

sTREM-1 as a Predictive Biomarker for Disease Severity and Prognosis in COVID-19 Patients

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Background: Research on biomarkers associated with the severity and adverse prognosis of COVID-19 can be beneficial for improving patient outcomes. However, there is limited research on the role of soluble TREM-1 (sTREM-1) in predicting the severity and prognosis of COVID-19 patients.

Methods: A total of 115 COVID-19 patients admitted to the emergency department of Beijing Youan Hospital from February to May 2023 were included in the study. Demographic information, laboratory measurements, and blood samples for sTREM-1 levels were collected upon admission.

Results: Our study found that sTREM-1 levels in the plasma of COVID-19 patients increased with the severity of the disease (moderate vs mild, $p=0.0013$; severe vs moderate, $p=0.0195$). sTREM-1 had good predictive value for disease severity and 28-day mortality (area under the ROC curve was 0.762 and 0.805, respectively). sTREM-1 also exhibited significant correlations with age, body temperature, respiratory rate, $\text{PaO}_2/\text{FiO}_2$, PCT, CRP, and CAR. Ultimately, through multivariate logistic regression analysis, we determined that sTREM-1 (OR 1.008, 95% CI: 1.002–1.013, $p=0.005$), HGB (OR 0.966, 95% CI: 0.935–0.998, $p=0.036$), D-dimer (OR 1.001, 95% CI: 1.000–1.001, $p=0.009$), and CAR (OR 1.761, 95% CI: 1.154–2.688, $p=0.009$) were independent predictors of 28-day mortality in COVID-19 patients. The combination of these four markers yielded a strong predictive value for 28-day mortality in COVID-19 cases with an AUC of 0.919 (95% CI: 0.857–0.981).

Conclusion: sTREM-1 demonstrated good predictive value for disease severity and 28-day mortality, serving as an independent prognostic factor for adverse patient outcomes. In the future, we anticipate conducting large-scale multicenter studies to validate our research findings.

Keywords: COVID-19, sTREM-1, inflammation-related markers, disease severity, 28-day mortality

Introduction

COVID-19 is an infectious disease caused by the novel coronavirus SARS-CoV-2. Currently, the world is experiencing persistent outbreaks of this disease on a global scale.¹⁻³ Although vaccines can effectively enhance the population's resistance to the virus and reduce the mortality rate among patients, the continuous mutation of the virus leads to immune escape.^{4,5} As a result, even individuals who have previously been infected with COVID-19 can still experience reinfection.⁶ Elderly individuals or those with weakened immune systems and underlying cardiovascular diseases are still at risk of death.⁷⁻⁹

Timely prediction of patient prognosis and early intervention play a crucial role in saving lives during the treatment of COVID-19.^{10,11} Current research suggests that COVID-19 is a systemic disease in which inflammatory responses play a significant role.^{12,13} In the context of COVID-19, inflammatory markers have shown promise in predicting patient prognosis. Early research has highlighted the influence of various biomarkers, including C-reactive protein (CRP), procalcitonin (PCT), D-dimer, ferritin, erythrocyte sedimentation rate (ESR), serum ferritin, IL-1, IL-6, IL-8, and IL-18, on the severity of the disease.¹⁴⁻²⁰

Triggering receptor expressed on myeloid cells 1 (TREM-1) is a member of the immunoglobulin superfamily, primarily expressed in bone marrow and epithelial cells.^{21,22} It is considered an amplifier of inflammation and, when activated, can induce the secretion of cytokines such as TNF- α , IL-6, and IL-1 β in monocytes, macrophages, and dendritic cells.^{23,24} Research has shown that TREM-1 expression can be induced by various viral infections, including influenza A virus and hepatitis C virus, as well as bacterial infections like *Staphylococcus aureus* and *Pseudomonas aeruginosa*.²⁵⁻²⁷ Soluble TREM-1 (sTREM-1) is a 27 kDa peptide composed of the extracellular domain of TREM-1, which can be shed into the bloodstream.^{28,29} Multiple studies have investigated the use of sTREM-1 for predicting mortality in sepsis patients.^{30,31} However, there is limited research on the role of sTREM-1 in predicting disease severity and prognosis in COVID-19 patients.³²

To investigate the predictive value of sTREM-1 for disease severity and prognosis in patients with COVID-19, we conducted this prospective study. We employed univariate and multivariate logistic regression analyses to explore independent predictive factors of COVID-19 and evaluate their predictive value for disease prognosis. The primary outcome of our study is the mortality status of patients within 28 days after hospital admission. This metric is commonly used in clinical studies and trials to assess the short-term outcomes and mortality rates associated with a particular condition or intervention. This study aims to provide reference for the early identification of critically ill patients in a clinical setting, thereby improving patient outcomes.

Patients and Methods

Study Design and Participants

We conducted prospective study involving 115 COVID-19 patients admitted to the emergency department of Beijing You'an Hospital between February 1, 2023, and May 31, 2023. All patients received a diagnosis based on the World Health Organization's recommendations. Following the guidelines outlined in the National Health Commission of China's "Diagnosis and Treatment protocol for COVID-19 patients (tentative 9 version)",³³ patients were categorized as having either mild/moderate or severe/critical COVID-19 cases. The objective of this study was to assess the predictive value of sTREM-1 and clinical parameters on the severity and prognosis of COVID-19 patients upon admission. The primary outcomes included the classification of patients as severe/critical cases and the occurrence of mortality within 28 days. The study obtained approval from the Ethics Committee of Beijing You'an Hospital, Capital Medical University, and adhered to the principles of the Helsinki Declaration (Approval No. LL-2023-006-K). Informed consent was acquired from all participating patients, and the data utilized in the study were anonymized.

Inclusion and Exclusion Criteria

The study's inclusion criteria encompassed patients who met the requirements outlined in the Diagnosis and Treatment protocol for COVID-19 patients (tentative 9th version)³³ released by the National Health Commission of China. Additionally, patients were required to provide informed consent and express their willingness to participate in the study.

Conversely, the exclusion criteria encompassed patients who declined to participate in the study. Furthermore, individuals under the age of 18, pregnant women, and patients who unfortunately passed away within 48 hours of hospital admission were also excluded. Additionally, patients for whom follow-up blood samples were either unavailable or lost were excluded from the study.

Data Collection

Demographic data, comorbidities, baseline characteristics, vital signs, arterial blood gas, laboratory data, and prognosis status were obtained from electronic medical records. The severity of illness categories were determined based on the COVID-19 treatment guidelines provided by the National Institute of Health. These categories encompass asymptomatic

infection, mild illness, moderate illness, severe illness, and critical illness, taking into account various clinical manifestations (source: <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>).

The study considered several comorbidities, including hypertension, diabetes mellitus (DM), coronary heart disease, chronic obstructive pulmonary disease (COPD), and malignant tumor. Vital signs assessed in the study included body temperature measured in degrees Celsius (°C), respiratory rate (RR) measured in breaths per minute, heart rate (HR) measured in beats per minute, and systolic blood pressure (SBP) measured in millimeters of mercury (mmHg). Arterial blood gas analysis parameters included pH, partial pressure of carbon dioxide (PaCO₂), partial pressure of oxygen (PaO₂), peripheral oxygen saturation (SpO₂), and the ratio of arterial oxygen partial pressure to fractional inspired oxygen concentration (PaO₂/FiO₂). The study included various laboratory parameters for analysis. The complete blood count (CBC) was assessed, which included measurements of hemoglobin (HGB) levels, white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, and eosinophil count. Infection-related indicators: procalcitonin (PCT) levels in ng/mL, C-reactive protein (CRP) levels in mg/L, and CAR (C-reactive protein-to-albumin ratio). Coagulation-related indicators: international normalized ratio (INR), D-dimer levels in mg/L. Additionally, biochemical function tests were conducted to measure glucose levels in mmol/L, alanine transaminase (ALT) levels in U/L, aspartate transaminase (AST) levels in U/L, total bilirubin (TBIL) levels in μmol/L, direct bilirubin (DBIL) levels in μmol/L, estimated glomerular filtration rate (eGFR) in mL/min/1.73 m², and B-type natriuretic peptide (BNP) levels in pg/mL. Derived scores for inflammatory markers were calculated by combining two or more laboratory parameters. These parameters included the NLR (Neutrophil-to-lymphocyte ratio), MLR (Monocyte-to-lymphocyte ratio), PLR (Platelet-to-lymphocyte ratio), LCR (Lymphocyte-to-monocyte ratio), SIRI (Systemic inflammation response index), and SII (Systemic inflammation index). The SIRI, which represents the systemic inflammation response index, was calculated using the formula: SIRI = (Neutrophil count × Monocyte count) / Lymphocyte count. Similarly, the SII, known as the systemic inflammation index, was calculated using the formula: SII = (Neutrophil count × Platelet count) / Lymphocyte count. These derived scores play a crucial role in evaluating the severity of inflammation and providing valuable insights into the inflammatory response associated with the condition under study. These parameters are summarized in Table 1.

Blood Sample Collection and Testing

At the time of admission, blood sample collection and testing were carried out simultaneously. The blood samples were collected using anticoagulant tubes containing ethylenediaminetetraacetic acid (EDTA). To obtain plasma, the collected whole blood was centrifuged at 1350g for 12 minutes. The concentration of plasma sTREM-1 was determined using the human sTREM-1 ELISA Kit (Keshun Biotechnology, Shanghai, China; REF: KS18244, Lot: 202305), following the instructions provided in the kit manual.

Table 1 Baseline Characteristics and Clinical Data After Hospitalization of Study Population

Variables	Total (n=115)	28-day Survival (n=100)	28-day Mortality (n=15)	P-value
Demographic data				
Sex, male, n (%)	69 (60%)	62 (62%)	7 (47%)	0.302
Age (years)	69.0 (59.5, 79.5)	68.5 (56.8, 78.3)	83.0 (69.0, 88.5)	0.014*
Co-morbidities				
Hypertension, n (%)	51 (44%)	41 (41%)	10 (67%)	0.062
Diabetes mellitus, n (%)	26 (23%)	20 (20%)	6 (40%)	0.104
Coronary heart disease, n (%)	22 (19%)	19 (19%)	3 (20%)	0.912
COPD, n (%)	15 (13%)	12 (12%)	3 (20%)	0.424
Malignant tumor, n (%)	20 (17%)	17 (17%)	3 (20%)	0.762
Vital signs				
Body temperature, °C	36.7 (36.3,37.2)	36.6 (36.3,37.0)	37.4 (36.9,38.0)	<0.001*
RR, breaths/min	20 (20,23)	20 (20,22)	25 (22,31)	0.017*
HR, beats/min	88 (78,100)	88 (78,99)	98 (85,104)	0.090
SBP, mmHg	130 (120,142)	130 (120,141)	127 (114,140)	0.516

(Continued)

Table 1 (Continued).

Variables	Total (n=115)	28-day Survival (n=100)	28-day Mortality (n=15)	P-value
Arterial blood gas				
PH	7.420 (7.400,7.453)	7.421 (7.400,7.450)	7.405 (7.322,7.480)	0.469
PaCO ₂ , mmHg	36.7 (32.1,39.8)	36.6 (32.5,39.7)	37.5 (24.9,39.9)	0.624
PaO ₂ , mmHg	93.1 (76.8,108.0)	95.0 (80.1,108.0)	75.5 (58.0,116.4)	0.114
SpO ₂ , %	98.0 (96.1,99.0)	98.1 (96.5,99.0)	95.4 (92.0,99.2)	0.127
PaO ₂ /FiO ₂ , mmHg	272 (202,334)	285 (224,341)	178 (57,222)	<0.001*
COVID-19 severity class, n (%)				
Mild illness	34 (30%)	34 (34%)	0 (0%)	<0.001*
Moderate illness	42 (37%)	42 (42%)	0 (0%)	
Severe/critical illness	39 (34%)	24 (24%)	15 (100%)	
Laboratory parameters				
sTREM-1, pg/mL	180 (79,480)	161 (68,300)	680 (635,703)	<0.001*
PCT, ng/mL	0.08 (0.05,0.23)	0.07 (0.05,0.178)	0.23 (0.115,1.68)	0.009*
CRP, mg/L	21.2 (7.28,56.6)	16.4 (5.9,49.5)	72.7 (48.9,109.2)	<0.001*
HGB, g/L	126 (107,138)	129 (110,138)	115 (91,130)	0.041*
Platelets count, ×10 ⁹ /L	148 (113,198)	151 (114,198)	148 (110,210)	0.960
WBC count, ×10 ⁹ /L	5.16 (3.49,7.21)	5.19 (3.46,7.16)	5.16 (4.10,7.92)	0.787
Neutrophils count, ×10 ⁹ /L	3.53 (2.18,5.82)	3.50 (2.18,5.65)	3.85 (2.66,6.87)	0.642
Lymphocytes count, ×10 ⁹ /L	0.92 (0.63,1.27)	0.93 (0.63,1.29)	0.77 (0.63,1.12)	0.313
Monocytes count, ×10 ⁹ /L	0.39 (0.26,0.58)	0.39 (0.26,0.57)	0.45 (0.27,0.64)	0.609
Eosinophils count, ×10 ⁹ /L	0.010 (0.00,0.045)	0.015 (0.00,0.050)	0.010 (0.00,0.020)	0.120
Glucose, mmol/L	6.80 (5.94,7.90)	6.70 (5.92,7.80)	8.19 (6.62,9.06)	0.051
ALT, U/L	20 (13,30)	19 (13,31)	23 (18,27)	0.706
AST, U/L	26 (19,36)	25 (18,33)	35 (22,52)	0.079
Albumin, g/L	35.8 (31.6,38.3)	36.2 (32.6,38.5)	30.8 (29.8, 35.9)	0.006*
TBIL, μ mol/L	11.15 (8.55,16.13)	11.20 (8.50,16.05)	10.80 (9.35,15.05)	0.970
DBIL, μ mol/L	4.5 (3.0,6.9)	4.2 (2.9,6.9)	5.8 (3.4,6.7)	0.456
Prothrombin time activity (%)	89 (78,97)	91 (79,97)	86 (73,94)	0.186
INR	1.05 (1.00,1.11)	1.04 (1.00,1.11)	1.08 (1.02,1.24)	0.190
D-dimer, mg/L	171 (0.775,588)	148 (0.600,473)	646 (5.00,2046)	0.021*
eGFR, mL/min/1.73 m ²	87 (69,100)	89 (72,101)	69 (57,85)	0.022*
BNP, pg/mL	79 (29,282)	76 (25,281)	83 (70,351)	0.132
CAR	0.668 (0.181,1.735)	0.456 (0.149,1.428)	2.315 (1.581,3.653)	<0.001*
BCDIMs				
NLR	3.80 (2.31,7.06)	3.63 (2.31,6.99)	5.36 (2.74,8.11)	0.368
MLR	0.40 (0.24,0.70)	0.39 (0.24,0.67)	0.49 (0.32,0.78)	0.325
PLR	168 (119,230)	167 (115,230)	171 (140,257)	0.457
LCR	0.040 (0.013,0.143)	0.053 (0.017,0.181)	0.011 (0.005,0.018)	<0.001*
SIRI	1.642 (0.609,3.356)	1.598 (0.607,3.268)	1.879 (1.148,4.471)	0.385
SII	522 (304,1203)	492 (294,1177)	812 (463,1203)	0.342

Notes: Normally distributed continuous variables are displayed as mean ± standard deviation (SD) and were compared using the independent-samples Student's *t*-test. Non-normally distributed continuous variables are displayed as a median with interquartile range (IQR) and were compared using the Mann-Whitney *U*-test. Categorical variables are expressed as counts with percentages and were compared using Pearson's chi-square or Fisher's exact test. SIRI = (Neutrophil count × Monocyte count) / Lymphocyte count; SII = (Neutrophil count × Platelet count) / Lymphocyte count. **p*-value <0.05 was considered significant.

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; PaCO₂, arterial carbon dioxide tension; PaO₂, oxygen tension; SpO₂, peripheral oxygen saturation; FiO₂, fraction of inspired oxygen; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; WBC, White blood cell; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; DBIL, Direct bilirubin; INR, International normalized ratio; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; CAR, C-reactive protein-to-albumin ratio; BCDIMs, blood count-derived inflammatory markers; NLR, Neutrophil-to-lymphocyte ratio; MLR, Monocyte-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LCR, Lymphocyte-to- C-reactive protein ratio; SIRI, Systemic inflammation response index; SII, Systemic inflammation index.

Statistical Analysis

The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables that were normally distributed are presented as mean \pm standard deviation (SD) and were compared using independent-samples Student's *t*-test. Non-normally distributed continuous variables are presented as median with interquartile range (IQR) and were compared using the Mann–Whitney *U*-test. Categorical variables are reported as counts with percentages and were compared using Pearson's chi-square or Fisher's exact test. Multiple samples were compared using the non-parametric Kruskal–Wallis test. Variables with *P* values < 0.05 were considered statistically significant. The Receiver Operating Characteristic (ROC) curve was employed to assess the predictive performance of parameters for disease severity and 28-day mortality in COVID-19 patients. Kaplan–Meier curves were used to evaluate the risk prediction of parameters for 28-day mortality in COVID-19 patients. Spearman's rank correlation is used to analyze the correlation between sTREM-1 and age, vital signs, and laboratory markers of inflammation. The results are visualized using a heat map. Univariable logistic regression analysis is employed to identify independent predictive factors for 28-day mortality ($P < 0.05$). Parameters showing statistical differences are included in the multivariable logistic regression analysis. Data were analyzed using SPSS software (version 22.0; IBM Corp) and R language (version 4.2.1; R Foundation for Statistical Computing) and illustrated using GraphPad Prism 9 (GraphPad Software Inc).

Results

Patient Characteristics and Clinical Parameters Upon Admission

Out of the 136 patients admitted to the emergency department, 115 patients were eligible for further analysis. [Figure 1](#) illustrates the process of patient enrollment. Among them, 34 cases (30.0%) were categorized as mild, 42 cases (37.0%) as moderate, and 39 cases (34%) as severe or critically ill. Finally, within 28 days of admission, 15 cases (13.0%) resulted in mortality.

[Table 1](#) provides an overview of the patients' baseline characteristics and clinical parameters. Of the patients, 69 (60%) were male, with a median age of 69 years. The most prevalent comorbidities in this group included hypertension (51/115, 44%) and diabetes (26/115, 23%).

When comparing the patients who survived for 28 days to those who passed away within that period, several notable differences emerged. The deceased patients were generally older, had higher body temperature upon admission, and exhibited faster respiratory rates and lower oxygenation index (all *p*-values < 0.05). In terms of laboratory parameters, the 28-day mortality group exhibited elevated levels of sTREM-1, PCT, CRP, D-dimer and CAR, while experiencing

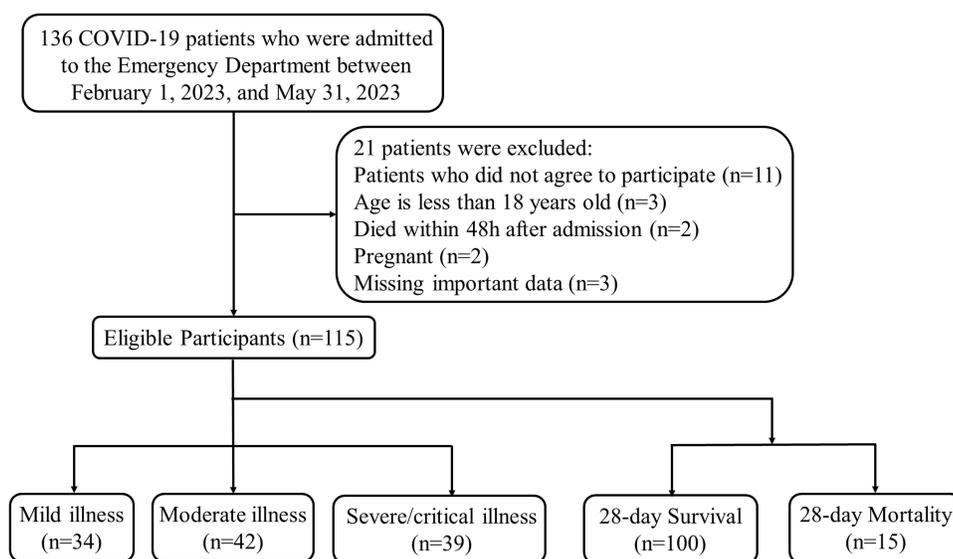


Figure 1 Flow diagram of patients enrollment.

decreased levels of Albumin, HGB, and eGFR (all p -values < 0.05). Furthermore, the level of LCR, which is a blood count-derived inflammatory marker, differed significantly between the two groups (p -value < 0.05).

The Predictive Value of sTREM-1 for the Severity and Prognosis of COVID-19 Patients

Similar to previous reports, the study uncovered a notable association between sTREM-1 levels and the severity of illness in COVID-19 patients. Patients with more severe conditions exhibited higher levels of sTREM-1 (Figure 2A). Additionally, patients who passed away within 28 days demonstrated elevated sTREM-1 levels (Figure 2B). We also compared sTREM-1 levels between the death and survival groups in critically ill patients. There was a trend, but currently no statistically significant difference between the two groups ($p=0.112$) (Figure 2C). sTREM-1 displayed commendable predictive value for assessing disease severity and 28-day mortality, as indicated by the area under the ROC curve of 0.762 (95% confidence interval [CI]: 0.669–0.855) and an area under the ROC curve (AUC) of 0.805 (95% CI: 0.697–0.914) respectively (Figure 2D and E). Furthermore, when patients were categorized based on the median value, those above the median exhibited a higher risk of mortality within 28 days compared to those below the median (p -value < 0.05) (Figure 2F).

The Correlations Between sTREM-1 and Age, Vital Signs, and Laboratory Inflammatory Markers

The heatmap in Figure 3 provides a visual representation of the correlations and corresponding p -values among sTREM-1, age, clinical scoring systems, and laboratory inflammatory markers, involving a total of 12 parameters (Figure 3A and B). Notably, sTREM-1 exhibited a significant correlation with age ($r=0.246$, $p=0.0081$), body temperature ($r=0.202$, $p=0.031$),

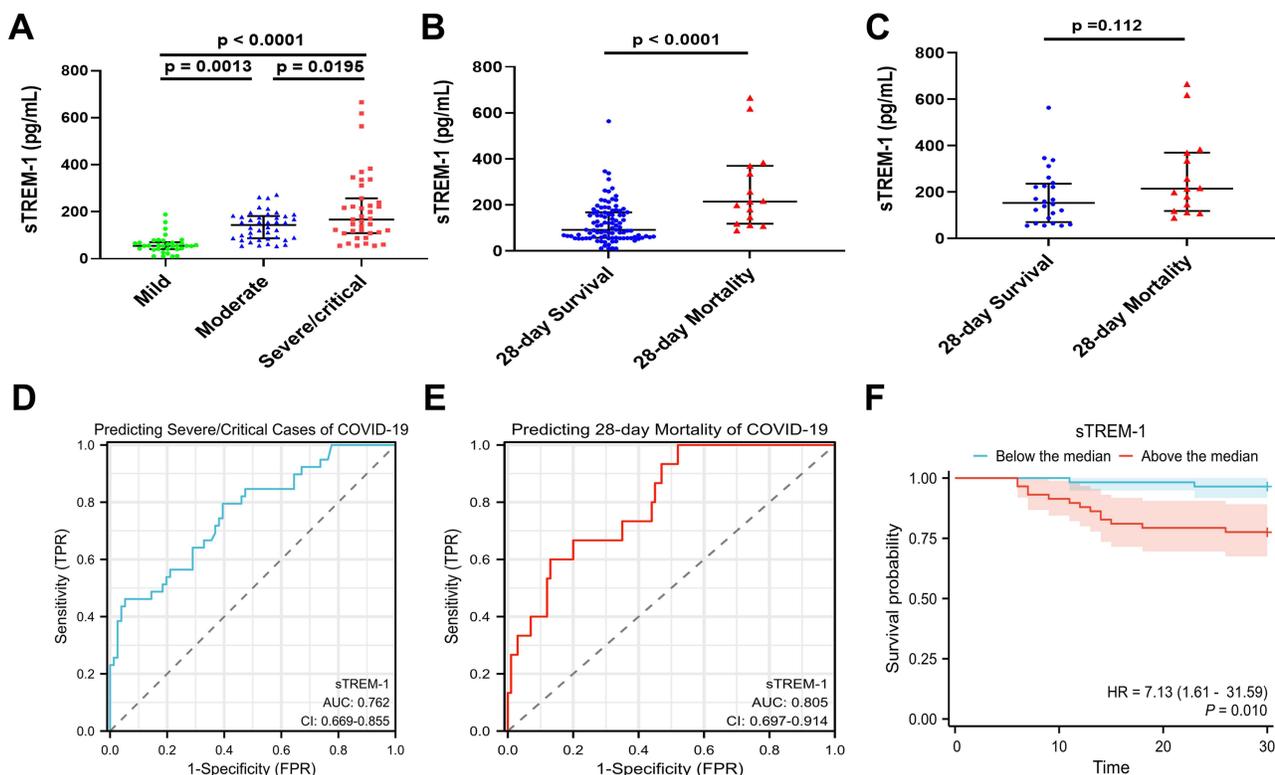


Figure 2 The predictive value of sTREM-1 for the severity of illness and 28-day mortality in COVID-19 patients. (A) Comparison of sTREM-1 levels among different severity groups of COVID-19 patients. (B) Comparison of sTREM-1 levels between the 28-day survival and death groups. (C) Comparison of sTREM-1 levels between the 28-day survival and death groups in critically ill patients. Data are displayed as a median with interquartile range (IQR) and were compared using the Mann–Whitney U -test. Multiple samples were compared using the non-parametric Kruskal–Wallis test. (D) Receiver Operating Characteristic (ROC) curve of sTREM-1 for predicting severity in COVID-19 patients, with an area under the ROC curve (AUC) of 0.762 (95% confidence interval [CI]: 0.669–0.855). (E) ROC curve of sTREM-1 for predicting 28-day mortality in COVID-19 patients, with an area under the ROC curve (AUC) of 0.805 (95% CI: 0.697–0.914). (F) Kaplan-Meier curve for patients divided into two groups based on the median sTREM-1 level: above-median group and below-median group, for 28-day survival. A p -value < 0.05 was considered significant.

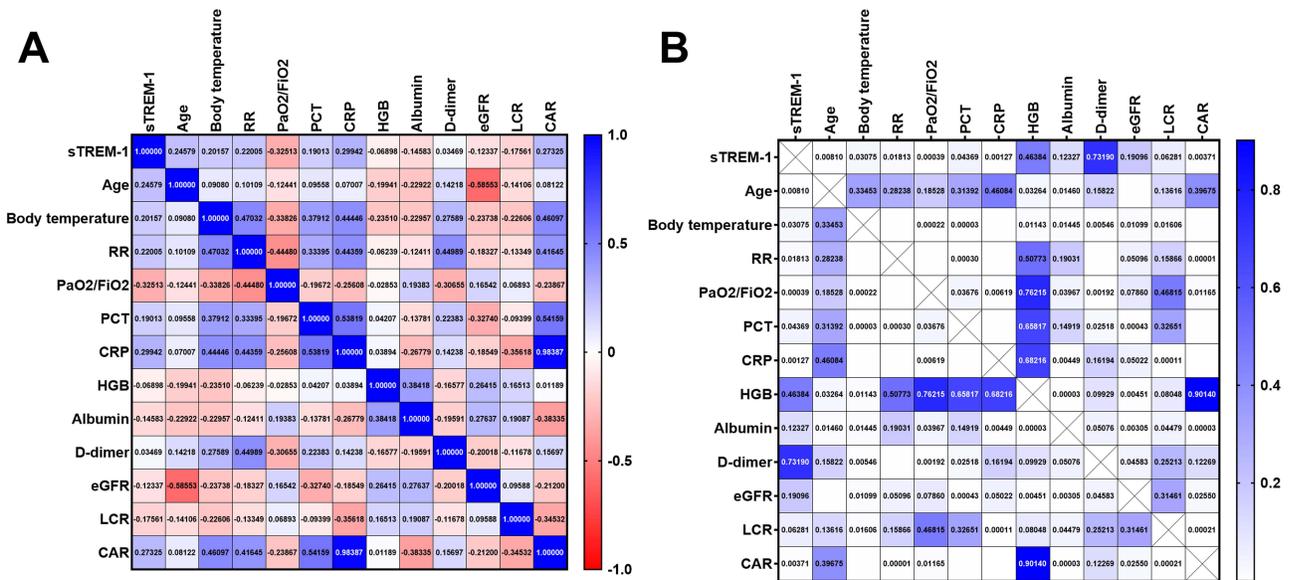


Figure 3 Heatmap depicting the correlation between sTREM-1 and age, Vital signs, and laboratory inflammatory markers. (A) The values are presented as Spearman's correlation coefficient (r) for a sample of 115 runners regarding sTREM-1. The colormap ranges from 1 to -1, with blue indicating the highest value and red indicating the lowest value. (B) The Heatmap of corresponding p-values. The colormap ranges from 0 to 1, with blue representing the largest value and white representing the smallest value. White cells without numerical values indicate that the p-value is smaller than 0.00001, indicating a highly significant correlation.

Abbreviations: RR, respiratory rate; PaO₂, oxygen tension; FiO₂, fraction of inspired oxygen; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; eGFR, estimated glomerular filtration rate; LCR, Lymphocyte-to-C-reactive protein ratio; CAR, C-reactive protein-to-albumin ratio.

respiratory rate ($r=0.220$, $p=0.018$), and PaO₂/FiO₂ ($r= - 0.325$, $p=0.0004$). Furthermore, significant correlations were observed between sTREM-1 and the following laboratory inflammatory markers: PCT ($r=0.190$, $p=0.044$), CRP ($r=0.299$, $p=0.001$), and CAR ($r=0.273$, $p=0.004$).

The Expression of sTREM-1 Demonstrates Equal or Better Predictive Value for Disease Severity and Prognosis in COVID-19 Patients Compared to Some Clinical Indicators

The receiver operating characteristic (ROC) curve was used to evaluate and compare the predictive value of sTREM-1 and laboratory indicators for assessing the disease severity and prognosis of COVID-19 patients. For predicting disease severity (Figure 4A and Table 2), sTREM-1 exhibited the highest predictive value among the evaluated parameters, with an area under the ROC curve of 0.762 (95% confidence interval [CI]: 0.669–0.855). PCT also showed good predictive value, with an AUC of 0.714 (95% CI: 0.607–0.822). CRP, Albumin, D-dimer, LCR, and CAR demonstrated moderate predictive values, with AUCs ranging from 0.654 to 0.691. On the other hand, HGB and eGFR showed relatively lower predictive values, with AUCs of 0.509 and 0.606, respectively. For predicting prognosis (Figure 4B and Table 2), CAR exhibited the highest predictive value with an AUC of 0.829 (95% CI: 0.732–0.927). sTREM-1 had an AUC of 0.805 (95% CI: 0.697–0.914), indicating significant predictive value. CRP and LCR also showed high predictive value, with AUCs of 0.821 and 0.801, respectively. Also, HGB had a relatively lower predictive value, with an AUC of 0.665.

sTREM-1 is an Independent Predictor of 28-Day Mortality in COVID-19 Patients

We conducted univariate logistic regression analysis on indicators that showed statistically significant differences ($p<0.05$) between the 28-day survival group and the deceased group. Among the 12 indicators, all except PCT demonstrated statistically significant differences ($p<0.05$). These variables with statistically significant differences were included in a multivariate logistic regression analysis. Finally, we found that sTREM-1 (OR 1.008, 95% CI: 1.002–1.013, $p=0.005$), HGB (OR 0.966, 95% CI: 0.935–0.998, $p=0.036$), D-dimer (OR 1.001, 95% CI: 1.000–1.001, $p=0.009$), and CAR (OR 1.761, 95% CI: 1.154–2.688, $p=0.009$) were independent predictors of 28-day mortality in

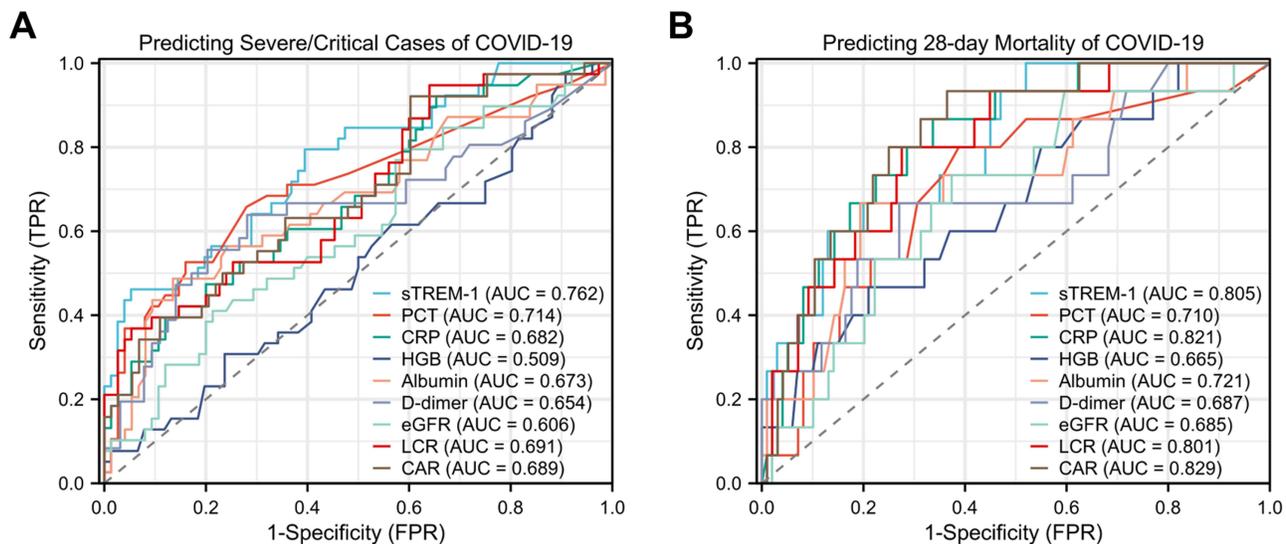


Figure 4 ROC curves of sTREM-1 and main clinical parameters for severity and prognosis of COVID-19 patients. **(A)** Predicting severity of COVID-19 patients. The area under the curve (AUC) for sTREM-1 was 0.762 (95% confidence interval [CI]: 0.669–0.855); PCT, AUC was 0.714 (95% CI: 0.607–0.822); CRP, 0.682 (95% CI: 0.577–0.787); HGB, AUC was 0.509 (95% CI: 0.395–0.623); Albumin, 0.673 (95% CI: 0.562–0.784); D-dimer, AUC was 0.654 (95% CI: 0.532–0.776); eGFR, AUC was 0.606 (95% CI: 0.496–0.717); LCR, AUC was 0.691 (95% CI: 0.585–0.796); CAR, AUC was 0.689 (95% CI: 0.584–0.793). **(B)** Predicting prognosis of COVID-19 patients. sTREM-1, AUC 0.805 (95% CI: 0.697–0.914); PCT, AUC 0.710 (95% CI: 0.565–0.855); CRP, AUC 0.821 (95% CI: 0.719–0.924); HGB, AUC 0.665 (95% CI: 0.515–0.814); Albumin, AUC 0.721 (95% CI: 0.575–0.867); D-dimer, AUC 0.687 (95% CI: 0.529–0.846); eGFR, AUC 0.685 (95% CI: 0.545–0.824); LCR, AUC 0.801 (95% CI: 0.691–0.912); CAR, AUC 0.829 (95% CI: 0.732–0.927).

Abbreviations: TPR, true positive rate; FPR, false positive rate; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; eGFR, estimated glomerular filtration rate; LCR, Lymphocyte-to- C-reactive protein ratio; CAR, C-reactive protein-to-albumin ratio.

COVID-19 patients (Table 3). The prognostic model for COVID-19 patients incorporating these four markers showed the highest predictive value for 28-day mortality, with an AUC of 0.919 (95% CI: 0.857–0.981) (Figure 5).

Discussion

Timely identification and intervention in critically ill patients play a pivotal role in reducing mortality among individuals with COVID-19. Our research elucidated a correlation between sTREM-1 levels in the plasma of COVID-19 patients and the severity of the disease. Moreover, sTREM-1 exhibited promising predictive capabilities for assessing the prognosis of COVID-19 patients. Additionally, our study unveiled associations between plasma sTREM-1 levels and various factors, including age, body temperature, respiratory rate, PaO₂/FiO₂, and laboratory inflammatory markers such as PCT, CRP, and CAR, in COVID-19 patients. Notably, the expression of sTREM-1 demonstrated comparable or superior predictive value for disease severity and prognosis in COVID-19 patients when compared to certain clinical indicators. Ultimately,

Table 2 Predicted Value Information of Different Variable Parameters for Disease Severity and Prognosis in COVID-19 Patients

Variables	Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden index
Predicting disease severity							
sTREM-1, pg/mL	105	0.79	0.61	0.51	0.85	0.74	0.40
PCT, ng/mL	0.115	0.66	0.72	0.54	0.81	0.70	0.38
CRP, mg/L	65.9	0.39	0.88	0.63	0.74	0.72	0.27
HGB, g/L	108	0.31	0.76	0.40	0.68	0.61	0.07
Albumin, g/L	31.7	0.49	0.86	0.66	0.76	0.73	0.35
D-dimer, mg/L	248	0.64	0.72	0.56	0.78	0.69	0.36
eGFR, mL/min/1.73 m ²	93.2	0.79	0.41	0.41	0.79	0.54	0.21
LCR	0.00879	0.37	0.95	0.78	0.75	0.75	0.32
CAR	0.224	0.92	0.40	0.44	0.91	0.58	0.32

(Continued)

Table 2 (Continued).

Variables	Cut off value	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden index
Predicting prognosis							
sTREM-1, pg/mL	198	0.60	0.87	0.41	0.94	0.86	0.47
PCT, ng/mL	0.105	0.8	0.61	0.24	0.95	0.63	0.41
CRP, mg/L	35.7	0.87	0.66	0.28	0.97	0.69	0.53
HGB, g/L	107	0.47	0.79	0.25	0.91	0.75	0.26
Albumin, g/L	31.7	0.67	0.81	0.34	0.94	0.79	0.47
D-dimer, mg/L	425	0.67	0.73	0.30	0.93	0.72	0.40
eGFR, mL/min/1.73 m ²	79.9	0.73	0.63	0.23	0.94	0.64	0.36
LCR	0.0187	0.8	0.72	0.31	0.96	0.73	0.52
CAR	0.86	0.93	0.64	0.29	0.98	0.68	0.57
Combined Model	0.0951	0.93	0.77	0.42	0.98	0.80	0.70

Abbreviations: PPV, Positive predictive value; NPV, Negative predictive value; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; eGFR, estimated glomerular filtration rate; LCR, Lymphocyte-to- C-reactive protein ratio; CAR, C-reactive protein-to-albumin ratio.

Table 3 Univariable and Multivariable Logistic Regression Analysis for the Predictors of 28-Day Mortality in COVID-19 Patients

Variables	UV			MV		
	Wald	OR (95% CI)	P-value	Wald	OR (95% CI)	P-value
Age (years)	4.606	1.047 (1.004–1.092)	0.032*			
Body temperature, °C	12.637	4.370 (1.938–9.854)	0.001*			
RR, breaths/min	10.179	1.151 (1.056–1.256)	0.001*			
PaO ₂ /FiO ₂ , mmHg	9.749	0.991 (0.986–0.997)	0.002*			
sTREM-1, pg/mL	11.793	1.009 (1.004–1.014)	0.001*	7.975	1.008 (1.002–1.013)	0.005*
PCT, ng/mL	2.348	1.045 (0.988–1.106)	0.125			
CRP, mg/L	10.295	1.017 (1.007–1.028)	0.001*			
HGB, g/L	5.170	0.973 (0.950–0.996)	0.023*	4.382	0.966 (0.935–0.998)	0.036*
Albumin, g/L	8.322	0.836 (0.741–0.944)	0.004*			
D-dimer, mg/L	7.466	1.001 (1.000–1.001)	0.006*	6.890	1.001 (1.000–1.001)	0.009*
eGFR, mL/min/1.73 m ²	4.595	0.979 (0.960–1.116)	0.032*			
LCR	4.221	0.000 (0.000–0.341)	0.040*			
CAR	10.671	1.747 (1.250–2.442)	0.001*	6.884	1.761 (1.154–2.688)	0.009*

Notes: *p-value <0.05 was considered significant.

Abbreviations: RR, respiratory rate; PaO₂, oxygen tension; FiO₂, fraction of inspired oxygen; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; eGFR, estimated glomerular filtration rate; LCR, Lymphocyte-to- C-reactive protein ratio; CAR, C-reactive protein-to-albumin ratio.

through multivariate logistic regression analysis, we determined that sTREM-1 and CAR, along with HGB and D-dimer, collectively serve as independent predictive factors for 28-day mortality in COVID-19 patients. The combination of these four markers yielded a strong predictive value for 28-day mortality in COVID-19 cases.

TREM-1 is a receptor belonging to the immunoglobulin superfamily, primarily expressed on neutrophils and mature monocytes/macrophages in the bloodstream.^{21,22} It is considered an amplifier of inflammation, capable of inducing the release of pro-inflammatory mediators such as IL-6, TNF- α , and IL-1 β . It may be associated with the cytokine storm observed in COVID-19 patients.^{32,34} sTREM-1 is the soluble counterpart of TREM-1, which can be proteolytically cleaved from the cell membrane and enter the plasma following stimulation by pro-inflammatory mediators.²⁴ Therefore, it is reasonable to associate sTREM-1 with disease severity and its predictive value for patient prognosis in COVID-19.

Current research shows some discrepancies in the predictive value of sTREM-1 for patient prognosis, particularly regarding the optimal cut-off value for prediction. In a recent study, the area under the ROC curve (AUC) for sTREM-1 in predicting severe COVID-19 was reported as 0.656, but the optimal cut-off value and its predictive value for prognosis

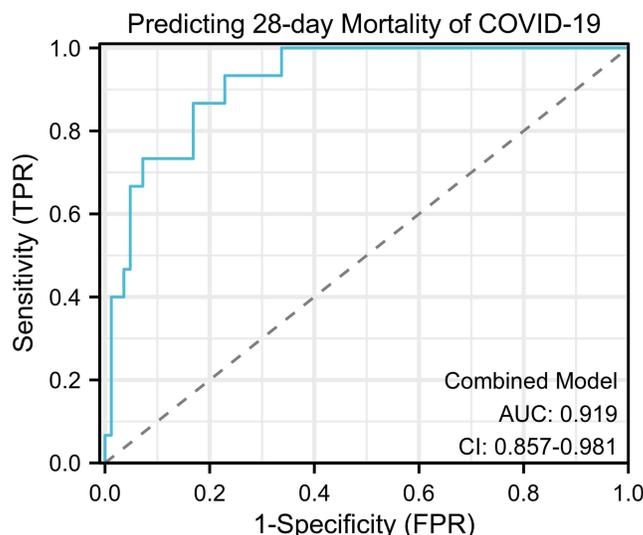


Figure 5 ROC curves for the combined model for the prognosis of COVID-19 patients. Combined model: sTREM-1, CAR, HGB and D-dimer; AUC 0.919 (95% CI: 0.857–0.981). **Abbreviations:** TPR, true positive rate; FPR, false positive rate; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; HGB, Hemoglobin; CAR, C-reactive protein-to-albumin ratio.

were not specified.³⁵ However, a study has indicated that sTREM-1 has high predictive value for severe COVID-19, with an AUC of 0.96 (95% CI: 0.94–0.98).³⁶ Regarding prognosis, an earlier study involving 76 COVID-19 patients found that sTREM-1 had an AUC of 0.86 (95% CI: 0.77–0.95) for predicting intubation/death at 30 days, with an optimal cut-off value of 689 pg/mL.³⁴ Another study reported that sTREM-1 had an AUC of 0.73 (95% CI: 0.62–0.83) for predicting mortality, with an optimal cut-off value of 315 pg/mL.³² Our study found that sTREM-1 had AUCs of 0.762 and 0.805 for predicting severe COVID-19 and 28-day mortality, respectively, which align with the current research. These studies compared the predictive value of sTREM-1 with conventional laboratory markers such as PCT, CRP, and others for disease severity and prognosis in patients. In all cases, it was found that sTREM-1 exhibited comparable or even superior predictive performance. Due to the availability of mature commercial ELISA test kits, detecting sTREM-1 in routine clinical practice is feasible. As the number of patients increases and the sample size for testing becomes sufficient, the cost of testing will become relatively lower. Dynamic monitoring of sTREM-1 levels is more meaningful and feasible for monitoring patients' conditions. It is important to note that the reference ranges for sTREM-1 levels used to monitor the severity of patients' diseases and prognosis may vary, especially among different ethnic groups, which requires further research to determine.

Several studies have compared the correlation between sTREM-1 and clinical parameters and laboratory inflammatory markers.^{37,38} Our study also found correlations ($p < 0.05$) between sTREM-1 and age, body temperature, respiratory rate, $\text{PaO}_2/\text{FiO}_2$, as well as laboratory inflammatory markers such as PCT, CRP, and CAR. For clinical parameters like age and body temperature, this may be due to their association with disease severity in patients. As for respiratory rate and $\text{PaO}_2/\text{FiO}_2$, these parameters directly reflect the severity of the patient's condition, and higher levels of sTREM-1 may be observed as a result of the increased inflammatory response associated with more severe disease. Interestingly, when meaningful indicators ($p < 0.05$) from univariate logistic regression analysis were included in the multivariable regression analysis, it was observed that, apart from sTREM-1, the other three independent predictive factors included were all laboratory markers. These three laboratory markers were HGB, D-dimer, and CAR. The measurement Results of HGB are commonly used to assess anemia, monitor blood status, and evaluate oxygen delivery and transport capacity. D-dimer is used to evaluate the activity of blood coagulation and the fibrinolytic system. CAR is a good indicator of clinical inflammatory response. These three markers have all been reported to be associated with the severity of COVID-19.^{39–44} In our study, apart from CAR, we did not find a correlation between sTREM-1 and the severity of the disease. Therefore, the combination of CAR, HGB, and D-dimer yielded a strong predictive value for 28-day mortality in COVID-19 cases, with an AUC of 0.919 (95% CI: 0.857–0.981).

Our study has several limitations. Firstly, it was a single-center prospective study, and the representativeness of the patient population needs to be validated. Secondly, the sample size was relatively small, mainly due to challenges in obtaining blood samples from enrolled patients. Thirdly, the primary outcome of our study focused on the 28-day mortality rate, and further investigation is needed to assess long-term survival outcomes. Fourthly, we did not conduct continuous monitoring and tracking of sTREM-1 levels in patients. Incorporating dynamic monitoring of sTREM-1 levels alongside changes in clinical conditions could offer more meaningful insights into disease progression. However, this is an aspect we intend to address in future research endeavors. We eagerly anticipate larger-scale, multicenter studies in the future to validate and expand upon our findings.

Conclusion

This study identified a correlation between sTREM-1 levels and the severity of COVID-19 in patients. sTREM-1 demonstrated good predictive value for disease severity and 28-day mortality, serving as an independent prognostic factor for adverse patient outcomes. In the future, we anticipate conducting large-scale multicenter studies to validate our research findings.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; PaCO₂, arterial carbon dioxide tension; PaO₂, oxygen tension; SpO₂, peripheral oxygen saturation; FiO₂, fraction of inspired oxygen; sTREM, soluble Triggering Receptors Expressed on Myeloid Cell; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; WBC, White blood cell; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; DBIL, Direct bilirubin; INR, International normalized ratio; eGFR, estimated glomerular filtration rate; BNP, B-type natriuretic peptide; CAR, C-reactive protein-to-albumin ratio; BCDIMs, blood count-derived inflammatory markers; NLR, Neutrophil-to-lymphocyte ratio; MLR, Monocyte-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; LCR, Lymphocyte-to-C-reactive protein ratio; SIRI, Systemic inflammation response index; SII: Systemic inflammation index. $SIRI = (\text{Neutrophil count} \times \text{Monocyte count}) / \text{Lymphocyte count}$; $SII = (\text{Neutrophil count} \times \text{Platelet count}) / \text{Lymphocyte count}$. SD, standard deviation; IQR, interquartile range; ROC, Receiver Operating Characteristic.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethical Committee of Beijing Youan Hospital (Approval No. LL-2023-006-K). All participating patients provided informed consent, and the data used in the study were anonymized.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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