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A nomogram to early predict isolation length for non-severe COVID-19 patients based on laboratory investigation: A multicenter retrospective study in Zhejiang Province, China

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ABSTRACT

Background: Majority coronavirus disease 2019 (COVID-19) patients are classified as mild and moderate (non-severe) diseases. We aim to develop a model to predict isolation length for non-severe patients.

Methods: Among 188 non-severe patients, 96 patients were enrolled as training cohort to identify factors associated with isolation length via Cox regression model and develop a nomogram. Other 92 patients formed as validation cohort to validate nomogram. Concordance index (C-index), area under the curve (AUC) and calibration curves were used to evaluated nomogram.

Results: Increasing absolute eosinophil count (AEC) after admission was correlated with shorter isolation length ($P = 0.02$). Baseline activated partial thromboplastin time (APTT) > 30 s was correlated with longer isolation length ($P = 0.03$). A nomogram to predict isolation probability at 11-, 16- and 21-day was developed and validated. The C-indices of training and validation cohort were 0.604 and 0.682 respectively. Both cohorts showed a good discriminative ability (AUC, 11-day: 0.646 vs 0.730; 16-day: 0.663 vs 0.750; 21-day: 0.711 vs 0.783; respectively) and calibration power.

Conclusions: Baseline APTT and dynamic change of AEC were two significant factors associated with isolation length of non-severe patients. Nomogram could predict isolation probability for each patient to estimate appropriate quarantine length.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global health emergency since outbroke in December 2019 [1,2]. According to the statistics of World Health Organization (WHO), up to October 18, 2020, over 40 million accumulated confirmed cases and 1.1 million deaths have been reported globally [3]. With dramatically increasing patients, the COVID-19 pandemic overburdened the worldwide medical system not only due to the influx of severe ill inpatients, but also the

Abbreviations: AEC, absolute eosinophil count; ALC, absolute lymphocyte count; ALT, alanine aminotransferase; AMC, absolute monocyte count; ANC, absolute neutrophil count; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AUC, area under the curve; CDC, Centers for Disease Control; C-index, Concordance index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Ct, Cycle threshold; CT, computed tomography; LDH, lactate dehydrogenase; MERS-CoV, middle east respiratory syndrome coronavirus; PNI, prognostic nutrition index; PT, prothrombin time; RBC, red blood cell count; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV, severe acute respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SII, systemic immune-inflammation index; WBC, white blood cell count; WHO, World Health Organization.

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inappropriate management for the asymptomatic or mild symptomatic patients.

At the early stage of pandemic, Chinese government adopted the extremely strict lockdown measure countrywide to block the viral spread. Meanwhile, National Health Commission issued the clinical guideline, which identified the diagnostic criteria and classified laboratory confirmed patients into four groups based on clinical and imaging manifestation, including mild, moderate, severe and critical disease, and designed different treatment strategy for each group [4]. According to the largest epidemiological investigation of Chinese Center for Disease Control and Prevention (CDC), mild and moderate diseases (also combined as non-severe patients) approximately accounted 81% of whole confirmed cases, and they were all isolated in general ward and received symptomatic treatment plus antiviral therapy [4,5]. Besides, patients were approved to discharge from quarantine after symptom remission and two successive negative results of SARS-CoV-2 nucleic acid test through real-time reverse transcription-polymerase chain reaction (RT-PCR) assay, which indicated the strict quarantine and appropriate management of non-severe patients were vital to control viral transmission in community [4].

However, for many areas where the medical recourse was extremely scarce, applying hospitalized isolation and initial discharge criteria of two negative PT-PCR tests has been very difficult [6–8]. Hence, WHO latest guidance recommended non-severe patients self-isolated in health facility or home, and could release from quarantine at least 13 days after symptom onset while without requiring SARS-CoV-2 RNA retesting [9,10]. Nevertheless, this guideline may exist viral transmission risk to some extent due to early discharge of some patients who still with positive SARS-CoV-2 test results. Merely depend on the length of symptom remission is not sufficient to be the sole discharge criterion for these patients. Previous researches also indicated that asymptomatic patients and symptomatic patients had a similar SARS-CoV-2 viral load value, which represented both groups have a parallel potential to transmit virus [11–13]. Moreover, these non-severe patients still had a SARS-CoV-2 positive period after symptom remission, which recommended the isolation for asymptomatic patients should be continued until nucleic acid test converse to negative [11–13].

Hence, on the one side, for medical resource constraint areas, identifying the appropriate home quarantine length for non-severe patients could help to prevent virus transmission due to patients' early discharge from isolation. On the other side, for areas with adequate medical resource where non-severe patients could receive hospitalization, identifying the appropriate quarantine length for them could alleviate hospital bed demand and allocate resource effectively. Previous studies had developed two different model to predict hospital stay of COVID-19 patients. Through using cut-off value (10 days and 14 days) to categorize patients into long-term hospital stay and short-term hospital stay, both models could predict the probability of whether patients have prolonged hospital stay [14,15]. Nonetheless, these studies did not predict the specific isolation length for each patient. Nomogram, a reliable and convenient predictive model, is widely used in clinical oncology practice to quantitatively predict the prognosis of cancer patients by numerical probability via combining significant prognostic factors [16,17].

In this study, we aim to describe the clinical characteristics and laboratory findings of non-severe COVID-19 patients in Zhejiang Province, China and develop a nomogram to predict specific isolation length for each patient.

2. Methods

2.1. Study design and populations

2.1.1. Participants enrollment

This retrospective multicenter study enrolled 188 laboratory confirmed COVID-19 patients in 5 designated hospitals in Zhejiang province from January 22, 2020 to March 1, 2020, and the final follow-up was on March 15th, 2020. This study is approved by the Ethical Committee of Sir Run Run Shaw Hospital (The certificate no: Scientific Research 20200331-45).

The exclusion criteria are as follows: (1). patients who classified as severe and critical diseases on admission and patients who deteriorated into severe or critical diseases during the treatment; (2). patients who infected with influenza virus A/B at the same time; (3). patients had underlying disorders associated with eosinophils such as parasitic disease, allergic disease, autoimmune disease and rheumatologic disease; (4). patients had coagulation dysfunction like hemophilia A, hemophilia B and hepatic disease, and patients who received any anticoagulant drug in the last month.

2.1.2. Disease severity classification and treatment

The classification of disease severity is based on the guideline for diagnosis and treatment of COVID-19 published by Chinese National Health Commission on February 5, 2020 [4].

(1). Mild diseases: patients have mild clinical symptoms and without pneumonia performance on CT imaging.
(2). Moderate diseases: patients present fever, cough, and other respiratory symptoms, and exist mild pneumonia performance on CT imaging.
(3). Severe diseases: patients present respiratory distress with respiratory rate higher than 30 times/min, or oxygen saturation lower than 93% in quiescent condition, or PaO2/FiO2 (partial pressure of arterial oxygen/inhalation oxygen concentration) lower than 300 mmHg.
(4). Critical diseases: patients present respiratory failure and require mechanical ventilation, or shock, or combine with other organic failure.

In this study, mild and moderate diseases were combined as "non-severe patients" while severe and critical diseases were combined as "severe patients". For therapeutic strategy, all patients received symptomatic support therapy. Majority patients receive oral antiviral drug lopinavir/ritonavir (200 mg/50 mg per tablet, two tablets twice a day) combined with interferon-α inhalation. Besides, antibiotics were used when identification of specific bacterial infections.

2.1.3. Discharge criteria

Patients who eligible for releasing from isolation must met following two criteria at same time: (1) without fever and respiratory symptoms at least 3 days; (2) the results of two consecutive SARS-CoV-2 RNA tests were negative (the sampling time shall be at least 24 h apart).

The isolation length was defined as the interval from the date on hospital admission to the date on discharge from isolation.

2.2. SARS-CoV-2 detection

Nasopharyngeal swab specimens of all 188 enrolled patients were collected on admission and every day after admission, and then transported to local CDC for laboratory diagnosis via real-time RT-PCR method. The SARS-CoV-2 testing kit was provided by Shanghai ZJ Bio-Tech Co., Ltd. (Shanghai, China). The detailed detection procedure was following the protocol of China CDC, which was also approved by the WHO [18]. For the interpretation of results, the Cycle threshold (Ct) < 37 indicated a positive result while the Ct value > 40 indicated a negative result. If the Ct value was between 37 and 40, we would report suspicious positive result and repeat the testing. The Ct value of retesting < 40 with an obvious peak of the amplification curve indicated a positive result otherwise negative.

2.3. Data collection

The epidemiological history, clinical characteristics and laboratory

parameters were obtained from electronic medical record of each patient. Laboratory investigation included a complete blood count (including red blood cell count [RBC], white blood cell count [WBC], absolute neutrophil count [ANC], absolute lymphocyte count [ALC], absolute monocyte count [AMC], absolute eosinophil count [AEC] and platelet count), serum biochemical test (including Aspartate aminotransferase [AST], Alanine aminotransferase [ALT], serum albumin concentration, C-reactive protein [CRP], lactate dehydrogenase [LDH]) and coagulation function (activated partial thromboplastin time [APTT], prothrombin time [PT] and D-Dimer). In addition, two novel indices based on two or more laboratory parameters named systemic immune-inflammation index (SII) and prognostic nutrition index (PNI) were also investigated, which were considered to reflect inflammatory and nutritional status respectively. SII was calculated as platelet count (10^9/L) × ANC (10^9/L)/ALC (10^9/L). PNI was calculated as the serum albumin concentration (g/L) + 5 × ALC (10^9/L).

Baseline laboratory parameters were collected on hospital admission and post-treatment laboratory parameters were collected 3 days after admission. Differences of parameters between post-treatment and baseline were calculated and presented as Δ. (Δparameter(a) = parameter (a) at post-treatment minus parameter(a) on baseline).

2.4. Statistical analysis and nomogram construction

All 188 patients were divided into two cohorts for nomogram construction and validation. Training cohort was consisted of 96 patients from Xixi Hospital of Hangzhou to identify significant predictive factors associated with isolation length and then combined to develop a nomogram. And 92 patients from other four hospitals (the third people's Hospital of Yueqing, Jinhua municipal central Hospital, Affiliated Hospital of Shaoxing University and Wenzhou Central Hospital) were enrolled as validation cohort for validating the nomogram.

Continuous variables with normal distribution were expressed as mean and standard deviation while continuous variables with skewed distribution were expressed as median and interquartile range and the categorical variables were reported as frequencies and percentages. Continuous variables including baseline and post-treatment laboratory parameters were converted into dichotomous variables according to the median. The differences of parameters were converted into dichotomous variables according to 0. In the training cohort, variables with a P value less than 0.1 in the univariate Cox model were included in multivariate Cox proportional hazards regression model, which was performed to identify variables ($P < 0.05$) significantly associated with isolation length. Based on identified predictive factors, a nomogram was constructed to predict probability of isolation at 11-, 16- and 21-day for each COVID-19 patient.

The nomogram was validated externally in the validation cohort. Concordance index (C-index) and the area under the curve (AUC) were used to assess the discriminative ability of nomogram. The calibration curves were used to compare the actual results and the nomogram-predicted probabilities. Both discrimination and calibration were evaluated by using bootstrap method with 1000 resamples. All statistical analyses were performed using the SPSS version 22.0 and R program (version 3.6.0). The two-sided $P < 0.05$ was considered as statistically significant difference.

3. Results

3.1. Patients characteristics

Among 188 patients, all of them were classified as non-severe diseases on admission. The median age was 44 years (range 33–54 years). There were 91 male patients (48.4%) and 97 female patients (51.6%). The mean isolation length was 16 ± 5 days. Comorbidities were presented in 39 patients, with hypertension (14.9%) and diabetes (5.9%). The most common symptoms on hospital admission were fever (138 [73.4%]) and dry cough (117 [62.2%]), while fatigue (61 [32.5%]) and diarrhea (18 [9.6%]) were less common. About epidemiological history, 20 (10.6%) patients were local residents of Wuhan, 56 (29.8%) patients had been to Wuhan recently, and 112 (59.6%) patients had not been to Wuhan while contacted with people from Wuhan. Laboratory investigations on admission showed that 85 patients present eosinopenia (45.2%), 67 with lymphopenia (35.6%) and 51 have prolonged APTT (27.1%). Detailed information of the validation and training cohorts were shown in the Table 1.

3.2. Predictive factors for isolation length

In the univariate Cox model, baseline APTT higher than 30 s, baseline PT higher than 12 s and baseline WBC higher than 5.5 × 10^9/L were associated with a longer isolation length (HR = 0.63, 95% CI: 0.41–0.96, P = 0.03; HR = 0.67, 95% CI: 0.43–1.02, P = 0.06; HR = 0.67, 95% CI: 0.44–1.03, P = 0.07; respectively). In the contrast, increasing AEC and increasing serum albumin concentration after admission were associated with a shorter isolation length (HR = 1.66, 95% CI: 1.09–2.54, P = 0.02; HR = 1.74, 95% CI: 1.09–2.78, P = 0.02; respectively). (see Table 2)

Given that these factors in univariate model might be covariates, we conducted multivariate Cox model to identify significant predictive factors associated with isolation length. And the multivariate Cox model revealed that, among 6 factors, increasing AEC after admission was independently correlated with shorter isolation length (HR = 1.68, 95% CI: 1.10–2.58, P = 0.02) while baseline APTT higher than 30 s was independently correlated with longer isolation length (HR = 0.62, 95% CI: 0.40–0.95, P = 0.03) (see Table 2).

3.3. Nomogram construction

Combining two significant factors associated with isolation length in training cohort, including baseline APTT and change of AEC, we constructed a nomogram to predict the probability of isolation for non-severe patients at 11-, 16- and 21-day. (see Fig. 1) Each factor was assigned a score on the points scale. For baseline APTT higher than 30 s and decreasing AEC after admission, the corresponding score was assigned as 0 points. For baseline APTT lower than 30 s, the corresponding score was assigned as 100 points. For increasing AEC, the corresponding score was assigned as 95 points. Through adding up the scores of each factor, we obtained a total score on the "total points line". By drawing a vertical line through that point, the number of the intersection on the three below "isolation probability line" represented the probability of isolation at 11-, 16- and 21-day for each COVID-19 patient.

3.4. Validation and evaluation of the nomogram

Our nomogram was validated both internally and externally. In training cohort, the C-index of nomogram to predict probability of isolation was 0.604 (95% CI: 0.542–0.666) and the AUC showed a good discriminative ability (11-day AUC: 0.646, 95% CI: 0.529–0.763; 16-day AUC: 0.663, 95% CI: 0.551–0.774; 21-day AUC: 0.711, 95% CI: 0.600–0.822; respectively). (Fig. 2A, B and C) In validation cohort, the C-index of nomogram was 0.682 (95% CI: 0.632–0.732) and the AUC showed a better discriminative ability compared with training cohort (11-day AUC: 0.730, 95% CI: 0.626–0.834; 16-day AUC: 0.750, 95% CI: 0.649–0.851; 21-day AUC: 0.783, 95% CI: 0.683–0.884; respectively). (Fig. 2D, E and F) Moreover, the calibration curves of the nomogram demonstrated a good consistency between the actual clinical results and the predicted outcomes both in the two cohorts (see Fig. 3).

4. Discussion

In this present study, we described the clinical characteristics and

Table 1
Demographics and characteristics of patients.

Parameters	Whole cohort (n = 188)	Training cohort (n = 96)	Validation cohort (n = 92)
Characteristics			
Age, Median, (25th, 75th)	44.00 (33.00, 54.00)	40.50 (33.00, 56.00)	46.00 (34.00, 54.00)
Gender, n (%)			
Male	91 (48.40)	42 (43.75)	49 (53.26)
Female	97 (51.60)	54 (56.25)	43 (46.74)
Incubation period, Days (25th, 75th)	4 (2, 7)	4 (2, 7)	5 (2, 7)
Clinical type, N (%)			
Mild	43 (22.87)	16 (16.67)	27 (29.35)
Moderate	145 (77.13)	80 (83.33)	65 (70.65)
Comorbidity, n (%)			
Hypertension	28 (14.89)	15 (15.63)	13 (14.13)
Diabetes	11 (5.85)	4 (4.17)	7 (7.61)
Epidemiological history, n (%)			
Local residents of Wuhan	20 (10.64)	12 (12.50)	8 (8.70)
Non-local residents: Recently been to Wuhan	56 (29.79)	20 (20.83)	36 (39.13)
Non-local residents: Contacted with people from Wuhan	112 (59.57)	64 (66.67)	48 (52.17)
Symptoms, n (%)			
Fever	138 (73.4)	69 (71.88)	69 (75.00)
Cough	117 (62.23)	62 (64.58)	55 (59.78)
Fatigue	61 (32.45)	31 (32.29)	30 (32.61)
Diarrhea	18 (9.57)	12 (12.50)	6 (6.52)
Abnormalities on chest CT, n (%)			
Local patchy shadowing	58 (30.85)	29 (30.21)	29 (31.52)
Bilateral patchy shadowing	98 (52.13)	58 (60.42)	40 (43.48)
Ground-glass opacity	23 (12.23)	6 (6.25)	17 (18.48)
No obvious abnormalities	9 (4.79)	3 (3.13)	6 (6.52)
Laboratory parameters, (25th, 75th)			
Baseline			
WBC, * 10^9/L	4.82 (3.81, 6.20)	5.47 (4.22, 7.35)	4.53 (3.47, 5.48)
ANC, *10^9/L	2.98 (2.14, 3.94)	3.30 (2.53, 4.68)	2.58 (1.97, 3.32)
ALC, * 10^9/L	1.30 (0.98, 1.93)	1.27 (0.86, 1.91)	1.31 (1.04, 2.04)
AMC, * 10^9/L	0.42 (0.31, 0.55)	0.43 (0.31, 0.56)	0.42 (0.30, 0.52)
AEC, *10^9/L	0.02 (0.00, 0.05)	0.01 (0.00, 0.06)	0.02 (0.01, 0.05)
RBC, *10^{12}/L	4.57 (4.28, 4.94)	4.57 (4.23, 4.93)	4.59 (4.33, 5.04)
Platelet, * 10^9/L	192.00 (154.50, 229.00)	203.00 (167.25, 242.00)	179.50 (145.25, 217.75)
CRP, mg/L	8.00 (3.15, 16.90)	8.00 (3.00, 17.00)	7.80 (3.60, 15.73)
APTT, seconds	30.20 (28.53, 32.28)	30.05 (28.65, 31.00)	30.50 (28.40, 33.55)
PT, seconds	12.25 (11.63, 12.70)	12.00 (11.43, 12.50)	12.45 (12.03, 12.90)
Albumin, g/L	41.09 (38.98, 43.56)	41.00 (38.25, 43.78)	41.14 (39.80, 43.27)
LDH, U/L	193.00 (153.00, 245.75)	165.00 (142.00, 209.00)	213.50 (178.50, 273.75)
D-dimer, mg/L	0.18 (0.12, 0.33)	0.21 (0.13, 0.41)	0.13 (0.10, 0.26)
ALT, UL	19.00 (13.00, 31.00)	16.50 (11.00, 30.00)	24.00 (15.00, 34.25)
AST, UL	23.00 (18.00, 30.00)	22.00 (17.00, 29.00)	24.00 (19.00, 31.75)
SII	421.76 (247.19, 689.21)	567.86 (350.06, 971.67)	336.96 (221.05, 514.74)
PNI	48.35 (44.26, 52.35)	47.60 (43.91, 52.50)	48.62 (45.39, 52.05)
Post-treatment			
WBC, * 10^9/L	5.33 (4.21, 6.69)	5.61 (4.41, 6.93)	5.10 (3.88, 6.25)
ANC, *10^9/L	3.43 (2.43, 4.68)	3.66 (2.69, 4.90)	3.08 (2.30, 4.20)
ALC, * 10^9/L	1.31 (0.97, 1.74)	1.30 (1.00, 1.73)	1.34 (0.93, 1.78)
AMC, * 10^9/L	0.41 (0.33, 0.51)	0.41 (0.33, 0.51)	0.42 (0.33, 0.54)
AEC, *10^9/L	0.03 (0.01, 0.07)	0.03 (0.01, 0.07)	0.03 (0.01, 0.07)
RBC, *10^{12}/L	4.52 (4.22, 4.91)	4.52 (4.13, 4.86)	4.52 (4.27, 4.95)
Platelet, * 10^9/L	215.50 (171.00, 268.50)	221.50 (180.25, 284.00)	205.50 (168.00, 248.75)
CRP, mg/L	9.87 (3.00, 22.73)	6.00 (1.50, 21.00)	12.65 (3.72, 25.11)
APTT, seconds	29.70 (27.70, 33.10)	29.45 (27.43, 31.48)	32.10 (28.60, 36.30)
PT, seconds	12.00 (11.40, 13.00)	11.80 (11.30, 12.38)	20.00 (12.10, 31.00)
Albumin, g/L	40.35 (37.33, 42.68)	39.35 (36.70, 42.30)	41.05 (37.90, 42.88)
LDH, U/L	179.00 (149.00, 231.00)	162.00 (143.25, 199.00)	206.00 (168.00, 350.00)
D-dimer, mg/L	0.21 (0.13, 0.37)	0.20 (0.14, 0.39)	0.23 (0.09, 0.36)
ALT, U/L	17.00 (12.33, 27.75)	16.00 (11.25, 26.00)	19.00 (12.85, 32.00)
AST, U/L	23.00 (18.00, 29.00)	20.00 (17.00, 26.00)	26.00 (21.00, 33.00)
SII	530.21 (342.50, 912.84)	645.05 (379.46, 1095.22)	473.90 (320.44, 760.09)
PNI	46.83 (43.05, 51.10)	46.15 (41.94, 50.63)	47.55 (43.70, 51.50)
Post-treatment - Baseline			
ΔWBC, * 10^9/L	0.27 (−0.83, 1.41)	0.18 (−1.11, 1.14)	0.40 (−0.70, 1.68)
ΔANC, * 10^9/L	0.36 (−0.59, 1.16)	0.24 (−0.87, 1.15)	0.38 (−0.44, 1.40)
ΔALC, * 10^9/L	−0.10 (−0.43, 0.39)	−0.08 (−0.36, 0.44)	−0.12 (−0.56, 0.38)
ΔAMC, * 10^9/L	0.00 (−0.10, 0.09)	0.00 (−0.10, 0.07)	0.01 (−0.10, 0.12)
ΔAEC, * 10^9/L	0.01 (0.00, 0.02)	0.01 (0.00, 0.03)	0.01 (−0.01, 0.02)
ΔRBC, *10^{12}/L	−0.05 (−0.36, 0.23)	−0.09 (−0.34, 0.19)	0.00 (−0.43, 0.37)
ΔPlatelet, * 10^9/L	24.50 (−9.50, 50.75)	16.50 (−7.50, 46.00)	32.50 (−10.75, 60.75)
ΔCRP, mg/L	0.85 (−3.68, 11.88)	0.00 (−3.00, 9.75)	1.10 (−3.94, 15.58)
ΔAPTT, seconds	−0.30 (−2.50, 1.10)	−0.20 (−1.88, 1.10)	−1.00 (−2.70, 1.00)
ΔPT, seconds	0.00 (−0.82, 1.10)	−0.15 (−1.08, 0.68)	8.80 (−0.13, 21.38)
ΔAlbumin, g/L	−1.12 (−3.63, 0.83)	−1.35 (−3.90, 0.28)	−0.75 (−3.37, 1.79)
ΔLDH, U/L	−5.00 (−37.00, 20.00)	−0.50 (−28.00, 17.75)	−12.00 (−65.00, 29.00)
ΔD-dimer, mg/L	0.00 (−0.08, 0.07)	−0.01 (−0.08, 0.09)	0.00 (−0.12, 0.01)

(continued on next page)

Table 1 (*continued*)

Parameters	Whole cohort (n = 188)	Training cohort (n = 96)	Validation cohort (n = 92)
Δ AST, U/L	−1.00 (−9.75, 4.00)	−1.00 (−5.00, 1.75)	−1.55 (−15.98, 9.75)
ΔALT, U/L	0.00 (−5.00, 5.00)	−1.00 (−5.00, 2.75)	2.00 (−5.00, 8.00)
ΔSII	139.33 (−73.36, 366.79)	134.93 (−194.60, 341.99)	142.70 (−4.19, 388.16)
ΔPNI	−1.25 (−5.01, 1.93)	−1.25 (−4.70, 1.39)	−1.29 (−5.74, 3.53)

Data were expressed as: n (%) and median (interquartile range). WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; RBC, red blood cell count; CRP, C-reactive protein; APTT, activated partial thromboplastin time; PT, prothrombin time; LDH, lactate dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase. SII was calculated as platelet count (10^9/L) × ANC (10^9/L)/ALC (10^9/L). PNI was calculated as the serum albumin concentration (g/L) + 5 × ALC (10^9/L). Δ was the difference of parameters and calculated as post-treatment parameters minus baseline parameters.

laboratory investigations of non-severe patients. All of 188 patients were isolated in hospital and received antiviral plus symptomatic treatment. None patient was deteriorated during the isolation. We found increasing AEC after admission was significant associated with shorter isolation length while baseline APTT higher than 30 s was a strong and independent predictor for prolonged isolation length. Besides, based on these two factors, a nomogram to predict probability of isolation at 11-, 16- and 21-day was constructed and validated.

In our present study, all 188 patients recruited were classified as non-severe diseases. The reason why we excluded the severe patients is mild and moderate diseases accounted majority of all confirmed COVID-19 cases [5]. Hence, we attempted to separate analyze the clinical characteristics and laboratory investigations of non-severe patients. Because the classification and treatment strategy of non-severe patients was consistent to the guideline of WHO [9], we considered our findings and predictive model could also applying to the non-severe patients outside China whether they are hospitalized or self-isolated in health facility. Our results could help to early identify the risk factors prolonged the quarantine. For non-severe COVID-19 patients who present higher APTT or decreasing AEC during the disease process, receiving a longer isolation length may be necessary. Besides, our model could estimate the appropriate isolation length for each patient, which not only help to prevent viral transmission effectively, but also enhance the efficacy of hospital beds turnover to alleviate the medical burden.

The mean isolation length was 16 ± 5 days in our study, which is similar to the mean hospital stay of non-severe patients in previous study (15 days) [19]. Besides, according to the results of series of researches targeting both non-severe and severe COVID-19 patients, the reported median hospital stay ranged from 10 days to 22 days [15,19–22]. Hence, we chose 11-day, 16-day and 21-day as three fix-time point corresponding to short-term isolation, median-term isolation term and long-term isolation respectively, which could well discriminate patients who need long-term quarantine or patients who could early discharge.

The specific mechanisms of APTT and eosinophils in the process of SARS-CoV-2 infection were still unknown but could be partially explained. APTT is the most commonly used sensitive screening test to reflect the coagulation activity of endogenous coagulation system in clinical practice. The coagulation dysfunction including prolonged APTT was one of prominent findings in patients with coronavirus infection including severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 and middle east respiratory syndrome coronavirus (MERS-CoV), which due to the imbalance between procoagulant and anticoagulant mechanisms triggered by viral infection [23,24]. A

Table 2
Univariate and Multivariate Cox analysis of isolation length.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Characteristics				
Age (>41 vs ≤ 41)	1.05 (0.70, 1.59)	0.81		
Comorbidity (yes > vs ≤ no)	0.72 (0.41, 1.28)	0.27		
Laboratory parameters				
Baseline				
WBC (>5.5 vs ≤ 5.5)	0.67 (0.44, 1.03)	0.07		
ANC (>3.3 vs ≤ 3.3)	0.85 (0.56, 1.28)	0.44		
ALC (>1.3 vs ≤ 1.3)	0.84 (0.55, 1.28)	0.41		
AMC (>0.4 vs ≤ 0.4)	0.84 (0.55, 1.26)	0.40		
AEC (>0.01 vs ≤ 0.01)	1.00 (0.66, 1.52)	1.00		
RBC (>4.6 vs ≤ 4.6)	0.98 (0.65, 1.49)	0.94		
Platelet (>203 vs ≤ 203)	0.88 (0.58, 1.35)	0.57		
CRP (>8 vs ≤ 8)	1.03 (0.68, 1.56)	0.88		
APTT (>30 vs ≤ 30)	0.63 (0.41, 0.96)	0.03	0.62 (0.40, 0.95)	0.03
PT (>12 vs ≤ 12)	0.67 (0.43, 1.02)	0.06		
Albumin (>41 vs ≤ 41)	0.85 (0.56, 1.28)	0.43		
LDH (>165 vs ≤ 165)	1.05 (0.69, 1.58)	0.83		
D-dimer (>0.2 vs ≤ 0.2)	1.07 (0.71, 1.62)	0.75		
ALT (>16.5 vs ≤ 16.5)	1.35 (0.89, 2.04)	0.16		
AST (>22 vs ≤ 22)	0.97 (0.64, 1.47)	0.89		
SII (>568 vs ≤ 568)	0.92 (0.61, 1.39)	0.69		
PNI (>48 vs ≤ 48)	0.94 (0.62, 1.42)	0.76		
Post-treatment				
WBC (>5.6 vs ≤ 5.6)	1.02 (0.67, 1.53)	0.94		
ANC (>3.7 vs ≤ 3.7)	1.03 (0.68, 1.56)	0.89		
ALC (>1.3 vs ≤ 1.3)	0.91 (0.60, 1.38)	0.66		
AMC (>0.4 vs ≤ 0.4)	1.26 (0.83, 1.92)	0.27		
AEC (>0.03 vs ≤ 0.03)	1.25 (0.83, 1.88)	0.29		
RBC (>4.5 vs ≤ 4.5)	1.00 (0.66, 1.51)	0.99		
Platelet (>222 vs ≤ 222)	1.19 (0.78, 1.80)	0.42		
CRP (>6 vs ≤ 6)	1.12 (0.74, 1.70)	0.58		
APTT (>29.5 vs ≤ 29.5)	0.77 (0.51, 1.18)	0.24		
PT (>11.8 vs ≤ 11.8)	0.87 (0.57, 1.32)	0.51		
Albumin (>39 vs ≤ 39)	1.02 (0.67, 1.54)	0.94		
LDH (>162 vs ≤ 162)	0.76 (0.50, 1.16)	0.21		
D-dimer (>0.2 vs ≤ 0.2)	1.24 (0.82, 1.88)	0.31		
ALT (>16 vs ≤ 16)	1.15 (0.76, 1.75)	0.50		
AST (>20 vs ≤ 20)		0.14		

(*continued on next page*)

Table 2 (*continued*)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
	0.73 (0.48, 1.11)			
SII (>645 vs ≤ 645)	1.11 (0.73, 1.68)	0.63		
PNI (>46 vs ≤ 46)	1.09 (0.72, 1.65)	0.68		
Post-treatment - Baseline				
ΔWBC (>0 vs ≤ 0)	1.00 (0.66, 1.52)	1.00		
ΔANC (>0 vs ≤ 0)	0.82 (0.54, 1.24)	0.35		
ΔALC (>0 vs ≤ 0))	1.17 (0.77, 1.77)	0.47		
ΔAMC (>0 vs ≤ 0)	1.24 (0.82, 1.88)	0.31		
ΔAEC (>0 vs ≤ 0)	1.66 (1.09, 2.54)	0.02	1.68 (1.10, 2.58)	0.02
ΔRBC (>0 vs ≤ 0)	1.04 (0.67, 1.60)	0.87		
ΔPlatelet (>0 vs ≤ 0)	0.94 (0.61, 1.46)	0.78		
ΔCRP (>0 vs ≤ 0)	0.92 (0.61, 1.40)	0.69		
ΔAPTT (>0 vs ≤ 0)	0.81 (0.53, 1.25)	0.34		
ΔPT (>0 vs ≤ 0)	1.17 (0.77, 1.79)	0.46		
ΔAlbumin (>0 vs ≤ 0)	1.74 (1.09, 2.78)	0.02		
ΔLDH (>0 vs ≤ 0)	0.93 (0.61, 1.40)	0.72		
ΔAST (>0 vs ≤ 0)	0.77 (0.50, 1.21)	0.26		
ΔALT (>0 vs ≤ 0)	0.74 (0.47, 1.15)	0.18		
ΔD-dimer (>0 vs ≤ 0)	1.07 (0.71, 1.62)	0.75		
ΔSII (>0 vs ≤ 0)	0.99 (0.65, 1.53)	0.97		
ΔPNI (>0 vs ≤ 0)	0.96 (0.62, 1.49)	0.86		

WBC, white blood cell count; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; AMC, absolute monocyte count; AEC, absolute eosinophil count; RBC, red blood cell count; CRP, C-reactive protein; APTT, activated partial thromboplastin time; PT, prothrombin time; LDH, lactate dehydrogenase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase. SII was calculated as platelet count (10^9/L) × ANC (10^9/L)/ALC (10^9/L). PNI was calculated as the serum albumin concentration (g/L) + 5 × ALC (10^9/L). Δ was the difference of parameters and calculated as post-treatment parameters minus baseline parameters.

previous study compared the coagulation parameters of COVID-19 patients between survivors and non-survivors and found that the APTT of non-survivors was significantly longer than survivors [25]. Besides, when SARS-Cov outbroke in 2003, a study retrospectively analyzed the laboratory parameters of 157 patients infected with SARS-CoV and indicated that 63% patients had a prolonged APTT (>40 s) which occurred mainly in the first two weeks of disease [26]. Similarly, we found patients with baseline APTT higher than 30 s have a longer isolation length, and these results suggested that SARS-CoV-2 infection could induce different degree of coagulation dysfunction, which was also associated with disease severity. Hence, the higher APTT on disease onset could be regarded as a risk factor prolonged the isolation length and may predict a worse outcome.

Eosinophils, derived from hematopoietic stem cells in the bone marrow, are components of granulocytes and have the function of eliminating pathogenic microorganism including bacteria, parasites and virus, which play an important role in the process of immune and allergic reactions [27]. The respiratory epithelia infected by virus would release various cytokines and chemokines which could react to environmental agents and recruit eosinophils to the lung tissue. And eosinophils in the allergic airways might alter host responses to virus infections [28]. According to a previous study, researchers investigated the laboratory parameters of COVID-19 patients on hospital admission and found that 52.9% patients had eosinopenia (AEC < 0.02 × 10^9/L). Moreover, they found that the increasing level of AEC and ALC were positively correlated in both severe and non-severe patients after hospital admission [29]. Based on our previous research, we also found that AEC value of COVID-19 patients was lower than normal range on admission, and then returned to normal before discharge, which meant a continuous improvement on eosinophils may be the sign of disease recovery [30]. As same in this present study, we have discovered that nearly half patients presented a low AEC value on admission and patients with increasing AEC after treatment have a shorter isolation length compared to patients with decreasing AEC. These findings hinted eosinophils may be affected by the SARS-CoV-2 infection and the dynamic change of eosinophils could reflect the outcomes to some extent.

In our study, the ALC value of 35.6% patients was below the normal range on admission while ALC is not associated with the duration of isolation. Although lymphocytes were the main immune cells infected by SARS-CoV-2, we found the lymphocytes were mild decline in majority patients, which may due to all patients are classified as mild and moderate diseases and the viral load was not high enough to damage the immune system. Elder age was another risk factor associated with disease progression and death in previous study [31]. However, in this study, we found age was not related to the isolation length. We considered the primary reason was that all patients were classified as mild and moderate diseases, whose median age is 44 years with only 19 patients elder than 60 years.

Here, by combining two predictive factors, the nomogram to predict the probability of isolation for each non-severe COVID-19 patient was constructed and validated. In addition, our model indicated that dynamic change of eosinophils has a significant predictive value in the duration of isolation, which suggested physicians should pay more attention on the dynamic change of AEC. We considered our results could help to recognize the risk factors in the early stage of disease and our nomogram could estimate the appropriate isolation length for each non-severe COVID-19 patient, which might offer some help to improve the discharge criteria and avoid the risk of early releasing from isolation causing the viral transmission.

Our study existed several limitations. First, the sample in this study was relatively small and we need a larger perspective study to further test our results and model. Second, a handful moderate patients in this study received intravenous antibiotic therapy due to specific bacterial infection, which may not feasible for patients isolated in home. Hence, further researches need to overcome these limitations.

In conclusion, we identified two significant factors associated with isolation length and constructed a nomogram to predict isolation probability at 11-, 16- and 21-day, which could estimate the appropriate isolation length for each non-severe COVID-19 patient and help to avoid the risk of early releasing from isolation causing the viral transmission.

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CRediT authorship contribution statement

Yan Xia: Methodology, Validation, Writing - original draft. **Yan Zhang:** Investigation, Resources, Visualization, Writing - original draft. **Shijin Yuan:** Software, Visualization, Data curation, Writing - original draft. **Jiangnan Chen:** Resources, Visualization. **Wei Zheng:** Resources,

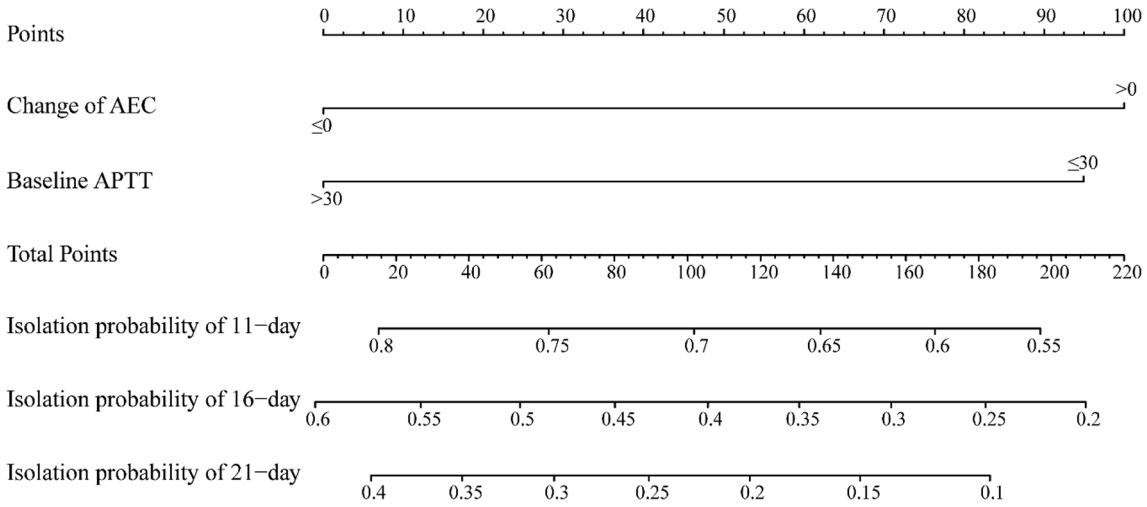

Fig. 1. Nomogram to predict the isolation probability at 11-, 16- and 21-day for non-severe COVID-19 patients. Nomogram was developed based on two factors including baseline APTT and change of AEC. Each level of two factors was assigned a score on the points scale. We obtained a total score through adding the scores of two factors. The prediction corresponding to this total score could help to estimate the isolation probability at 11-, 16- and 21-day for each non-severe COVID-19 patient. APTT: activated partial thromboplastin time; AEC: absolute eosinophil count.

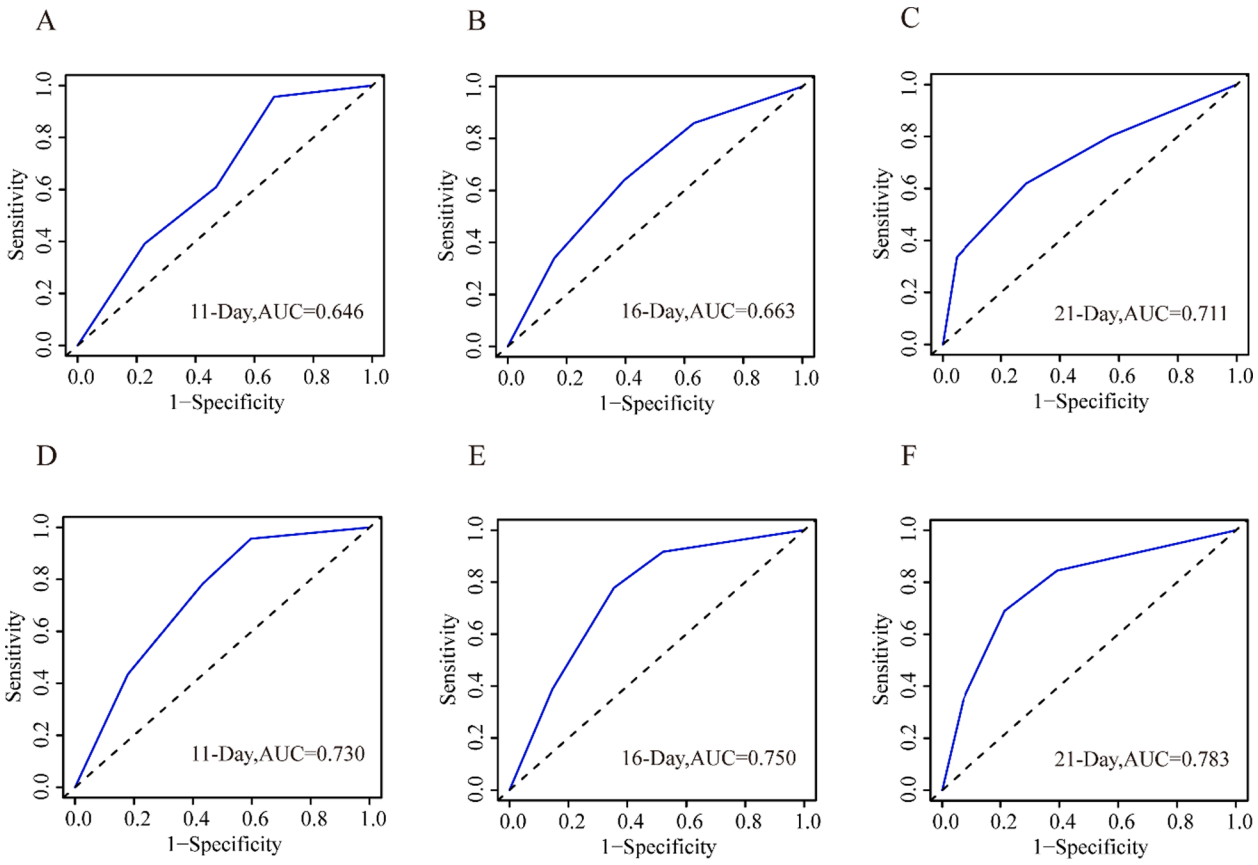

Fig. 2. ROC curves of the nomogram to predict isolation probability at 11-, 16- and 21-day in both training and validation cohort. The ROC curve reflects the relationship between sensitivity and specificity. X-axis is 1-specificity, which is also called false positive rate. The closer the value of the curve on the X-axis is to 0, the higher the accuracy will be. Y-axis is sensitivity, which is also called true positive rate. The greater the value of the curve on the Y-axis is, the higher the accuracy will be. According to the position of the ROC curve, the whole figure is divided into two parts. The area under the curve is called AUC, which represents the prediction accuracy. The higher the AUC value is, the larger the area under the curve is, the higher the prediction accuracy will be. The closer the curve is to the upper left corner, the more accurate the prediction will be. **(A)** AUC of isolation probability of 11-day in training cohort is 0.646 (95% CI: 0.529–0.763). **(B)** AUC of isolation probability of 16-day in training cohort is 0.663 (95% CI: 0.551–0.774). **(C)** AUC of isolation probability of 21-day in training cohort is 0.711 (95% CI: 0.600–0.822). **(D)** AUC of isolation probability of 11-day in validation cohort is 0.730 (95% CI: 0.626–0.834). **(E)** AUC of isolation probability of 16-day in validation cohort is 0.750 (95% CI: 0.649–0.851). **(F)** AUC of isolation probability of 21-day in validation cohort is 0.783 (95% CI: 0.683–0.884). ROC, receiver operating characteristic curve; AUC, areas under the ROC curve.

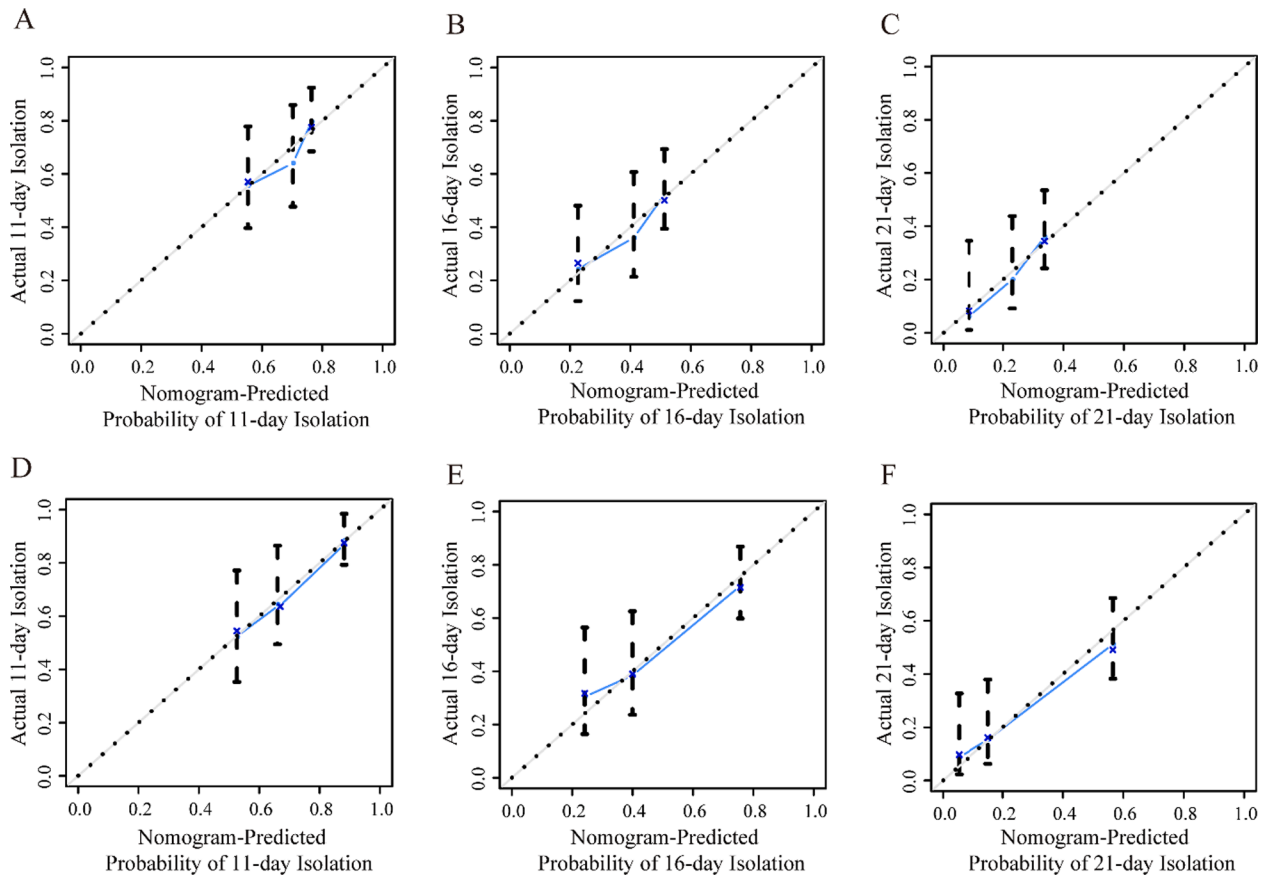

Fig. 3. The calibration curves of nomogram in both training and validation cohort. Nomogram-predicted probability is plotted on the X-axis, with actual probability on the Y-axis. Dashed line along the 45° line represents a perfect consistence between predicted probability and actual probability of nomogram. The distance between the calibration curves and the 45-degree line is a measure of the absolute error of the nomogram's prediction. **(A, B, C)** Calibration curves of isolation probability of 11-, 16- and 21-day in the training cohort. **(D, E, F)** Calibration curves of isolation probability of 11-, 16- and 21-day in the validation cohort.

Visualization. **Xiaoping Xu:** Resources, Visualization. **Xinyou Xie:** Project administration, Formal analysis, Writing - review & editing. **Jun Zhang:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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