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ORIGINAL RESEARCH

# The Predictive Value of Soluble Fms-Like Tyrosine Kinase-1 for Prognosis in COVID-19 Patients

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**Background:** Coronavirus Disease 2019 (COVID-19), caused by the novel coronavirus, has posed a significant threat to global public health, leading to substantial morbidity, mortality, and strain on healthcare resources. Despite the availability of vaccines and treatments, effective biomarkers for predicting disease progression remain limited. This study aimed to investigate the prognostic value of soluble fms-like tyrosine kinase-1 (sFlt-1) in COVID-19 patients.

**Methods:** A prospective cohort study was conducted involving 154 COVID-19 patients, with comprehensive clinical data and laboratory parameters analyzed to evaluate the effectiveness of sFlt-1 in determining disease severity and prognosis.

**Results:** The results revealed that sFlt-1 levels correlated significantly with disease severity, showing higher levels in severe/critical cases compared to mild cases ($P<0.05$). In the deceased group, sFlt-1 levels were notably higher compared to survivors, with an area under the curve (AUC) of 0.840, showing good predictive power for 28-day mortality. Multivariable logistic regression identified sFlt-1, respiratory rate, and albumin as independent prognostic factors, with a combined AUC of 0.938 (95% CI: 0.886–0.991) for predicting mortality risk.

**Conclusion:** These findings underscore the potential of sFlt-1 as a valuable biomarker for clinical decision-making in managing COVID-19 patients. Future studies should focus on the clinical application of sFlt-1 and explore its underlying mechanisms to enhance patient management strategies.

**Keywords:** COVID-19, sFlt-1, 28-day mortality, disease severity

## Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an RNA virus belonging to the Coronaviridae family. It was first identified in Wuhan, China, at the end of 2019 and quickly led to a global pandemic (COVID-19). The virus has drawn significant attention due to its high transmissibility and diverse clinical manifestations, ranging from mild asymptomatic infections to severe respiratory failure and multi-organ dysfunction. SARS-CoV-2 is primarily transmitted through respiratory droplets and close contact, with evidence of some airborne transmission capability.[1–3] As of the latest data, the World Health Organization has reported over 777 million confirmed cases of COVID-19 and more than 7.08 million deaths globally.[4,5] Research has also indicated that the excess mortality associated with the COVID-19 pandemic exceeds 14.83 million deaths, as estimated by the World Health Organization.[6] SARS-CoV-2 continues to circulate worldwide. While vaccination coverage has significantly increased and most patients experience favorable outcomes, certain populations, such as those with immune deficiencies, advanced age, or comorbidities, still face poor prognoses.[7]

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Studies have shown that diabetes is associated with the prognosis of COVID-19 patients.[8] Compared to non-diabetic patients, those with diabetes have a significantly higher incidence of severe cases.[9] Insulin infusion may be an effective method for achieving glycemic targets and improving outcomes in COVID-19 patients.[10] Glycemic control is also associated with the risk of SARS-CoV-2 breakthrough infections.[11,12] Currently, seasonal peaks of the disease continue to emerge, emphasizing the importance of early identification of critically ill patients and early intervention to improve patient outcomes.[13] However, there are still limitations in the evaluation of prognosis and disease monitoring for critically ill patients, such as the lack of effective biomarkers to predict disease progression.[14–18] Endothelial dysfunction is a major cause of death in COVID-19 patients, and oxidative stress and endothelial dysfunction have been shown to play a critical role in the pathophysiology of COVID-19.[19,20]

sFlt-1, a crucial biomarker, primarily regulates angiogenesis by binding with vascular endothelial growth factor (VEGF) and placental growth factor. Its association with the prognosis of various diseases, especially in pregnancy-related conditions, is well established.[21] Elevated levels of sFlt-1 have been significantly linked to the onset of conditions like preeclampsia and fetal growth restriction.[22] Moreover, fluctuations in sFlt-1 concentrations may also be related to the prognosis of cardiovascular diseases, sepsis, and other ailments, highlighting its value as a biomarker in clinical settings.[23–26] Since the emergence of COVID-19, studies have explored the prognostic significance of sFlt-1 in specific patient groups, such as pregnant women.[27–29] However, research on its predictive value in the general population with COVID-19 remains limited, especially in different populations such as mainland China.[30,31]

To address this question, our study employed a prospective cohort design involving 154 confirmed COVID-19 patients. Through a systematic analysis of clinical data and laboratory parameters, we aimed to evaluate the effectiveness of sFlt-1 in assessing disease severity and predicting patient outcomes. Our goal is for this approach to contribute to real-time clinical decision-making and benefit patients.

# Methods

## Study Design and Participants

A study was conducted prospectively on 154 COVID-19 patients admitted to Beijing You'an Hospital's emergency department from July 1, 2022, to November 30, 2022. Patient selection adhered to the criteria outlined in the "Diagnosis and Treatment Protocol for COVID-19 (Trial Version 9)" by the National Health Commission of China and the COVID-19 treatment guidelines from the National Institutes of Health.[32,33] Diagnosis confirmation relied on reverse transcription-quantitative polymerase chain reaction testing, segregating patients into severe/critical and mild/moderate COVID-19 categories. The study, approved by the Ethics Committee of Beijing You'an Hospital under Approval No. LL-2023-006-K in alignment with the Helsinki Declaration's standards, aimed to evaluate sFlt-1's predictive significance at admission regarding prognosis and disease severity in COVID-19 cases. Enrolled patients, who provided informed consent, were categorized into severe/critical groups, with mortality monitored over a 28-day period. Inclusion criteria mandated a confirmed COVID-19 diagnosis and willingness to participate, while exclusion criteria comprised individuals under 18, expectant mothers, and patients deceased within 48 hours of admission, as well as those lacking follow-up blood samples or with missing specimens.

## Data Collection

Initial patient characteristics, underlying health conditions, demographic information, arterial blood gas assessments, vital signs, laboratory findings, and patient outcomes were extracted from digital medical records. This investigation encompassed a range of comorbidities, including but not limited to diabetes, hypertension, cerebrovascular disorders, coronary artery disease, liver ailments, heart failure, chronic obstructive pulmonary disease (COPD), and malignancies. The primary vital signs monitored were body temperature, arterial systolic blood pressure, breathing rate, and pulse oximetry-derived heart rate. In addition to these, the study gathered hematological metrics, liver and kidney function evaluations, coagulation profiles, as well as infection-related markers such as C-reactive protein (CRP) and procalcitonin (PCT) as part of standard COVID-19 screenings. Blood samples were obtained upon admission for sFlt-1 quantification, as detailed in Table 1.

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

| Variables | Total (n=154) | 28-day Survival (n=136) | 28-day Mortality (n=18) | P-value |
|---|---|---|---|---|
| **Demographic data** | | | | |
| Sex, male, n (%) | 91 (59%) | 82 (60%) | 9 (50%) | 0.40 |
| Age (years) | 69 (59–79) | 69 (57–77) | 84 (69–89) | 0.002* |
| **Co-morbidities** | | | | |
| Hypertension, n (%) | 65 (42%) | 55 (40%) | 10 (56%) | 0.22 |
| Diabetes mellitus, n (%) | 35 (23%) | 27 (20%) | 8 (44%) | 0.033* |
| Coronary heart disease, n (%) | 31 (20%) | 28 (21%) | 3 (17%) | 0.954 |
| Cerebrovascular disease, n (%) | 20 (13%) | 13 (9.6%) | 7 (39%) | 0.003* |
| COPD, n (%) | 21 (14%) | 19 (14%) | 2 (11%) | 0.967 |
| Liver disease, n (%) | 17 (11%) | 20 (15%) | 4 (22%) | 0.49 |
| Heart failure, n (%) | 20 (11%) | 13 (9.6%) | 7 (39%) | 0.003* |
| Malignant tumor, n (%) | 17 (11%) | 13 (9.6%) | 4 (22%) | 0.581 |
| **Vital signs** | | | | |
| Body temperature, °C | 36.6 (36.3–37.0) | 36.6 (36.2–37.0) | 37.4 (37.0–38.0) | <0.001* |
| RR, breaths/min | 23 (20–23) | 20 (20–22) | 31 (24–36) | <0.001* |
| HR, beats/min | 88 (78–99) | 88 (78–98) | 96 (80–104) | 0.14 |
| SBP, mmHg | 130 (120–144) | 130 (120–144) | 127 (114–137) | 0.28 |
| **Arterial blood gas** | | | | |
| PH | 7.42 (7.39–7.45) | 7.42 (7.40–7.44) | 7.44 (7.37–7.49) | 0.35 |
| $PaCO_2$, mmHg | 36.9 (33.4–40.2) | 36.9 (33.9–40.3) | 37.4 (24.5–39.9) | 0.32 |
| $PaO_2$, mmHg | 97.0 (78.9–114.8) | 97.2 (80.6–115.3) | 75.7 (58.5–108.5) | 0.062 |
| $SpO_2$, % | 98.2 (96.2–99.2) | 98.3 (96.6–99.2) | 96.1 (92.9–99.3) | 0.19 |
| $PaO_2/FiO_2$, mmHg | 291 (210–357) | 297 (244–378) | 111 (87–175) | <0.001* |
| **COVID-19 severity class, n (%)** | | | | <0.001* |
| Mild/Moderate illness | 118 (77%) | 117 (86%) | 1 (6%) | |
| Severe/critical illness | 36 (23%) | 19 (14%) | 17 (94%) | |
| **Laboratory parameters** | | | | |
| sFlt-1, pg/mL | 143.7 (88.2–368.9) | 128.3 (84.1–324.9) | 385.3 (323.3–559.6) | <0.001* |
| PCT, ng/mL | 0.08 (0.05–0.21) | 0.07 (0.05–0.15) | 0.36 (0.12–1.23) | <0.001* |
| CRP, mg/L | 18.47 (5.70–53.43) | 15.6 (4.45–46.82) | 70.50 (38.65 −112.29) | <0.001* |
| HGB, g/L | 125 (106–138) | 125 (109–137) | 117 (96–130) | 0.10 |
| WBC count, $\times 10^9$/L | 5.00 (3.68–6.88) | 4.96 (3.70–6.65) | 5.41 (3.85–7.20) | 0.69 |
| Neutrophils count, $\times 10^9$/L | 3.47 (2.28–5.22) | 3.45 (2.27–5.10) | 4.00 (2.58–6.62) | 0.47 |
| Lymphocytes count, $\times 10^9$/L | 0.95 (0.66–1.29) | 1.01 (0.70–1.33) | 0.73 (0.61–0.96) | 0.06 |
| INR | 1.05 (1.00–1.14) | 1.05 (1.00–1.13) | 1.09 (1.01–1.25) | 0.19 |
| Glucose, mmol/L | 6.8 (6.1–7.8) | 6.7 (6.1–7.8) | 7.2 (6.4–8.9) | 0.15 |
| ALT, U/L | 18 (13–28) | 18 (13–28) | 23 (17–27) | 0.35 |
| AST, U/L | 22 (18–32) | 21 (17–30) | 36 (21–54) | 0.008* |
| Albumin, g/L | 36 (32–38) | 36 (33–38) | 31 (30–34) | <0.001* |
| TBIL, μ mol/L | 10.3 (7.9–15.2) | 9.9 (7.7–15.1) | 11.4 (9.5–17.0) | 0.13 |
| DBIL, μ mol/L | 3.8 (2.6–6.5) | 3.7 (2.5–6.2) | 6.2 (3.7 −7.6) | 0.021* |

**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: Q1-Q3) 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.

**Abbreviations**: COPD, Chronic Obstructive Pulmonary Disease; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; $PaCO_2$, arterial carbon dioxide tension; $PaO_2$, oxygen tension; $SpO_2$, peripheral oxygen saturation; $FiO_2$, fraction of inspired oxygen; sFlt-1, Soluble fms-like tyrosine kinase-1; PCT, Procalcitonin; CRP, C-reactive protein; HGB, Hemoglobin; WBC, White blood cell; INR, International normalized ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; DBIL, Direct bilirubin. *p-value <0.05 was considered significant.


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## Detection of Plasma sFlt-1 Levels

Upon hospital admission, blood specimens were procured and analyzed. Anticoagulant tubes containing ethylenediaminetetraacetic acid were employed for blood collection. Plasma was isolated by subjecting the collected whole blood to centrifugation at 1200g for a duration of 10 minutes. Subsequently, all blood samples were preserved at −80°C until they underwent further examination. The quantification of human sFlt-1 concentrations in plasma was conducted utilizing a human sFlt-1 ELISA kit (Shanghai, China; Keshun Biotechnology, REF: KS13928) following the procedural guidelines outlined in the kit's manual.[34]

## Statistical Analysis

The study evaluated variable normality, presenting normally distributed data as mean ± SD and non-normally distributed data as median with IQR. Categorical variables were summarized as counts and percentages. Significant variables ($p < 0.05$) were identified. Receiver operating characteristic (ROC) and Kaplan-Meier curves assessed predictiveness and risk for disease severity and 28-day mortality. Spearman correlation explored relationships between sFlt-1, age, clinical parameters, and lab markers. Logistic regression identified mortality predictors. Statistical analyses were performed using R language (version 4.2.1; R Foundation for Statistical Computing) and SPSS software (version 22.0; IBM Corp)., with data visualization in GraphPad Prism 9 (GraphPad Software Inc).[35]

# Results

## Patient Enrollment and Baseline Clinical Data

After screening, a total of 154 patients were included in the analysis, comprising 63 cases (41%) of mild patients, 55 cases (36%) of moderate patients, and 36 cases (23%) of severe/critical patients, with 18 patients (12%) ultimately experiencing mortality within 28 days, as shown in Figure 1.

Comparison between patients who survived and those who died within 28 days revealed that deceased patients were older and had a higher prevalence of diabetes, cerebrovascular diseases, and heart failure. Deceased patients exhibited higher body temperatures, respiratory rates, and lower oxygenation indices. In terms of laboratory findings, deceased patients within 28 days had higher levels of sFlt-1, PCT, CRP, Aspartate aminotransferase (AST), and Direct bilirubin (DBIL), with lower levels of Albumin. These parameters showed statistically significant differences between the two groups (all P values <0.05). Refer to Table 1 for details.

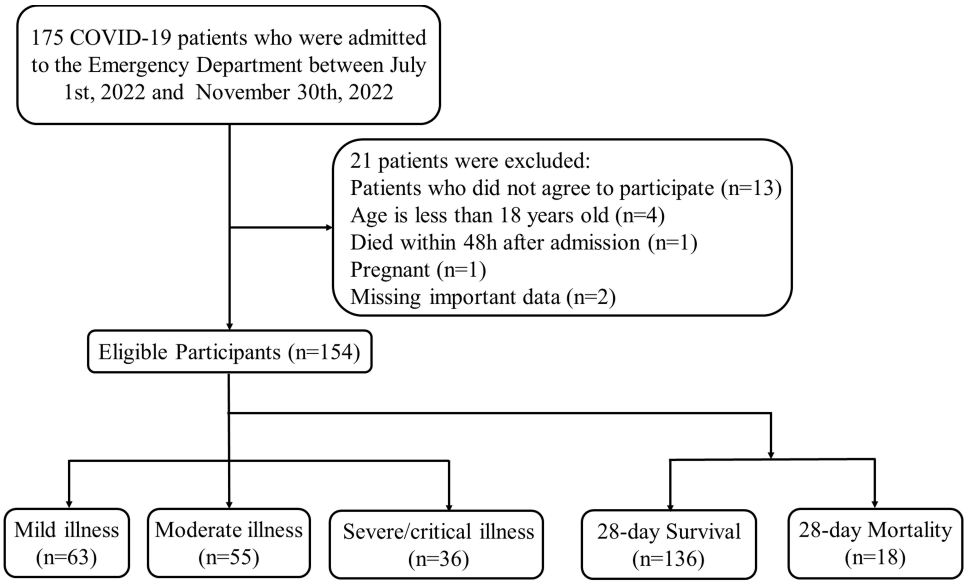


**Figure 1** Flow diagram of patients enrollment.

## Value of sFlt-1 in Predicting Prognosis and Disease Severity of COVID-19 Patients

There is a notable link between sFlt-1 levels and the seriousness of illness in individuals with COVID-19. As disease severity escalates, sFlt-1 levels proportionally increase. Statistically significant variations were observed in pairwise comparisons among the four groups, with exceptions in the severe and critical subgroups (Figure 2A). Patients necessitating mechanical ventilation exhibited elevated sFlt-1 levels compared to those not requiring such intervention (Figure 2B), and individuals in the 28-day mortality cohort demonstrated higher sFlt-1 levels (Figure 2C). Notably, sFlt-1 proved to be a robust predictor of 28-day mortality and disease severity, with the respective areas under the ROC curve

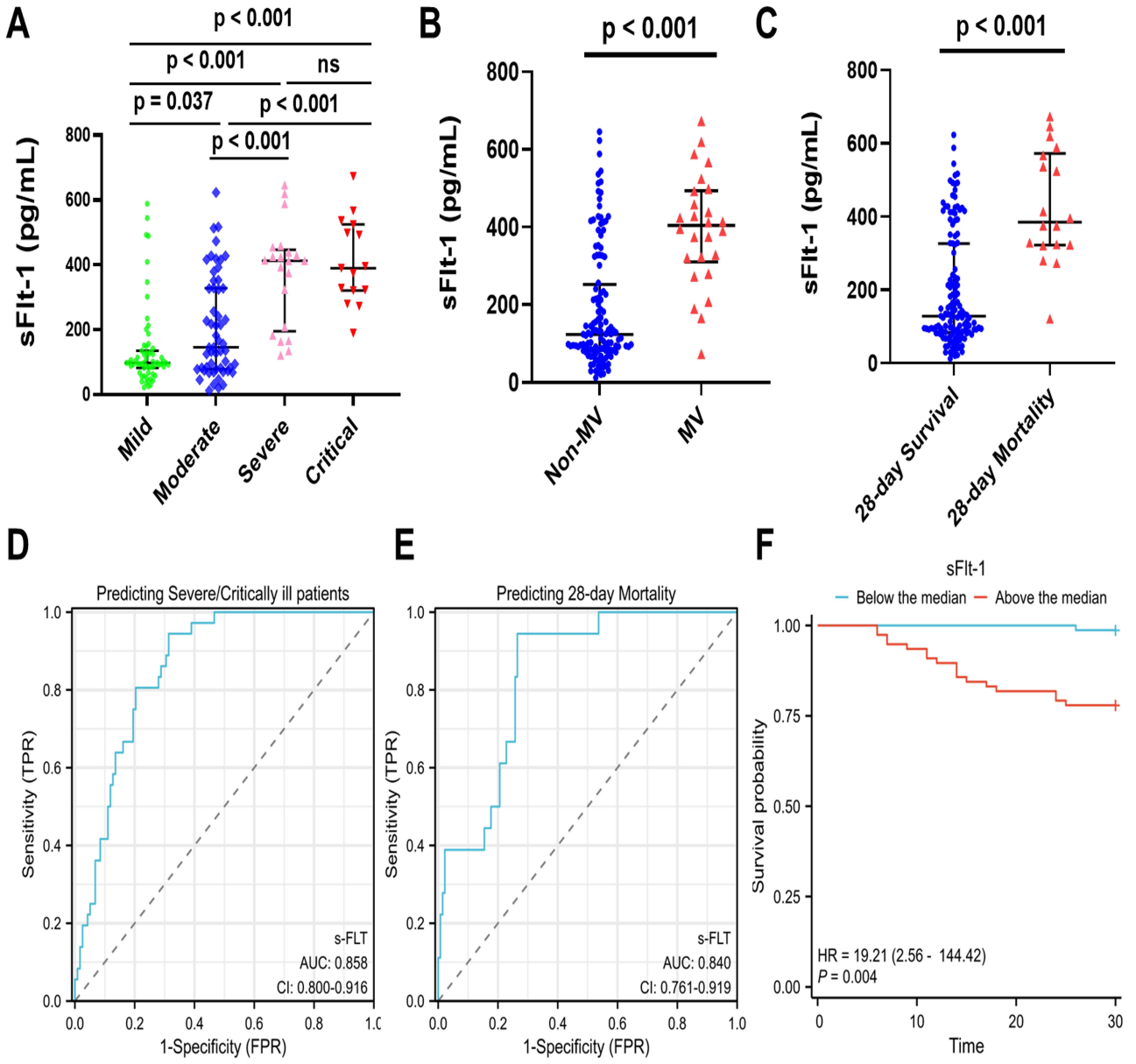


**Figure 2** The predictive value of sFlt-1 for the severity of illness and 28-day mortality in COVID-19 patients. (**A**) Comparison of sFlt-1 levels among different severity groups of COVID-19 patients. (**B**) Comparison of sFlt-1 levels between the non-mechanical ventilation and mechanical ventilation groups. (**C**) Comparison of sFlt-1 levels between the 28-day survival and death groups. 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 sFlt-1 for predicting Severe/Critically ill patients, with an area under the ROC curve (AUC) of 0.858 (95% confidence interval [CI]: 0.800–0.916). (**E**) ROC curve of sFlt-1 for predicting 28-day mortality in COVID-19 patients, with an AUC of 0.840 (95% confidence interval [CI]: 0.761–0.919). (**F**) Kaplan-Meier curve for patients divided into two groups based on the median sFlt-1 level: above-median group and below-median group, for 28-day survival. A p-value <0.05 was considered significant.


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values of 0.858 and 0.840 (Figure 2D and E). Stratification of patients based on the median sFlt-1 value revealed a markedly elevated risk of 28-day mortality in the subgroup exceeding the median (P=0.004) (Figure 2F).

## Correlation Analysis of sFlt-1 With Age, Laboratory Markers, and Clinical Parameters

In the heatmap (Figure 3A), we illustrate the correlations among sFlt-1, age, body temperature, respiratory rate, and a total of nine factors. The study reveals significant correlations between sFlt-1 and body temperature, respiratory rate, PCT, CRP, albumin, and DBIL (all P values <0.05) (Figure 3B).

## The Value of sFlt-1 in Predicting Prognosis and Disease Severity in COVID-19 Patients Is Not Inferior to Conventional Laboratory Markers

ROC curve analysis revealed that sFlt-1 has a high predictive value for 28-day mortality and disease severity in COVID-19 patients (Figure 4A and B and Table 2), comparable to or even better than conventional laboratory markers in clinical diagnosis and treatment processes (Table 3).

## sFlt-1 Is an Independent Predictive Factor for Poor Prognosis in COVID-19 Patients

By employing univariate logistic regression analysis on variables showing statistically significant variances between the 28-day mortality and survival groups in Table 1, variables with statistical significance were included in a multivariate logistic regression analysis. Ultimately, sFlt-1, respiratory rate, and albumin emerged as three factors independently predicting poor prognosis in COVID-19 patients (Table 4). Combining these three independent predictive factors yields a high predictive value for 28-day mortality in patients, with an AUC of 0.938 (95% CI: 0.886–0.991) (Figure 5).

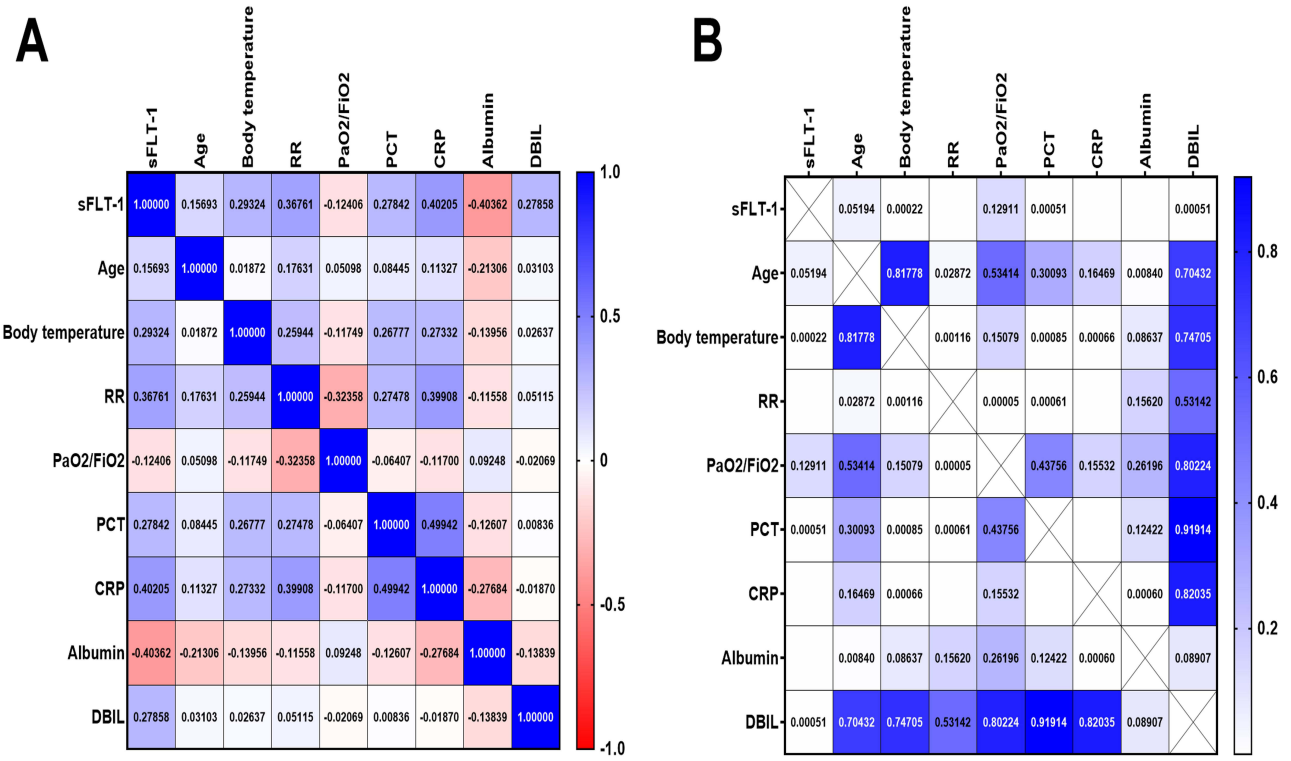


**Figure 3** Heatmap depicting the correlation between sFlt-1 and age, clinical parameters, and laboratory markers. (**A**) The values are presented as Spearman correlation coefficient (r) for a sample of 154 runners regarding sFlt-1. The colormap ranges from 1 to −1, with blue indicating the highest 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; s-FLT, Soluble fms-like tyrosine kinase-1; PCT, Procalcitonin; CRP, C-reactive protein; AST, Aspartate aminotransferase; DBIL, Direct bilirubin. p-value <0.05 was considered significant.

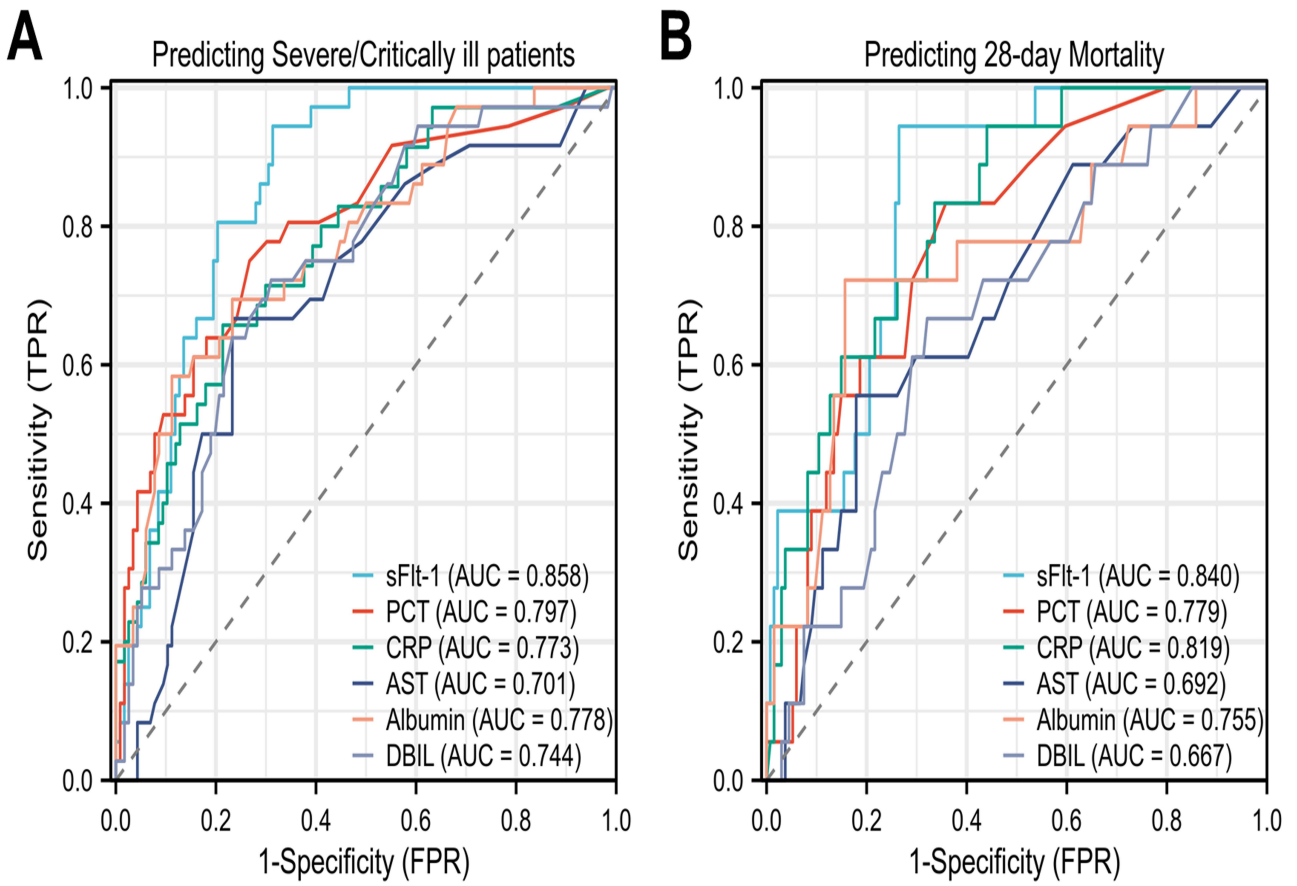


**Figure 4** ROC curves of sFlt-1 and laboratory markers for disease severity and prognosis in COVID-19 patients. (**A**) Predicting severity of COVID-19 patients. The area under the curve (AUC) for sFlt-1 was 0.858 (95% confidence interval [CI]: 0.800–0.916); PCT, 0.797 (95% CI: 0.709–0.885); CRP, AUC was 0.773 (95% CI: 0.685–0.862); AST, 0.701 (95% CI: 0.603–0.798); Albumin, AUC was 0.778 (95% CI: 0.689–0.868); DBIL, AUC was 0.744 (95% CI: 0.653–0.834). (**B**) Predicting prognosis of COVID-19 patients. sFlt-1 was 0.840 (95% confidence interval [CI]: 0.761–0.919); PCT, 0.779 (95% CI: 0.678–0.880); CRP, AUC was 0.819 (95% CI: 0.728–0.909); AST, 0.692 (95% CI: 0.562–0.821); Albumin, AUC was 0.755 (95% CI: 0.622–0.887); DBIL, AUC was 0.667 (95% CI: 0.541–0.794).
**Abbreviations**: TPR: true positive rate; FPR: false positive rate; AUC, area under the receiver operating characteristic curve; s-FLT, soluble fms-like tyrosine kinase-1; PCT, Procalcitonin; CRP, C-reactive protein; AST, Aspartate aminotransferase; DBIL, Direct bilirubin.

## Discussion

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, represents a significant global health challenge, leading to severe respiratory illnesses and notable mortality rates. The disease spectrum ranges from asymptomatic cases to critical illness, with factors such as age and comorbidities influencing clinical outcomes.

**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** | | | | | | | |
| sFlt-1, pg/mL | 160 | 0.94 | 0.68 | 0.48 | 0.98 | 0.75 | 0.63 |
| PCT, ng/mL | 0.115 | 0.75 | 0.73 | 0.47 | 0.90 | 0.74 | 0.48 |
| CRP, mg/L | 31.6 | 0.71 | 0.69 | 0.70 | 0.71 | 0.70 | 0.40 |
| AST, U/L | 28.5 | 0.67 | 0.77 | 0.47 | 0.88 | 0.74 | 0.43 |
| Albumin, g/L | 31.7 | 0.58 | 0.89 | 0.62 | 0.87 | 0.82 | 0.47 |
| DBIL, μ mol/L | 4.65 | 0.64 | 0.72 | 0.56 | 0.78 | 0.69 | 0.41 |

(*Continued*)


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**Table 2** (Continued).

| Variables | Cut Off Value | Sensitivity | Specificity | PPV | NPV | Accuracy | Youden Index |
|---|---|---|---|---|---|---|---|
| **Predicting prognosis** | | | | | | | |
| sFlt-1, pg/mL | 265 | 0.94 | 0.74 | 0.32 | 0.99 | 0.76 | 0.68 |
| PCT, ng/mL | 0.105 | 0.83 | 0.64 | 0.24 | 0.97 | 0.64 | 0.48 |
| CRP, mg/L | 32.4 | 0.83 | 0.67 | 0.71 | 0.80 | 0.75 | 0.50 |
| AST, U/L | 34.5 | 0.55 | 0.82 | 0.29 | 0.93 | 0.79 | 0.38 |
| Albumin, g/L | 31.7 | 0.72 | 0.84 | 0.38 | 0.96 | 0.83 | 0.57 |
| DBIL, μ mol/L | 5.05 | 0.67 | 0.68 | 0.22 | 0.94 | 0.68 | 0.35 |

**Abbreviations**: PPV, Positive predictive value; NPV, Negative predictive value; s-FLT, Soluble fms-like tyrosine kinase-1; PCT, Procalcitonin; CRP, C-reactive protein; AST, Aspartate aminotransferase; DBIL, Direct bilirubin.

**Table 3** Comparing the AUC for Different Clinical Parameters for Disease Severity and Prognosis in COVID-19 Patients

| Variables | sFlt-1 | PCT | CRP | AST | Albumin | DBIL |
|---|---|---|---|---|---|---|
| **Predicting disease severity** | | | | | | |
| sFlt-1, pg/mL | **AUC=0.858** | | | | | |
| PCT, ng/mL | P = 0.2565 | **AUC=0.797** | | | | |
| CRP, mg/L | P = 0.1162 | P = 0.7093 | **AUC=0.773** | | | |
| AST, U/L | P = 0.0071 | P = 0.1530 | P = 0.2821 | **AUC=0.701** | | |
| Albumin, g/L | P = 0.1432 | P = 0.7724 | P = 0.9350 | P = 0.2467 | **AUC=0.778** | |
| DBIL, μ mol/L | P = 0.0372 | P = 0.4079 | P = 0.6465 | P = 0.4219 | P = 0.5527 | **AUC=0.744** |
| **Predicting prognosis** | | | | | | |
| sFlt-1, pg/mL | **AUC=0.840** | | | | | |
| PCT, ng/mL | P = 0.3532 | **AUC=0.779** | | | | |
| CRP, mg/L | P = 0.7289 | P = 0.5685 | **AUC=0.819** | | | |
| AST, U/L | P = 0.0559 | P = 0.2972 | P = 0.1159 | **AUC=0.692** | | |
| Albumin, g/L | P = 0.2791 | P = 0.7739 | P = 0.4350 | P = 0.5320 | **AUC=0.755** | |
| DBIL, μ mol/L | P = 0.0238 | P = 0.1774 | P = 0.0575 | P = 0.7435 | P = 0.3240 | **AUC=0.667** |

**Notes**: The table displays the p-values (DeLong's test) for each comparison. A p-value less than 0.05 indicates a statistically significant difference in the area under the curve (AUC) between the two parameters. The diagonal contains the AUC values, which are highlighted in bold.
**Abbreviations**: s-FLT, Soluble fms-like tyrosine kinase-1; PCT, Procalcitonin; CRP, C-reactive protein; AST, Aspartate aminotransferase; DBIL, Direct bilirubin.

**Table 4** 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) | 7.295 | 1.058 (1.015–1.102) | 0.007* | 1.479 | 1.036 (0.978–1.098) | 0.224 |
| Body temperature, °C | 14.228 | 3.392 (1.804–6.377) | < 0.001* | 0.516 | 1.421 (0.545–3.709) | 0.472 |
| RR, breaths/min | 26.311 | 1.285 (1.168–1.414) | < 0.001* | 8.534 | 1.251 (1.076–1.453) | 0.003* |
| $PaO_2/FiO_2$, mmHg | 4.327 | 0.995 (0.991–1.000) | 0.037* | 0.033 | 1.001 (0.994–1.007) | 0.856 |
| sFlt-1, pg/mL | 20.264 | 1.008 (1.004–1.011) | < 0.001* | 4.941 | 1.006 (1.001–1.012) | 0.026* |
| PCT, ng/mL | 2.568 | 1.049 (0.989–1.113) | 0.109 | | | |
| CRP, mg/L | 13.894 | 1.019 (1.009–1.029) | < 0.001* | 0.211 | 1.003 (0.990–1.017) | 0.646 |
| AST, U/L | 0.686 | 1.004 (0.995–1.013) | 0.408 | | | |
| Albumin, g/L | 13.318 | 0.806 (0.718–0.905) | < 0.001* | 4.521 | 0.814 (0.673–0.984) | 0.033* |
| DBIL, μ mol/L | 0.022 | 1.002 (0.977–1.028) | 0.882 | | | |

**Notes**: *p-value <0.05 was considered significant.
**Abbreviations**: RR, respiratory rate; $PaO_2$, oxygen tension; $FiO_2$, fraction of inspired oxygen; s-FLT, Soluble fms-like tyrosine kinase-1; PCT, Procalcitonin; CRP, C-reactive protein; AST, Aspartate aminotransferase; DBIL, Direct bilirubin.

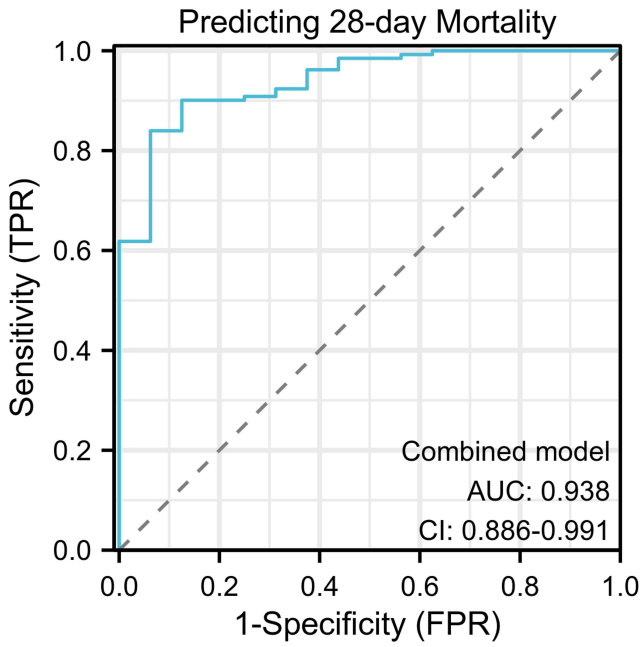


**Figure 5** ROC curves for the combined model for the prognosis of COVID-19 patients. Combined model: sFlt-1, respiratory rate and Albumin; AUC 0.938 (95% CI: 0.886–0.991).
**Abbreviations**: TPR: true positive rate; FPR: false positive rate; s-FLT, Soluble fms-like tyrosine kinase-1.

Understanding biomarkers associated with disease severity is crucial for enhancing patient management and treatment interventions, especially as the pandemic continues to evolve with the emergence of viral variants.[36–38]

Our study focused on soluble fms-like tyrosine kinase-1 (sFlt-1) as a potential biomarker for COVID-19 patients. We conducted a prospective cohort study involving 154 COVID-19 patients to assess the relationship between sFlt-1 levels and disease severity as well as 28-day mortality outcomes. The results of the study indicated a significant association between elevated sFlt-1 levels and poorer clinical outcomes, highlighting its potential utility for risk stratification and decision-making in clinical settings. By comparing sFlt-1 with other traditional biomarkers, this study provides important insights into the predictive ability of sFlt-1 in forecasting adverse outcomes in COVID-19 patients, paving the way for its integration into routine clinical practice.

sFlt-1 is an important VEGF inhibitor encoded by the Flt-1 gene. It is characterized by a complete tyrosine kinase domain and an extracellular binding domain, allowing it to bind to VEGF and PlGF, thereby inhibiting their binding to endothelial cell surface receptors and halting the process of angiogenesis.[39,40] The expression levels of sFlt-1 vary significantly in pregnancy and various pathological conditions, particularly in diseases such as preeclampsia and gestational hypertension, where its elevated levels are closely associated with disease onset.[41] Furthermore, sFlt-1 has been found to participate in regulating endothelial cell function and structural changes, affecting cell proliferation and migration, thereby exerting a significant impact on vascular stability and function.[42] Studies suggest that overexpression of sFlt-1 may lead to endothelial dysfunction, consequently triggering a range of cardiovascular diseases such as heart failure and atherosclerosis.[43]

After the emergence of the COVID-19 pandemic, multiple clinical studies have shown a positive correlation between sFlt-1 levels and the severity of COVID-19. For example, one study found that sFlt-1 levels in severe COVID-19 patients were significantly higher than those in mild cases, suggesting that sFlt-1 may play an important role in the pathophysiology of COVID-19.[44] Additionally, the association between sFlt-1 and endothelial dysfunction and organ failure has been confirmed, which may be one of the mechanisms through which COVID-19 leads to severe clinical outcomes.[27] In pregnant women, elevated levels of sFlt-1 have also been associated with the severity of COVID-19. Studies have shown a significant correlation between the sFlt-1/Angiotensin-II ratio and the occurrence of severe COVID-19 in pregnant individuals.[29] These research findings indicate that sFlt-1 serves not only as a prognostic indicator but also as a potential biomarker for COVID-19-related endothelial damage, providing essential information for clinical management.


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The main drawback of these studies is that the research results are mainly derived from pregnant women, with insufficient research on COVID-19 in the general population. Our findings indicate a significant correlation between elevated sFlt-1 levels and disease severity as well as 28-day mortality in COVID-19 patients, establishing sFlt-1 as a potential biomarker for clinical assessment. Furthermore, there is currently a lack of a unified cutoff value in studies on the prognostic prediction of sFlt-1 for COVID-19 patients. Our study provides some reference for future research in this regard.

While this study has yielded valuable insights, it is important to acknowledge its limitations. Firstly, the relatively small sample size and the observational nature of the study may limit the generalizability of the results. Additionally, the lack of long-term follow-up data restricts our understanding of the sustained impact of sFlt-1 levels on patient outcomes post-infection. Selection bias is another potential concern, as recruited participants may not fully represent the broader demographic characteristics of COVID-19 patients. Furthermore, although we have identified a significant association between sFlt-1 levels and clinical outcomes, the lack of relevant wet lab experimental data necessitates cautious interpretation. Finally, variability within the dataset may introduce detection differences, potentially affecting result consistency, and underscoring the importance of external validation in future research. Basic research to explore the mechanisms of sFlt-1 in the disease progression of COVID-19 patients is also important, and we plan to conduct related studies in the future.

In conclusion, this study underscores the promising role of sFlt-1 as a prognostic biomarker for COVID-19 patient assessment, emphasizing the importance of a comprehensive understanding of patient characteristics and comorbidities in determining outcomes. Our findings suggest that integrating sFlt-1 into clinical decision-making may enhance the management of COVID-19 cases and potentially improve patient outcomes. Future research should prioritize larger-scale multicenter studies to further elucidate the clinical utility of sFlt-1 and explore its mechanistic pathways, which may ultimately aid in developing targeted treatment strategies for COVID-19 and more effective risk stratification schemes.

## Abbreviations

sFlt-1, Soluble Fms-Like Tyrosine Kinase-1; COVID-19, Coronavirus Disease 2019; AUC, Area Under the Curve; ROC, Receiver Operating Characteristic; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; VEGF, vascular endothelial growth factor; COPD, Chronic Obstructive Pulmonary Disease; RR, respiratory rate; HR, heart rate; SBP, systolic blood pressure; $PaCO_2$, arterial carbon dioxide tension; $PaO_2$, oxygen tension; $SpO_2$, peripheral oxygen saturation; $FiO_2$, fraction of inspired oxygen; PCT, Procalcitonin; CRP, C-reactive protein; SD, standard deviation; IQR, interquartile range; HGB, Hemoglobin; WBC, White blood cell; INR, International normalized ratio; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; DBIL, Direct bilirubin.

## 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.

## Consent for Publication

All authors approved the publication of this manuscript.

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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 in this work.

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