patients

Since December 2019, coronavirus disease 2019 (COVID-19) swept around the world and resulted in 2 463 153 confirmed cases with 172 260 deaths by April 22, 2020. Several studies had reported that severe patients showed higher levels of D-dimer, prothrombin time (PT), and activated partial thromboplastin time (APTT).¹ Alex et al suggested the use of thromboprophylaxis in COVID-19 patients, particularly those with evidence of activation of the coagulation system on admission.² However, the effective predictor of the interval between the admission time and negative RT-PCR detection (ATN) is unknown.

We conducted retrospective study between February 13, 2020 and March 13, 2020 in Cancer Center of Wuhan Union Hospital (Wuhan, China), which was designated hospital to centralized admission COVID-19 patients since February 13, 2020, to reveal the potential role for coagulation parameters in COVID-19 patients. The diagnosis was confirmed according to the diagnostic standards in the “Guidelines for the Diagnosis and Treatment of Novel Coronavirus (2019-nCoV) Infection” by the National Health Commission of the People’s Republic of China. Based on this, disease severity was divided into mild type (I, with mild clinical symptoms but without imaging features of COVID-19 infection), common type (II, with clinical symptoms such as fever and/ or respiratory symptoms and with imaging features of COVID-19 infection), and severe type (III, comply with any one of the followings: respiratory rate $\geq 30/\text{min}$, Oxygen saturation $\leq 93\%$, $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$, and/or focus of COVID-19 infection progress rapidly ($\geq 50\%/24 \text{ h}$)), and critical type (IV, ICU patient). Clinical characteristics and lab test results, including coagulation tests data, and time to get the endpoint (negative RT-PCR detection for twice, in minimum 24 h sampling interval) were obtained from electronic medical records using a standardized data collection form. All these data were checked and reviewed by independent and experienced doctors. Critical type patients were excluded from our current study based on our research purpose. Blood samples were collected within 24 h after admission to perform coagulation testing,

including APTT, PT, D-dimer, AT III, FDP, INR, FIB, and TT.

The baseline clinical characteristics of non-critical patients with COVID-19 were shown in Table 1, and the coagulation results showed that the level of D-dimer (1.42 ± 2.27) and fibrinogen (FIB, 4.36 ± 1.27) were higher in COVID-19 patients compared with regular people, which indicated that the COVID-19 patients were suffered from coagulation dysfunction.

Studies had shown that the disease severity and prognosis of COVID-19 patients were significantly affected by multiple confounding factors, especially by age and coagulation function.^{3–5} Consistently, our result showed that the higher disease severity population had a higher proportion of patients with abnormal coagulation function, especially for AT III, D-dimer, and FIB, which showed significant differences ($P < .05$, Figure 1A).

Ling et al, showed that the median time from the onset of symptoms to first negative RT-PCR results for oropharyngeal swabs in convalescent patients was 9.5 (6.0–11.0) days.⁶ Inconsistently, median time for ATN was 23.7 ± 5.4 days (Table 1), which may contribute to the older age for COVID-19 patients in our study (62.3 years vs 44 years). More importantly, we set the negative RT-PCR detection for two times as the observed outcome, which could avoid false negatives with maximum degree. Zhang et al. had respectively reported the prognostic value of D-dimer on admission in COVID-19 patients,⁵ but predicted value of D-dimer level on ATN was still unclear. In this study, the COVID-19 patients were divided into two groups and univariate analyze were conducted according to the median cutoff value of $\text{ATN} = 26$, and the result demonstrated that the coagulation function, especially D-dimer, together with diagnosed age and disease severity were associated with ATN (Table 1). The area under the ROC (receiver operator characteristic) curve (AUC) showed that age, disease severity level, and D-dimer level had the better predictive effect to ATN in COVID-19 patients, the AUC were 0.719, 0.744, and 0.723, respectively (Figure 1B and C).


TABLE 1 Univariate analysis of clinical characteristics of patients according to ATN (cutoff value = 26). Continuous variables are presented as mean \pm SD

Parameter	All patients	Percentage (%)	Normative values	ATN < 26	ATN \geq 26	P
No.	110			52	58	
Age, years	62.3 \pm 13.3			56.83 \pm 14.38	67.22 \pm 10.06	<.001
Sex						.129
Male	51	46.4		32(61.5%)	27(46.6%)	
Female	59	53.6		20(38.5%)	31(53.4%)	
With underlying health conditions						
Hypertension	33	30.0				
Diabete	15	13.6				
COPD	3	2.7				
Cancer	4	3.6				
APTT, s	37.45 \pm 4.61		28-43.5s	36.94 \pm 4.20	38.50 \pm 4.77	.070
PT, s	13.46 \pm 0.96		11-16s	13.21 \pm 0.84	13.69 \pm 1.00	.007
D-dimer, mg/l FEU	1.42 \pm 2.27		<0.5 mg/L FEU	36.94 \pm 4.20	38.50 \pm 4.77	.070
AT III, %	84.57 \pm 15.28		80-120%	13.21 \pm 0.84	13.69 \pm 1.00	.007
FDP, ug/ml	5.12 \pm 9.38		<5ug/ml	36.94 \pm 4.20	38.50 \pm 4.77	.070
INR	1.05 \pm 0.10		0.8-1.31	13.21 \pm 0.84	13.69 \pm 1.00	.007
FIB, g/l	4.36 \pm 1.27		2.0-4.0 g/l	36.94 \pm 4.20	38.50 \pm 4.77	.070
TT, s	17.57 \pm 1.28		14-21 s	13.21 \pm 0.84	13.69 \pm 1.00	.007
Disease severity						<.001
I	18	16.4		18(34.6%)	0(0%)	
II	62	56.4		28(53.8%)	34(58.6%)	
III	30	27.2		6(11.5%)	24(41.4%)	
ATN, days	23.7 \pm 5.4			19.15 \pm 4.36	27.81 \pm 1.89	<.001

Continuous variables are presented as mean \pm SD. (COPD: Chronic Obstructive Pulmonary Disease; PT: prothrombin time; APTT: activated partial thromboplastin time; AT III: antithrombin III; FDP: Fibrinogen degradation product; INR: International standard ratio; FIB: fibrinogen; TT: thrombin time; ATN: admission time to negative. Continuous variables were presented as means and standard deviations (mean \pm SD) and categorical variables were presented as counts and percentages. Patient characteristics were compared using Student's t test for continuous variables. Pearson's chi-square test or Fisher exact tests were conducted for categorical variables.)

1 | CONCLUSION

In conclusion, our study revealed the correlation between highly deviating of coagulation function and high disease severity, also poor prognosis. Importantly, the result proved the accurately predicted value of high D-dimer levels to longer ATN in non-critical COVID-19 patients.

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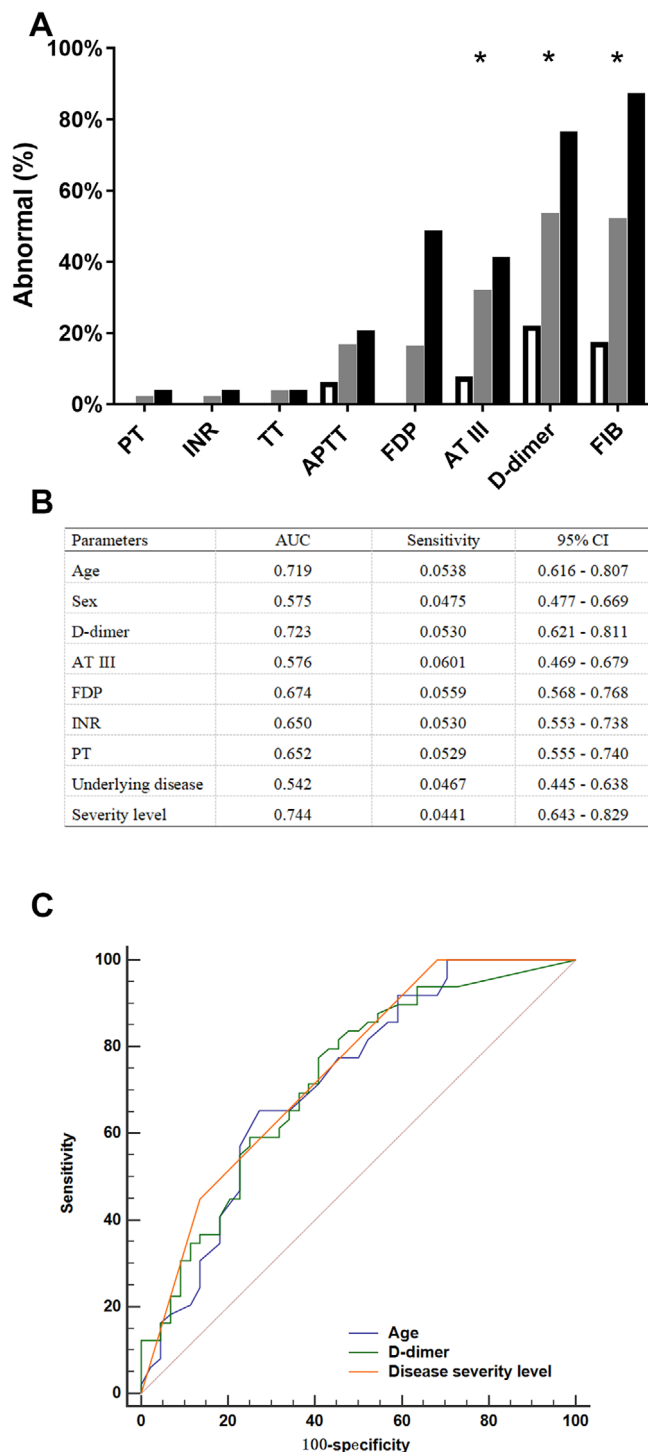


FIGURE 1 A, the proportion of patients with abnormal coagulation function test parameters in different disease severity groups. “*” represents $P < .05$. B, AUC of parameters to predict ATN for patients with COVID-19. (AUC, area under curve; 95% CI, 95% confidence interval). C, ATN-dependent ROC analysis for patients with COVID-19

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