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Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count

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Abstract

Concomitant coagulation disorder can occur in severe patients withCOVID-19, but in-depth studies are limited. This study aimed to describe the parameters of coagulation function of patients with COVID-19 and reveal the risk factors of developing severe disease. This study retrospectively analyzed 113patients with SARS-CoV-2 infection in Taizhou Public Health Center. Clinical characteristics and indexes of coagulation function were collected. A multivariate Cox analysis was performed to identify potential biomarkers for predicting disease progression. Based on the results of multivariate Cox analysis, a Nomogram was built and the predictive accuracy was evaluated through the calibration curve, decision curve, clinical impact curve, and Kaplan–Meier analysis. Sensitivity, specificity, predictive values were calculated to assess the clinical value. The data showed that Fibrinogen, FAR, and D-dimer were higher in the severe patients, while PLTcount, Alb were much lower. Multivariate Cox analysis revealed that FAR and PLT count were independent risk factors for disease progression. The optimal cutoff values for FAR and PLT count were 0.0883 and $135*10^9$/L, respectively. The C-index [0.712 (95% CI = 0.610–0.814)], decision curve, clinical impact curve showed that Nomogram could be used to predict the disease progression. In addition, the Kaplan–Meier analysis revealed that potential risk decreased in patients with FAR<0.0883 and PLT count>$135*10^9$/L.The model showed a good negative predictive value [(0.9474 (95%CI = 0.845–0.986)].This study revealed that FAR and PLT count were independent risk factors for severe illness and the severity of COVID-19 might be excluded when FAR<0.0883 and PLT count>$135*10^9$/L.

Keywords

Coagulation and Fibrinolysis, COVID-19, fibrinogen-to-Albumin Ratio (FAR), non-Severe Survival (NSS), platelet count (PLT), prediction

History

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Introduction

In December 2019, several coronavirus disease 2019 (COVID-19) cases were reported in Wuhan, Hubei province, China, and rapidly spread globally [1]. The mortality rate of COVID-19 in China is about 2.7%, higher than that of ordinary influenza [2]. Most of the patients were mild, but some patients progressed rapidly to acute respiratory distress syndrome (ARDS), septic shock, and dysfunction of blood coagulation [3]. As it has indicated that activation of the coagulation system might be associated with a sustained inflammatory response in COVID-19 [4,5]. Many studies on SARS-CoV and MERS-CoV had suggested that hyper coagulation and fibrinolysis can increase the risk of microthrombus formation and furthermore aggravate the risk of organ failure inflammation [6]. Despite the prevailing study, information on the early prediction of severe cases is still limited and more studies are needed. In this study, we compared the differences in the indexes of coagulation function and dynamic changes in patients with severe and non-severe COVID-19 to investigate the risk factors of developing severe disease.

METHODS

Patient Selection

One hundred and thirteen patients of COVID-19 were enrolled in Taizhou Public Health Medical Center, Taizhou Hospital, Zhejiang Province, China, from January 23 to February 4, 2020. Clinical diagnosis and classifications were made according to the Chinese management guideline for COVID-19 (version 6.0) [7]. According to the guideline, COVID-19 patients are classified into four categories: 1) Mild, mild symptoms and no pneumonia manifestation; 2) Typical, fever, or respiratory symptoms and imaging manifestation of pneumonia; 3) Severe, having any of the three conditions: respiratory distress, respiratory rate ≥30 beats/min; means oxygen saturation ≤93% in a resting state; arterial blood oxygen partial pressure/oxygen concentration ≤300 mm Hg (1 mm Hg = 0.133 kPa); 4) Critical, having one of the three conditions: shock incidence; respiratory failure and requiring mechanical ventilation; admission to ICU with other organ function failure. The endpoint of this study was the occurrence of severe illness. The clinical outcomes were monitored until February 15, 2020. All patients were classified into either the severe or non-severe group, the severe group contained severe and critically severe patients, while the non-severe group included

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mild and moderate patients. On admission, all patients were classified as non-severe. We collected a total of 28 COVID-19 patients from February 5 to February 20 as an external validation group. The endpoint of follow-up was March 1, 2020.

Data Collection

The information of epidemiology history, clinical features, radiological characteristics, and days from on admission were collected from electronic medical records. Two researchers independently reviewed the data collection forms. Laboratory indicators including indexes of coagulation function, hemocyte count, blood chemistry were collected.

Statistical Analysis

Categorical variables were expressed as frequency and percentage, and continuous variables were shown as median, and interquartile range (IQR). χ^2 test was used to compare categorical variables, while Mann–Whitney U test was conducted for continuous variables. A multivariate analysis was performed to predict the disease progression. Considering the total number of severe cases (n = 22) in our study and to avoid overfitting in the model, four variables were chosen for multivariable analysis on the basis of previous findings and clinical constraints. Cutoff points were identified following Youden's index of receiver operator characteristic (ROC) curve. Based on the results of multivariate analysis, a Nomogram was established. The C-index, calibration, decision curve, and the clinical impact curve were used to verify the Nomogram. Kaplan–Meier analysis was drawn, and risk stratification was compared by the log-rank test. Sensitivity, specificity, predictive values were calculated. Ninety-five percent confidence intervals (95% CI) of hazard ratio(HR) were used as common measures to assess relative risk. All statistical analysis were performed using SPSS (version 24.0), R program (version 3.6.2).P < .05 were considered to be statistically significance.

Results

Clinical Characteristics of Patients with COVID-19

One hundred and thirteen confirmed patients with SARS-COV-2 infection were included in this study, 91 (80.5%) patients were grouped into non-severe cases and 22 were (19.5%)severe cases, as shown in Table I. The median age was 46 years(IQR, 37–45 years); 64 (56.6%) of them were male; 44 (38.9%) patients had the basic disease; Forty-seven(41.6%) had a fever (with a body temperature> 37.3°C) on admission; X-ray or CT findings showed involvement of chest radiographs in 110 patients (97.3%). Seventy-two (63.7%) had a Wuhan exposure, the others had a close exposure history to those patients withCOVID-19.Four (3.5%) patients developed a secondary infection during hospitalization. The median age of severe patients was older than non-severe patients (54 years *vs*. 44 years, *P* = .000). Compared with non-severe patients, the Median time from illness onset to admission was much longer in severe patients (3 days *vs*. 2 days, *P* = .034).

Comparison of Initial Indexes of Coagulation Function between Severe and Non-severe Patients

It was shown that Fibrinogen, FAR, and D-dimer were significantly higher in the severe group than in the non-severe group (4.23 g/L *vs*. 3.07 g/L, 0.10 *vs*. 0.078,0.32 mg/L *vs*.0.24 mg/L, *P* = .002,0.046,0.009, respectively),while PLT count and Alb were much lower (166*10^9/L *vs*. 199*10^9/L,38.3 g/L *vs*.40.6 g/L, *P* = .034,0.005),as shown in Figure 1.

Dynamic changes of Coagulation Indexes in Severe COVID-19 Patients

To perform the dynamic profile that appeared during COVID-19 progression, we had been following up for 23 days since on admission at 5-day intervals. As of February 4, 2020, 11 severe patients were analyzed (Figure 2). Coagulation time such as PT, aPTT had shortened from the beginning of hospitalization, then

Table I. Clinical characteristics of patients with 113 COVID-19 between the severe and non-severe group.

	Non-severe(N = 91)	Severe (N = 22)	ALL (N = 113)	P value
Age, year	44 (36–54)	54 (47–62)	46 (37–55)	0.000
≦50	61 (67.0%)	6 (27.3%)	67 (59.3%)	0.001
>50	30 (33.0%)	16 (72.7%)	46 (40.7%)	
Gender				0.796
Male	51 (56%)	13 (59.1%)	64 (56.6%)	
Female	40 (44%)	9 (40.9%)	49 (43.4%)	
Current smoking	3 (5.3%)	5 (8.9%)	8 (92.9%)	0.490
Comorbidity	32 (72.7%)	12 (54.5%)	44 (38.9%)	0.143
Temperature on admission, °C				
≦37.3	56 (61.5%)	10 (45.5%)	66 (58.4%)	0.459
>37.3	35 (38.5%)	12 (54.5%)	47 (41.6%)	
Symptom				
Pharyngalgia	8 (8.0%)	2 (9.1%)	10 (8.8%)	0.743
Cough	53 (58.2%)	13 (59.1%)	66 (58.4%)	0.570
Expectoration	26 (28.6%)	7 (31.8%)	33 (29.2%)	0.797
CT:				
Involvement of chest radiographs	84 (92.3%)	22 (100%)	110 (97.3%)	0.210
Exposure				0.615
Outside Wuhan	33 (36.3%)	8 (36.3%)	41 (36.3%)	
Wuhan	58 (63.7%)	14 (63.7%)	72 (63.7%)	
Involvement				
With bacterial infection	2 (2.2%)	2 (9.1%)	4 (3.5%)	0.504
disturbance of consciousness	0	1 (4.5%)	1 (0.8%)	0.714
Timeline after onset of illness				
Days from illness onset to admission time	2 (0–5)	3 (1–7.0)	2 (0–5)	0.034
Days from admission time to severe illness		15 (8.3–20)		

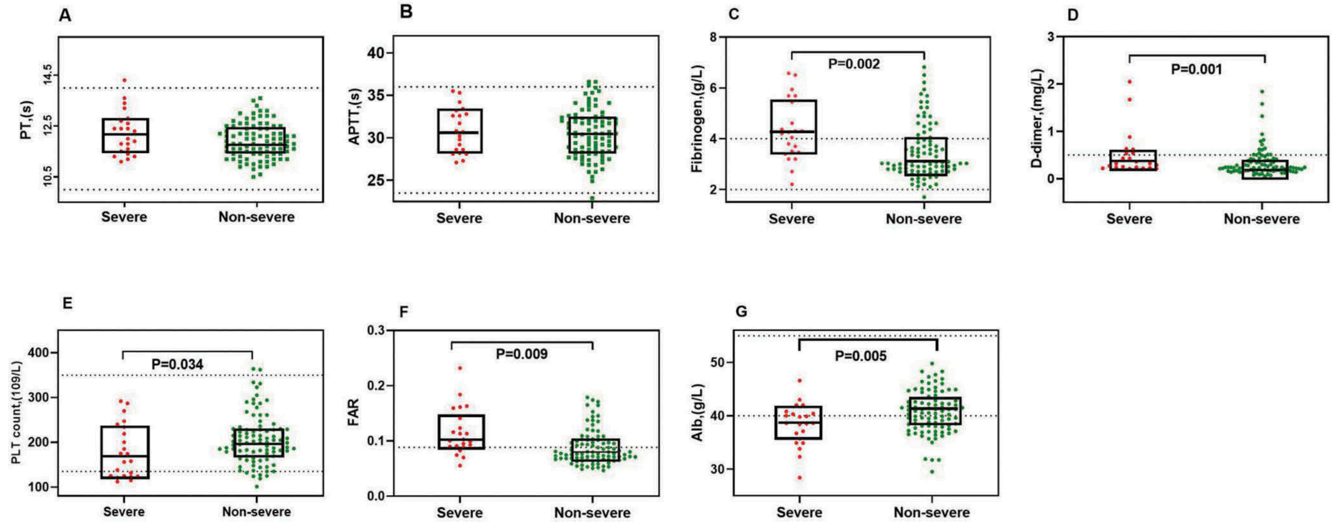

Figure1. Comparison of initial indexes of coagulation function between severe and non-severe patients. Fibrinogen, D-dimer and FAR were significantly higher in the severe group than in the Non-Severe group (4.23 g/L *vs*.3.07 g/L, 0.32 mg/L *vs*. 0.24 mg/L,0.10 *vs*.0.078,

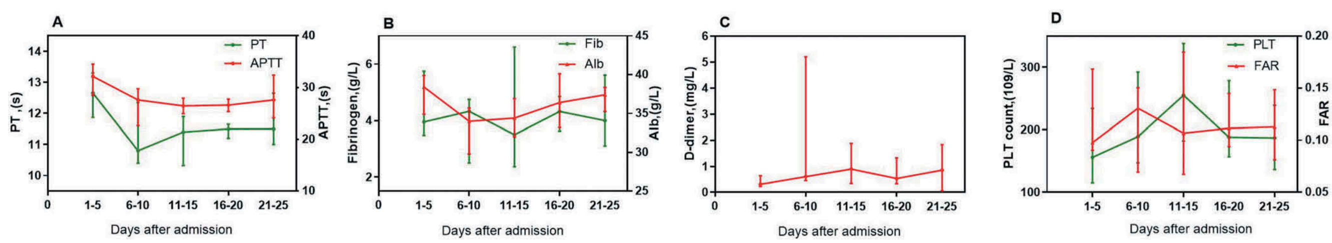

Figure 2. Temporal changes in markers of coagulation function over time inpatients with severe COVID-19. Dynamic changes in PT and aPTT (A), Fibrinogen and Alb(B), D-dimer(C), PLT and FAR(D).Coagulation time such as PT, aPTT shorten over time and leveled off in about 11–15 days in the hospital. Fibrinogen and D-dimer showed similar volatility changes, therein, Fibrinogen was lowest on day 11–15 after on admission, the median value was 3.5, while D-dimer was the highest of 0.89.FAR was highest on day 11–15 after admission and decreased during hospitalization,whilePLTcount increased rapidly before the stage of severe illness, than decreased from day 15th.All data were displayed by median and inter quartiles range.

leveled off after 6-10 days in the hospital. Fibrinogen showed an unstable variation, the minimum level (3.5mg/L) appeared on the 11-15days after admission, and the maximum level (0.89mg/L) of D-dimer occurred at the same time. The level of FAR elevated with the progression of severe disease, then reached the highest at 6-10 days after admission, but as the patients got better, the FAR decreased gradually.PLT count increased rapidly before the occurrence of severe illness, the maximum level appeared on the 11–15 days, then declined rapidly.

Prediction of Severity Degree of COVID-19 Patients

We then investigated the ability of the indexes of coagulation function to predict the progression of severe disease. Multivariate analysis revealed that FAR(HR=4.058, 95%CI=1.246-13.222, P=0.020) and PLT (HR=4.047, 95%CI=1.313-12.472, P=0.015) were independent factors for disease progression (Table II).The cut-off value of FAR was 0.0883 and PLT countwas135*10^9/L (Figure 3e). Area under the ROC curve (AUC) of FAR, PLT and FAR-PLT combined were 0.730,0.637, and 0.754 (P=0.001,0.015,0.030, respectively).

Establishment and Accuracy Prediction of a Novel Nomogram

We then performed a novel Nomogram that integrated FAR and PLT count for 10-day non-severe survival and 20-day nonsevere survival to predict the disease progression for each COVID-19 (Figure 3a). The Harrell's C-indexes was 0.712 (95% CI=0.610–0.814), which showed the model had a potential value to predict disease progression. Through internal verification, the calibration curve (Figure 3d) did not deviate from the reference line. The decision curve (Figure 3b) and the clinical impact curve (Figure 3c) also indicated that the Nomogram had good net benefits for the identification of severe of COVID-19 patients. The model showed a good negative predictive value (0.9474,95%CI=0.845–0.986) through clinical calculation (Table III). Kaplan–Meier analysis showed that FAR<0.0883 and PLT>135*10^9/L were associated with non-severe survival (Figure 3f).

External Validation

Twenty-eight newly confirmed patients were enrolled to perform an external validation,7(25%) were classified into severe group and 21 (75%) were non-severe. The sensitivity was 0.857 (95% CI = 0.420–0.992) and the negative predictive value was 0.900 (95% CI = 0.541–0.994), as shown in Table III.

Discussion

In this paper, we studied on 113 COVID-19 patients from Taizhou Public Health Medical Center, Taizhou Hospital, Zhejiang Province, as of February 4, 2020. To our knowledge, the sample size was largest outside the Wuhan region and composite indexes of coagulation function were surveyed in our study. The most important finding was that FAR and PLT count were independent risk factors to predict the development of severe

Table II. Univariate and multivariate analysis of severe illness by Cox regression model with COVID-19.

	Univariate Analysis		Multivariate Analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
Age		0.009		0.598
≦50	1		1	
>50	3.133 (1.327–7.400)		1.299 (0.492–3.428)	
Sex		0.626		
Male	1			
Female	0.812 (0.351–1.876)			
With bacterial infection		0.104		
YES	1			
None	2.005 (0.866–4.642)			
Temperature on admission		0.325		
≦ 37.3	1			
>37.3	1.539 (.652–11.833)			
WBC		0.068		
>9.5	1			
≦9.5	1.117 (1.011–1.234)			
Alb		0.161		
≧40	1			
<40	1.840 (0.771–4.389)			
PT		0.004		0.625
<14.0	1		1	
>14.0	3.401 (1.491–7.761)		1.388 (0.373–5.168)	
aPTT		0.526		
<36	1			
>36	1.601 (.374–6.860)			
FIB		0.009		0.818
<4.0	1		1	
>4.0	3.284 (1.338–8.060)		1.154 (0.339–3.927)	
FAR		0.003		0.020
≦0.0883	1		1	
>0.0883	5.212 (1.762–15.417)		4.058 (1.246–13.222)	
D-dimer		0.215		
<0.5	1			
>0.5	1.765 (0.719–4.333)			
PLT		0.000		0.015
≧135	1		1	
<135	5.191 (2.109–12.777)		4.047 (1.313–12.472)	

illness in COVID-19. Patients with FAR<0.0883 and PLT count>135*10^9/L were unlikely to develop into severe disease.

The results of this study showed that numerous differences of indexes of coagulation function were detected between severe and non-severe patients. Severe patients suffered a higher level of Fibrinogen and D-dimer at the earliest stage and became more remarkable as the disease progressed. Previous studies had uncovered that markedly elevated D-dimer levels were common in death patients with COVID-19 [8,9]. Similar to their results, we presumed that severe patients with COVID-19 had increased coagulation and fibrinolysis activity, marked by elevated D-dimer concentrations [10,11]. Notably, one severe patients in our study was developed into critical disease 7 day after admission with a D-dimer level of 13.61 mg/L, which further validated our speculation.

The result of this study showed that FAR and PLT count were closely associated with the disease progression.FAR levels in patients with severe disease were much higher than those with non-severe. As the illness recovered, FAR returned to normal levels gradually. FAR has been widely used as an effective marker of inflammation and tend to elevated extremely among various conditions such as severe infection and malignant disorders [12]. We speculated that the increased level of FAR may be related to cytokine storms induced by virus invasion [4].In this study, compared with non-severe cases, thrombocytopenia was detected in severe patients. As severe disease occurred, a rapid decrease of PLT count appeared simultaneously. Lippi, G [13] had revealed that low platelet count was associated with an increased risk of severe disease and mortality in patients with COVID-19. Hyper activity of Fibrinolysis often lead to the increase of platelets consumption. Corticosteriods may further cause thrombocytopenia when they had been widely used in the treatment of severe COVID-19 patients [14]. This two reasons mentioned above may explain the similar phenomenon we had observed.

Limitation

There are limitations in our study, for we just displayed the changes of laboratory index and explored possible explanations, mechanism researches such as proteomics and metabonomics are needed to confirm our hypothesis.

Conclusion

According to our results, we believed the dynamic changes of FAR and PLT count were related to the disease progression. Furthermore, the model integrated FAR and PLT count could be used to predict the development of severe illness. Patients on admission with FAR<0.0883 and PLT count>135*10^9/L had a low probability of severe illness development.

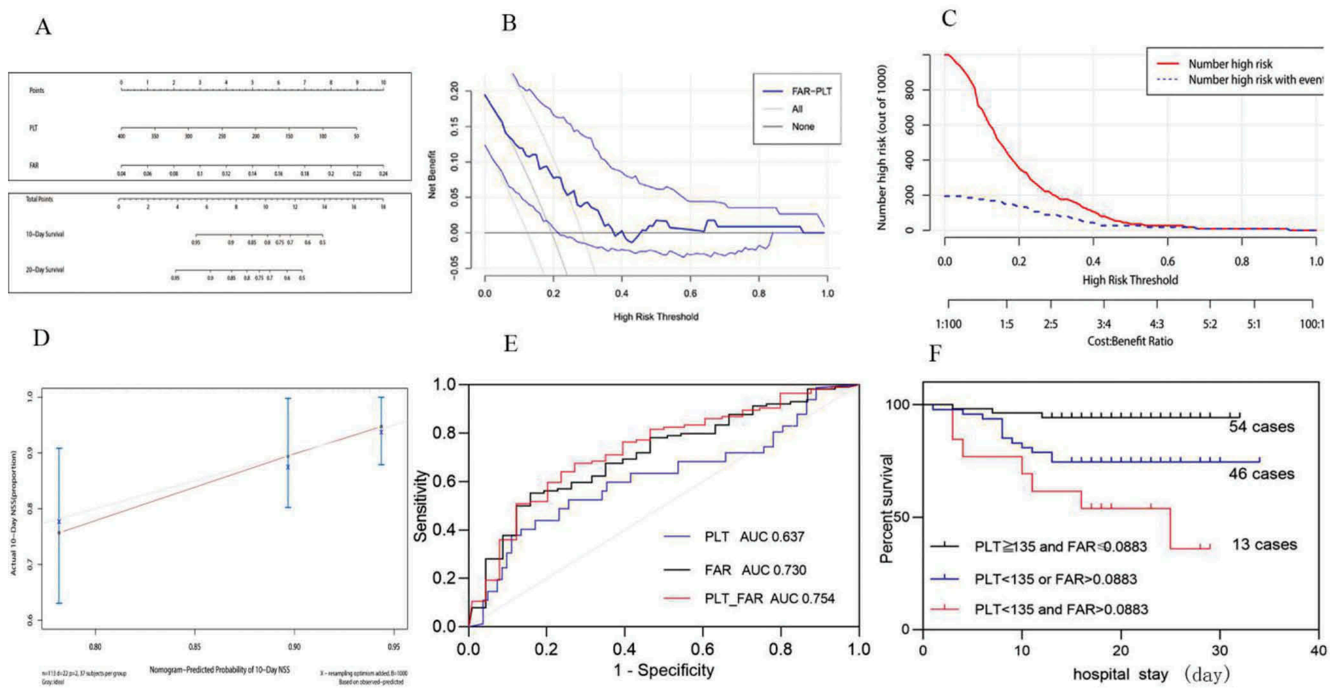

Figure 3. Prediction of severity degree of COVID-19 patients. Nomograms were conveyed using PLT and FAR to predict 10-day non-severe survivaland 20 day non-severe survival ofCOVID-19 patients (A). Decision curve (B) and Clinical impact curve (C) of the Nomogram for non-severe survival in the 2019-nCoV cohort, in which the predicted probability of survival was compared well with the actual survival and had superior standardized net benefit. Calibration plot for 10-day non-severe survival using Nomograms with FAR and PLT count are shown (D), the c-index = 0.712 (95% CI = 0.610–0.814).(E) Area under the ROC curve (AUC) of FAR, PLT and FAR-PLT combination was 0.730,0.637 and 0.754, P = .001,0.015,0.030, respectively. The optimal cutoff values for FAR and PLT count were 0.0883 and 135*10/L.(F) Kaplan–Meier plots were determined by using the cutoff values, Group A *vs*. Group B long-rank $\chi 2 = 7.511$ P = .006, GroupA *vs*. Group C long-rank $\chi 2 = 20.944$ P = .000, while Group B *vs*. Group C long-rank $\chi 2 = 3.615$ P = .056; Group A:PLT≧135*10/L andFAR≤0.0883, Group B:PLT<135*10/Lor.

Table III. Sensitivity, specificity, predictive value of 113 and newly confirmed 28 patients with COVID-19.

		Severe illness		Total	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value
113 patients		+	−					
Prediction model	+	37	19	56	0.863(0.640–0.964)	0.593(0.485–0.694)	0.9474(0.845–0.986)	0.339(0.222–0.0.479)
	−	54	3	57				
Total		101	22	113				
Newly confirmed 28 patients		+	−					
Prediction model	+	6	12	18	0.857(0.420–0.992)	0.429(0.226–0.556)	0.9 (0.541–0.994)	0.333(0.143–0.588)
	−	2	8	10				
Total		8	20	28				

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Author Contributions

X.B and Z.S analyzed the data, composed the manuscript. L.C collected data.M.P and S.C revised the paper and approved the final version.H.Y and J.D role the lab investigation, J.W and GE collected the data and revised the paper.B.S and J.L designed the study.

Disclosure statement

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Disclosure of Interest

The researchers identified no potential conflict of interest with any entity regarding the content discussed.

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Informed Consent

Informed consent was obtained from all individual participants included in the study. Research involving human participants. The Faculty of Medicine's Research Ethics Medical Review Board at Taizhou hospital of Zhejiang province has approved the protocol for the study under number K20200211.

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