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ORIGINAL RESEARCH

Association of Serum Irisin With Severity and Prognosis in Patients With Coronavirus Disease 2019: A Prospective Cohort Study

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Background: Irisin is the cleaved form of fibronectin type III domain-containing protein 5 (FNDC5), which can confer antioxidant and anti-inflammatory effects. Several studies have revealed that irisin can alleviate lung injury and affect the pathology of coronavirus disease 2019 (COVID-19). The aim of this study was to assess the relationships of serum irisin with the severity and prognosis of COVID-19.

Methods: A total of 328 COVID-19 patients were recruited. Peripheral blood samples were collected. The level of serum irisin was determined by ELISA. The associations of serum irisin with COVID-19 severity and prognosis were evaluated through linear and logistic regression models on the basis of a prospective cohort study.

Results: Serum irisin levels were lower in severe patients than in mild patients. The level of serum irisin was gradually decreased with the worsening of COVID-19. Spearman correlation analysis revealed that serum irisin concentration was inversely correlated with several clinical characteristics. Moreover, linear and logistic regression analyses revealed that serum irisin concentration was negatively correlated with the severity score. Interestingly, chronic heart and kidney diseases significantly affected the associations between serum irisin and severity scores. The results of the follow-up study suggested that the level of serum irisin upon admission was reduced in patients who died within one month of hospitalization. A lower serum irisin level at admission increased the risk of death within one month.

Conclusion: Serum irisin levels at admission were negatively correlated with disease severity and prognosis, suggesting that irisin is involved in the pathological process of COVID-19. Serum irisin may be used as a biomarker for diagnostic and prognostic assessment of COVID-19.

Keywords: COVID-19, irisin, severity scores, prognostic outcomes, cohort study

Introduction

In December 2019, a type of pneumonia caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appeared in Wuhan, Hubei Province, and since then, it spread widely among the population, caused infections, and quickly became a major global public health event.[1] On February 11, 2020, the World Health Organization (WHO) officially named the disease caused by SARS-CoV-2 "coronavirus disease 2019" (COVID-19).[2] Research has shown that COVID-19 is a severe respiratory disease accompanied by fever, dry cough, fatigue, nasal congestion, runny nose, sore throat, myalgia, diarrhoea, and even dyspnoea and/or hypoxemia in severe cases; acute respiratory distress syndrome;

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septic shock; intractable metabolic acidosis; coagulopathy; and multiple organ failure.[3,4] Since the outbreak of the global pandemic, COVID-19 has spread extremely quickly and has even caused a substantial number of deaths.[5,6] Therefore, early and timely diagnosis can play a central role in making a proper decision and slowing disease progression.

Irisin, a myocyte factor discovered and reported in 2012, is the cleaved form of fibronectin type III domain-containing protein 5 (FNDC5),[7] and it is produced mainly in skeletal and cardiac muscle cells during exercise and physical activity.[8] Numerous studies have indicated that cold exposure, leptin, and inflammatory cytokines can regulate the secretion of irisin.[9–11] In addition, increasing evidence has confirmed the antiapoptotic, anti-inflammatory and antioxidant properties of irisin, which can participate in the occurrence and development of various diseases.[12] Recent research has revealed the potential role of irisin in lung diseases, including chronic obstructive pulmonary disease (COPD), acute lung injury, idiopathic pulmonary fibrosis, and pulmonary embolism.[13] However, the exact role of irisin in patients with COVID-19 remains unclear.

Previous research has revealed that COVID-19 is an inflammatory disease and that the inflammatory storm is activated.[14] Additionally, a previous study with a small sample size reported that there was no difference in the serum irisin concentration between COVID-19 patients at admission and healthy volunteers.[15] However, other studies revealed that irisin levels were decreased in COVID-19 patients and that irisin may enter injured cells in lung tissues and subsequently exert a protective effect against SARS-CoV-2 infection.[16–18] Therefore, we speculated that the expression of irisin was related to the severity and prognosis of COVID-19. Consequently, the purpose of this study was to investigate the relationship between serum irisin and COVID-19 severity and prognosis through a prospective study. COVID-19 patients were enrolled, and serum irisin levels were measured. The current study suggested that the serum irisin level was negatively correlated with disease severity and poor prognosis in hospitalized COVID-19 patients. Thus, our investigation provides the first evidence of the important function of irisin in COVID-19 patients.

Materials and Methods

Study Design and Participants

All patients were enrolled at the Second Affiliated Hospital of Anhui Medical University from December 2022 to January 2023. After the patients provided their consent, 328 patients were recruited. The demographic characteristics and clinical data were collected. All patients had COVID-19 confirmed by nucleic acid testing and chest CT prior to hospitalization and were at least 18 years of age. All selected COVID-19 patients met the following inclusion criteria: (1) positive COVID-19 nucleic acid test results or specific antibodies were observed; and (2) clinical symptoms related to COVID-19, such as fever, respiratory symptoms, and obvious imaging features, were present. The exclusion criteria were as follows: (1) pregnancy; (2) other lung diseases, such as asthma and COPD; (3) immune deficiency or autoimmune diseases; (4) other infectious diseases; and (5) malignancy. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University. After admission, the severity of COVID-19 was estimated by the scoring system, including SMART-COP (systolic blood pressure, multilobar chest radiography, low albumin level, respiratory rate, tachycardia, confusion, low oxygen, arterial pH), CURB-65 (confusion, urea, respiratory rate, blood pressure, age 65 years or older), CURXO (confusion, urea, respiratory rate, X-ray, oxygen), COVID-GRAM (pathological changes typical of COVID-19 in chest radiographs, patients' age, haemoptysis, dyspnoea, loss of consciousness, number of comorbidities, history of malignancy, neutrophil-to-lymphocyte ratio, LDH value, and bilirubin concentration), Pneumonia Severity Index (PSI), Coronavirus Clinical Characterisation Consortium Mortality (4C) Mortality, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (DTPNCP), MuLBSTA (multilobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hypertension, and age), and A-DROP (age, dehydration, respiratory failure, orientation disturbance, and low blood pressure). In this study, the SMART-COP, CURB-65, CURXO, PSI, and DTPNCP scores were used to evaluate the severity of disease in COVID-19 patients. In addition, COVID-GRAM, 4C-Mortality, MuLBSTA, and A-DROP were used mainly for assessing the risk of death. In addition, all participators have been informed about the purpose and all volunteered to take part in the subsequent follow-up research.

Enzyme-Linked Immunosorbent Assay (ELISA)

Peripheral blood samples were collected using EDTA anticoagulation. Blood samples were centrifuged, and serum samples were collected and stored in a −80°C ultralow temperature freezer. Irisin ELISA kits (CSB-EQ027943HU) were obtained from CUSABIO Corporation in Wuhan, China (https://www.cusabio.com/). In accordance with previous studies, ELISA was used to detect the serum irisin level.[19–21] Briefly, the frozen serum samples were thawed slowly and mixed gently before the assay. The standard curve was established by diluting the standards. The plates were prepared, and 50 μL of the standards, serum samples, or blank samples were added to the plates. The plates were subsequently incubated for 2 h at 37°C. After the liquid was removed and the mixture was washed three times, 100 μL of biotin-labelled antibody working solution was added, and the mixture was incubated for 2 h at 37°C. Then, 50 μL of horseradish peroxidase-labelled avidin was added, and the mixture was incubated for 1.5 h at 37°C. Finally, 50 μL of stop solution was added, and the optical density of each well was measured at a wavelength of 450 nm using a microplate reader.

Statistical Analysis

In the present study, we used a cohort design. The sample size of this cohort was calculated with PASS software. Preliminary calculations indicated that the minimum sample size was 260 cases. Considering the missed follow-up rate, 380 cases were selected. Due to incomplete information and unavailable serum samples, 328 COVID-19 patients were ultimately enrolled. All analyses were performed with SPSS version 22.0. Continuous variables are expressed as the means and standard deviations or the medians and interquartile ranges (IQRs). Categorical variables are expressed as numbers and percentages. The clinical characteristics of continuous variables were compared with one-way ANOVA and the Mann–Whitney *U*-test. According to the different sample sizes, chi-square tests or Fisher's precision probability tests were used to evaluate the differences in categorical variables. The relationships between the serum irisin concentration and clinical characteristics were explored via Spearman correlation coefficients. A linear regression model was used to investigate the correlations between serum irisin levels and disease severity scores in COVID-19 patients. Moreover, COVID-19 patients were divided into three grades on the basis of tertiles of serum irisin levels, including the tertile 1 (T1) group, with a serum irisin level<65.18 ng/mL; the T2 group, with a serum irisin level ranging from 65.18 to 210.84 ng/mL; and the T3 group, with a serum irisin level>210.84 ng/mL. The correlations between the tertiles of serum irisin and severity scores were explored by logistic regression analysis. The relationships between the tertiles of serum irisin and clinical outcomes were estimated by chi-square tests or Fisher's precision probability tests and logistic regression analysis. Lastly, the 30-day mortality risk was predicted using by receiver operating characteristic (ROC) curve. A P value <0.05 was considered to indicate statistical significance.

Results

Demographic Characteristics of COVID-19 Patients

In this study, 328 patients who were confirmed to have COVID-19 participated. As shown in Table 1, COVID-19 patients were divided into three subgroups on the basis of tertiles of serum irisin levels. The results revealed obvious differences in sex, the number of chronic kidney diseases, the number of other chronic heart diseases, corticosteroid therapy status, antibiotic therapy status, and anticoagulant therapy status among the three subgroups of COVID-19 patients. Additionally, the severity stages of COVID-19 patients were analysed. There was no evident difference in severity among COVID-19 patients in different serum irisin tertile groups (Table 1). Moreover, the clinical characteristics of the patients were compared. As shown in Table 1, we observed prominent differences in lymphocytes, creatine kinase (CK), myoglobin, D-dimer, C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin (PCT) among COVID-19 patients with different serum irisin levels.

Serum Irisin Levels in COVID-19 Patients

The level of serum irisin was detected and compared in COVID-19 patients. As shown in Figure 1A, the level of serum irisin was lower in those with scores of 5~6 and 7~8 than in those with scores of 0~2 and 3~4 according to the SMART-

Table 1 Demographic Characteristics of Participators at Baseline

Characteristic	Tertile of Serum Irisin (ng/mL)			*P*
	T1 (<65.18)	T2 (65.18~210.84)	T3 (>210.84)	
N	109	110	109	
Age, years	71.7±1.41	70.8±1.26	69.1±1.50	0.396
Male, n (%)	77 (70.6)	64 (58.2)	50 (45.9)	**0.010**
Hypertension, n (%)	47 (43.1)	60 (54.5)	55 (50.5)	0.233
Diabetes mellitus, n (%)	25 (22.9)	27 (24.5)	20 (18.3)	0.527
Coronary heart diseases, n (%)	16 (14.7)	30 (27.3)	22 (20.2)	0.076
Other chronic heart diseases, n (%)	20 (18.3)	17 (15.5)	5 (4.6)	**0.014**
Cerebrovascular diseases, n (%)	31 (28.4)	20 (18.2)	23 (21.1)	0.183
Chronic liver diseases, n (%)	6 (5.5)	3 (2.7)	3 (2.8)	0.540
Hepatitis B, n (%)	3 (2.8)	3 (2.7)	2 (1.8)	1.000
Chronic kidney diseases, n (%)	4 (3.7)	14 (12.7)	10 (9.2)	**0.043**
Bronchiectasis, n (%)	2 (1.8)	3 (2.7)	2 (1.8)	1.000
Corticosteroids therapy, n (%)	80 (73.4)	90 (81.8)	101 (92.7)	**0.001**
Antibiotics therapy, n (%)	108 (99.1)	108 (98.2)	100 (91.7)	**0.013**
Antiviral therapy, n (%)	46 (42.2)	50 (45.5)	55 (50.5)	0.478
Anticoagulant therapy, n (%)	57 (52.3)	59 (53.6)	74 (67.9)	**0.015**
Systolic pressure (mmHg)	133.5±2.34	135.5±1.70	134.4±1.88	0.770
Diastolic pressure (mmHg)	77.6±1.32	79.7±1.14	80.1±1.09	0.299
PaO2 (mm Hg)	91.7±3.56	85.4±3.54	84.8±2.51	0.242
PaCO2 (mm Hg)	37.2±0.99	36.4±1.08	36.2±0.58	0.672
SpO2 (%)	94.5±0.52	93.5±0.71	93.7±0.57	0.515
FiO2 (%)	32.4±0.97	32.9±1.13	30.5±0.59	0.127
PaO2/FiO2 (%)	302.2±13.24	273.9±12.43	288.1±9.89	0.257
Severity stage, n (%)				0.195
Mild	3 (2.8)	5 (4.5)	1 (0.9)	
Moderate	16 (14.7)	20 (18.2)	11 (10.1)	
Severe	89 (81.7)	85 (77.3)	97 (89.0)	
WBC (10^9/L)	8.1±0.39	7.5±0.34	8.2±0.33	0.288
Neutrophil (10^9/L)	6.7±0.38	5.9±0.33	6.0±0.29	0.182
Lymphocyte (10^9/L)	0.9±0.06	1.0±0.06	1.5±0.14	**<0.001**
Monocyte (10^9/L)	0.5±0.02	0.5±0.03	0.6±0.04	0.086
ALT (U/L)	30.8±2.03	33.3±2.72	34.5±2.96	0.587
AST (U/L)	34.9±2.96	36.7±3.42	32.7±2.34	0.624
Uric acid (μmol/L)	216.0 (168.0, 294.0)	237.9 (193.0, 324.5)	256.0 (202.0, 329.3)	0.075
Urea nitrogen (mmol/L)	7.0 (5.4, 9.4)	6.3 (4.7, 8.8)	6.3 (5.0, 8.0)	0.179
Creatinine (μmol/L)	65.0 (55.7, 83.0)	67.0 (56.0, 85.0)	66.4 (54.3, 83.1)	0.736
CK (U/L)	62.0 (35.0, 89.0)	55.0 (34.8, 118.0)	46.0 (30.0, 69.0)	**0.038**
CK-MB (U/L)	12.0 (7.0, 20.0)	14.0 (7.0, 19.0)	11.0 (7.0, 18.0)	0.249
Myoglobin (ng/mL)	65.5 (34.7, 116.8)	94.3 (54.9, 448.8)	42.6 (25.3, 73.0)	**0.012**
LDH (U/L)	239.0 (177.8, 335.8)	257.0 (208.0, 337.0)	245.0 (194.0, 294.0)	0.404
D-Dimer (ng/mL)	0.84 (0.43, 2.22)	0.72 (0.36, 1.99)	0.60 (0.32, 1.31)	**0.022**
CRP (mg/L)	69.0±8.38	50.2±5.67	41.4±5.51	**0.012**
IL-6 (pg/mL)	29.3 (10.1, 96.6)	17.1 (6.0, 58.4)	13.3 (5.5, 50.7)	**0.049**
PCT (ng/mL)	0.09 (0.03, 0.43)	0.05 (0.03, 0.12)	0.04 (0.03, 0.11)	**0.001**

Note: Data in bold denote statistically significant results.

COP. In addition, the level of serum irisin was lowest in critical cases according to the 4C mortality score (Figure 1B). The CURB-65 score revealed that the level of serum irisin was lower in COVID-19 patients with scores of 3~5 than in those with scores of 0~1 and 2 (Figure 1C). Moreover, the concentration of serum irisin was compared in COVID-19 patients with different A-DROP scores. As shown in Figure 1D, the level of serum irisin was evidently lower in severe

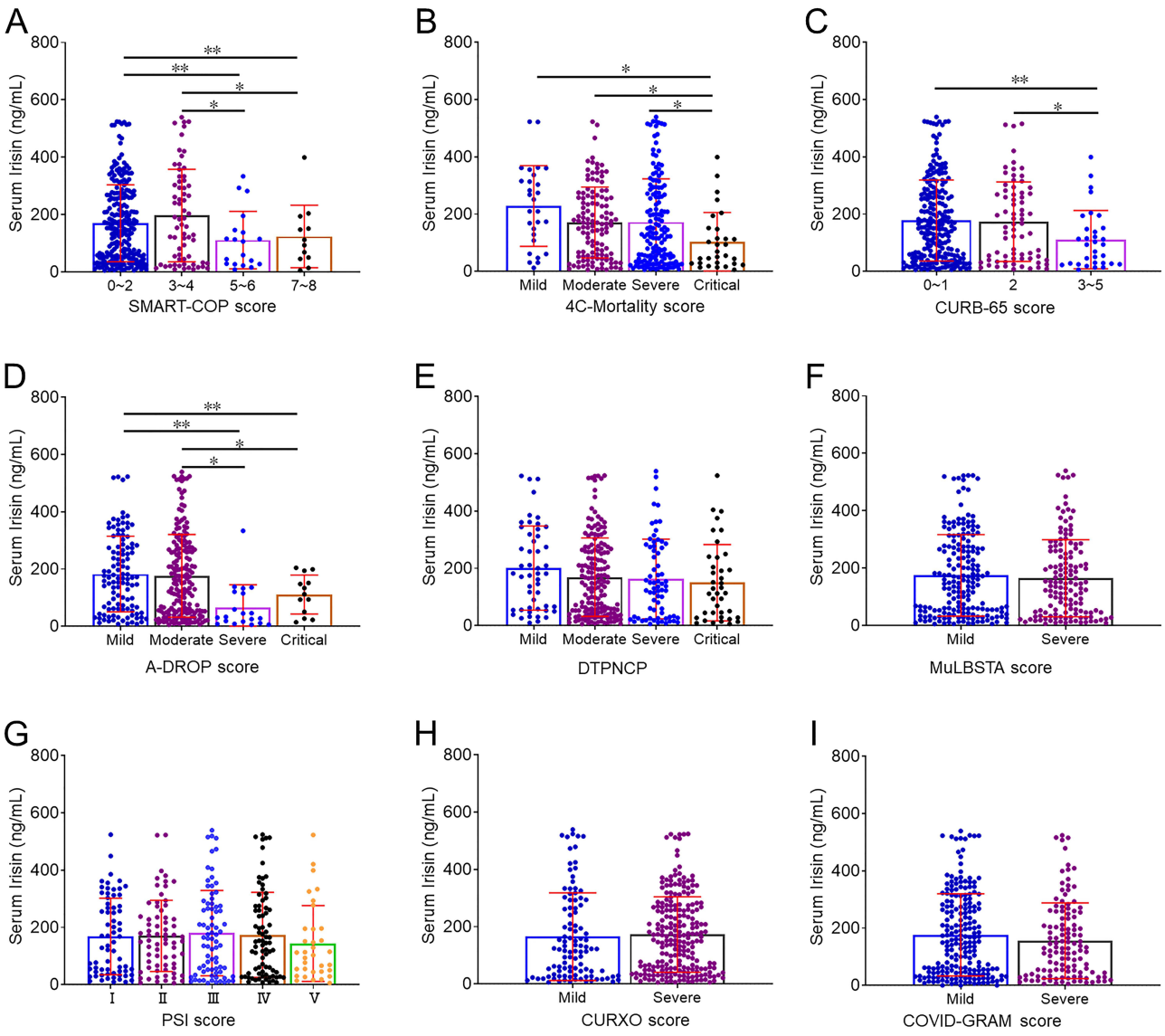

Figure 1 Serum irisin levels in COVID-19 patients with different disease severities. The concentration of serum irisin was determined by ELISA. (**A-I**) The differences in serum irisin levels were compared in COVID-19 patients with different severity scores. (**A**) SMART-COP score. (**B**) 4C-Mortality score. (**C**) CURB-65 score. (**D**) A-DROP score. (**E**) DTPNCP score. (**F**) MuLBSTA score. (**G**) PSI score. (**H**) CURXO score. (**I**) COVID-GRAM score. *P<0.05, **P<0.01.

and critical patients than in mild and moderate patients. Moreover, there was no difference in the serum irisin level among COVID-19 patients with different MuLBSTA, PSI, CURXO, COVID-GRAM, and DTPNCP scores (Figure 1E-I).

Relationships of Serum Irisin With Clinical Features in COVID-19 Patients

The relationships of serum irisin with clinical features in COVID-19 patients were evaluated via Spearman correlation coefficients. As shown in Figure 2, the serum irisin level was positively associated with the lymphocyte count (R=0.365; P<0.0001). In addition, serum irisin levels were inversely correlated with IL-6 (R=−0.234; P<0.01), CRP (R=−0.349; P<0.01), D-dimer (R=−0.401; P<0.01), and PCT (R=−0.462; P<0.0001) levels among COVID-19 patients (Figure 2).

Relationships of Serum Irisin With Disease Severity in COVID-19 Patients

The relationships of serum irisin with different severity scores were evaluated in COVID-19 patients. Multivariate linear regression analysis revealed that each 1 ng/mL increase was associated with a decrease in the SMART-COP score of

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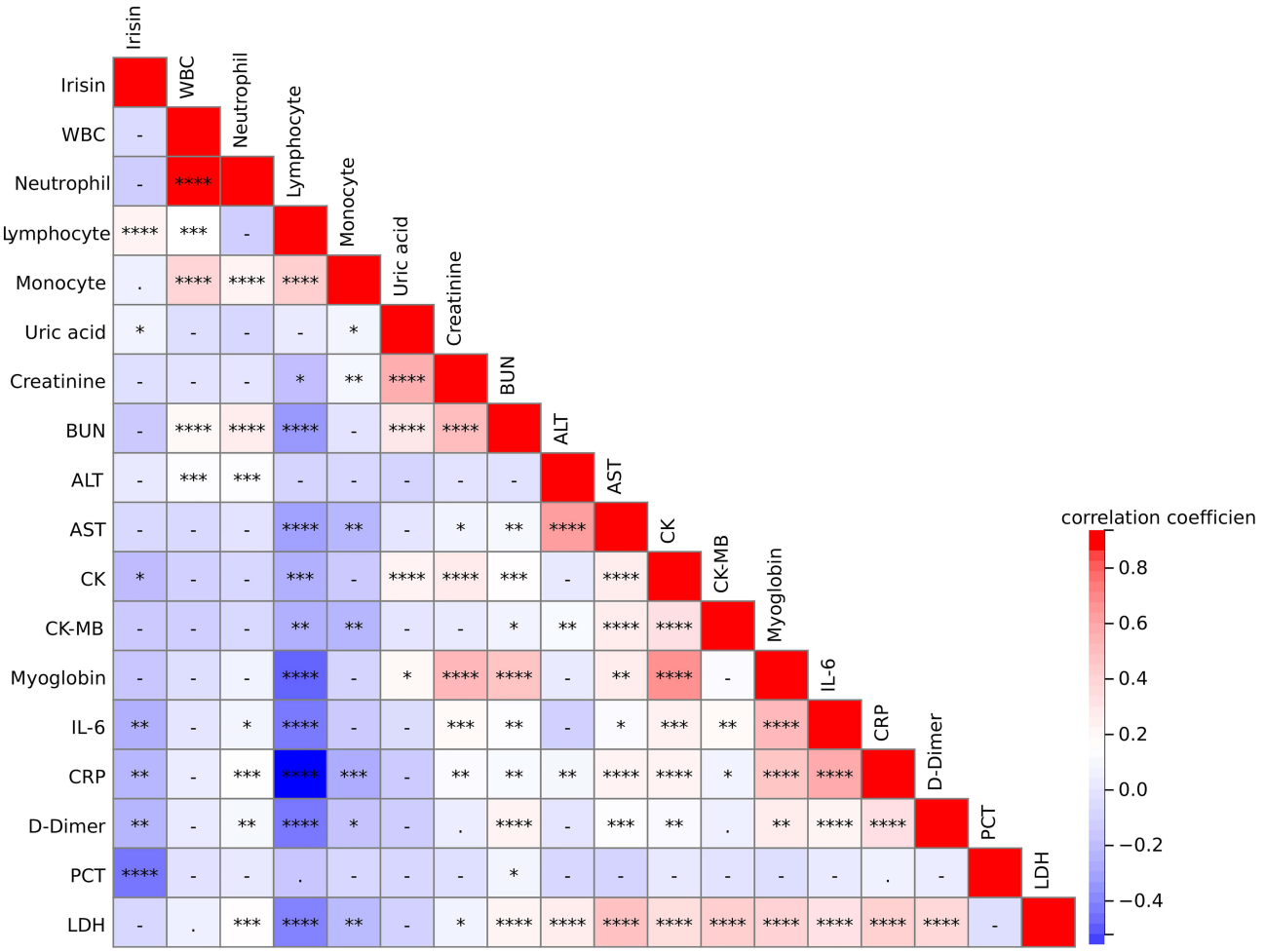

Figure 2 Relationships between serum irisin levels and the clinical characteristics of COVID-19 patients. The relationships between the serum irisin concentration and clinical characteristics were evaluated via Spearman correlation coefficients. Clinical characteristics mainly consisted of white blood cells (WBCs), neutrophils, lymphocytes, monocytes, uric acid, creatinine, blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), creatine kinase-MB (CK-MB), myoglobin, interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer, procalcitonin (PCT), and lactic dehydrogenase (LDH). Red represents a positive relationship, and blue represents a negative relationship. The darker the colour is, the stronger the correlation. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

0.086, the MuLBSTA score of 0.733, the A-DROP score of 0.139, and the 4C-mortality score of 0.942 (Table 2). Additionally, multivariate logistic regression analysis revealed that the level of serum irisin in the T3 subgroup was moderately inversely associated with the SMART-COP (OR=0.624; 95% CI: 0.282~0.983), MuLBSTA (OR=0.326; 95% CI: 0.146~0.728), and 4C-mortality (OR=0.315; 95% CI: 0.136~0.728) scores among COVID-19 patients. To exclude the effects of confounding factors on the associations, stratified analysis was conducted. As shown in Table 3, other chronic heart diseases and chronic kidney diseases significantly affected the associations between serum irisin with SMART-COP and 4C-mortality scores among COVID-19 patients.

Relationship Between Serum Irisin and Prognosis in COVID-19 Patients

As shown in Table 4, the number of deaths gradually increased in the T1 group compared with the T3 group among hospitalized COVID-19 patients. Compared with that in the T1 group, the number of deaths was dramatically lower in the T3 group (11 vs 2) among COVID-19 patients. In addition, confounding factors were eliminated. Multivariate logistic regression analysis further demonstrated that higher serum irisin levels reduced the risk of 30-day mortality (RR=0.423; 95% CI: 0.103~0.742) during hospitalization. The level of serum irisin was subsequently compared between non-survivors and survivors. As shown in Figure 3A, the serum irisin level at admission was decreased in non-survivors.

Table 2 Associations Between Serum Irisin and Severity in COVID-19 Patients

Variables	Estimated Changes by Continues Irisin (ng/mL)	Estimated Changes (95% CI) by Tertiles of Irisin (ng/mL)			*P* Trend
		T1 (<65.18)	T2 (65.18~210.84)	T3 (>210.84)	
N	328	109	110	109	
SMART-COP	**−0.086 (−0.468, 0.297)**	1.0 (Ref)	1.165 (0.561, 2.420)	**0.624 (0.282, 0.983)**	**0.042**
CURB-65	−0.090 (−0.282, 0.102)	1.0 (Ref)	0.693 (0.353, 1.363)	0.798 (0.399, 1.594)	0.667
CURXO (Severe)	0.047 (−0.055, 0.149)	1.0 (Ref)	0.728 (0.382, 1.387)	0.744 (0.385, 1.436)	0.460
COVID-GRAM	−1.191 (−12.579, 10.197)	1.0 (Ref)	1.234 (0.611, 2.490)	1.073 (0.515, 2.236)	0.676
MuLBSTA	**−0.733 (−1.663, 0.197)**	1.0 (Ref)	0.712 (0.361, 1.405)	**0.326 (0.146, 0.728)**	**0.014**
A-DROP	**−0.139 (−0.344, 0.067)**	1.0 (Ref)	0.633 (0.298, 1.345)	0.603 (0.308, 1.426)	0.504
PSI	4.804 (−3.562, 13.171)	1.0 (Ref)	0.434 (0.148, 1.269)	0.986 (0.304, 3.201)	0.890
4C-Mortality	**−0.942 (−1.492, −0.392)**	1.0 (Ref)	0.656 (0.303, 1.423)	**0.315 (0.136, 0.728)**	**0.019**
DTPNCP	−0.058 (−0.257, 0.140)	1.0 (Ref)	1.288 (0.687, 2.412)	1.158 (0.608, 2.203)	0.653

Notes: Models were adjusted for age, gender, smoker, hypertension, diabetes mellitus, coronary heart diseases, cerebrovascular diseases, chronic liver diseases, hepatitis B, chronic kidney diseases, and bronchiectasis. Data in bold denoted statistically significant results.

Table 3 Stratified Analysis for the Associations Between Serum Irisin and Severity Scores in COVID-19 Patients

Stratification Characteristic		SMART-COP	MuLBSTA	4C-Mortality
Gender				
	Male	−0.351 (−0.888, 0.186)	**−0.551 (−1.755, 0.652)**	**−1.150 (−1.962, −0.338)**
	Female	0.294 (−0.232, 0.820)	−1.078 (−2.670, 4.593)	**−0.568 (−0.514, 2.712)**
	$P_{interaction}$	0.205	0.136	0.325
Other chronic heart diseases				
	Yes	−0.041 (−0.929, 0.847)	**−1.292 (−3.446, 0.862)**	**−2.053 (−3.432, −0.673)**
	No	−0.648 (−2.692, 1.397)	−0.638 (−1.669, 0.393)	**−0.817 (−1.414, −0.220)**
	$P_{interaction}$	0.325	0.105	**0.036**
Chronic kidney diseases				
	Yes	**−0.576 (−3.267, 2.116)**	−0.465 (−6.007, 5.077)	**−0.333 (−3.305, 2.639)**
	No	**−0.096 (−0.484, 0.291)**	−0.684 (−1.646, 0.278)	−1.007 (−1.569, −0.446)
	$P_{interaction}$	**0.015**	0.098	0.207

Notes: Models were adjusted for age, gender, smoker, hypertension, diabetes mellitus, coronary heart diseases, cerebrovascular diseases, chronic liver diseases, hepatitis B, chronic kidney diseases, and bronchiectasis. Data in bold denoted statistically significant results.

Receiver operating characteristic (ROC) curve analysis revealed that the usefulness of admission serum irisin levels for predicting death was 0.602, and the serum irisin cut-off value was 115.4 ng/mL (Figure 3B).

Discussion

In the present epidemiological study, we mainly analysed the relationships of serum irisin levels with severity and poor prognosis among COVID-19 patients. The results primarily revealed that serum irisin levels were inversely related to the severity of COVID-19. In addition, the serum irisin concentration was strongly associated with many of the clinical characteristics of COVID-19 patients. The serum irisin concentration at admission was reduced in COVID-19 patients who died during hospitalization within one month. There was a negative correlation between the serum irisin concentration at admission and the risk of death among COVID-19 patients. These results suggest that irisin may be involved in the onset and pathogenesis of COVID-19.

Irisin is the cleaved form of FNDC5, which is expressed mainly in skeletal and cardiac muscle cells.[7,8] Most previous studies have demonstrated that irisin can confer antioxidant and anti-inflammatory effects.[12] In addition, several studies have revealed that irisin is involved in the development of many lung diseases.[13] In vivo and in vitro experiments have suggested that tumour necrosis factor alpha (TNF-α) exposure obviously reduces

Table 4 Associations Between Serum Irisin and Prognostic Outcomes in COVID-19 Patients

Variables	Serum Irisin (ng/mL)			*P*trend
	T1 (<65.18)	T2 (65.18~210.84)	T3 (>210.84)	
N	**109**	**110**	**109**	
Mechanical ventilation				
N, (%)	8 (7.3)	9 (8.2)	2 (1.8)	0.085
Adjusted RR (95% CI)	Ref (1.0)	2.021 (0.496, 8.238)	0.454 (0.088, 2.330)	0.300
Vasoactive agent				
N, (%)	6 (5.5)	9 (8.2)	3 (2.8)	0.224
Adjusted RR (95% CI)	Ref (1.0)	2.049 (0.503, 8.344)	0.457 (0.089, 2.347)	0.218
ICU admission				
N, (%)	10 (9.2)	9 (8.2)	5 (4.6)	0.375
Adjusted RR (95% CI)	Ref (1.0)	1.240 (0.379, 4.057)	0.399 (0.102, 1.557)	0.308
Death				
N, (%)	11 (10.1)	8 (7.3)	2 (1.8)	**0.030**
Adjusted RR (95% CI)	Ref (1.0)	1.122 (0.310, 4.065)	**0.423 (0.103, 0.742)**	**0.046**
Longer hospital stays				
N, (%)	26 (23.9)	25 (22.7)	16 (14.7)	0.186
Adjusted RR (95% CI)	Ref (1.0)	1.149 (0.551, 2.396)	0.432 (0.249, 1.235)	0.205

Notes: Models were adjusted for age, gender, smoker, hypertension, diabetes mellitus, coronary heart diseases, cerebrovascular diseases, chronic liver diseases, hepatitis B, chronic kidney diseases, bronchiectasis, corticosteroids therapy, antibiotics therapy, antiviral therapy, and anticoagulant therapy. Data in bold denoted statistically significant results.
Abbreviation: RR: Relative risk.

FNDC5 protein expression in skeletal muscle cells.[11] In addition, previous research revealed that the level of serum irisin is lower in COVID-19 patients than in healthy volunteers.[22] Due to the features of inflammatory disease in COVID-19 patients, SARS-CoV-2 infection may affect the expression of irisin in this group. The level of serum irisin was subsequently measured, and the correlation of serum irisin with COVID-19 severity was estimated. The results revealed that the concentration of serum irisin at admission was lower in severe patients than in mild patients. Moreover, the concentration of serum irisin gradually decreased with increasing severity of COVID-19. A case–control study also revealed that serum irisin was dramatically higher in healthy volunteers

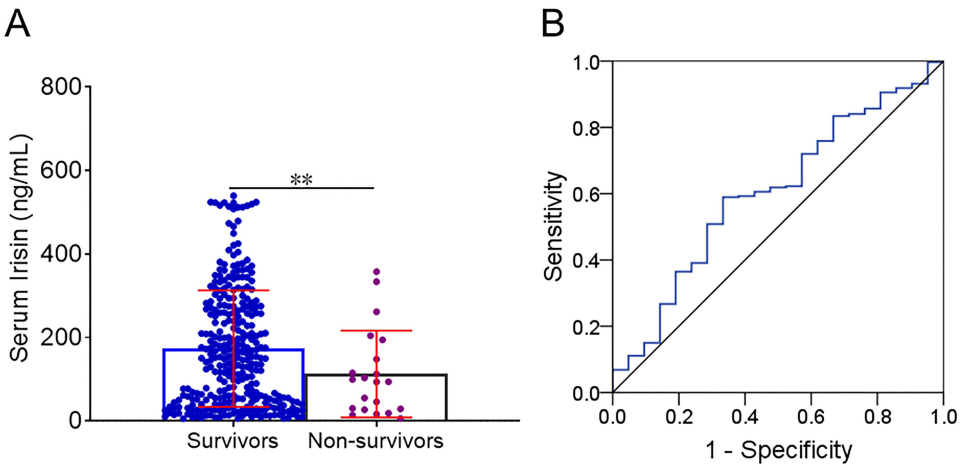

Figure 3 The predictive power of serum irisin for death among COVID-19 patients. The concentration of serum irisin was determined in COVID-19 patients on admission. (**A**) The levels of serum irisin was compared between survivors and non- survivors. (**B**) The predictive capacity of serum irisin for 30-day mortality was analyzed by ROC curve. $^{**}P < 0.01$.

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than in patients with chronic kidney diseases.[23] Moreover, the Spearman correlation analysis revealed that the concentration of serum irisin was inversely correlated with the lymphocyte count and the levels of IL-6, CRP, D-dimer, and PCT. Linear and logistic regression analyses further demonstrated that serum irisin levels at admission were inversely related to the severity of COVID-19. Several investigations have also confirmed that serum irisin levels are reduced and inversely associated with APACHE II scores in sepsis patients and with blood pressure in dialysis patients.[24,25] Interestingly, stratified analysis revealed that the presence of chronic heart and kidney diseases affected the relationship between serum irisin levels and disease severity in COVID-19 patients. A search of the related literature revealed that irisin is involved in the pathological process of cardiovascular and renal diseases.[26–28] These findings explain why there were interaction effects of chronic heart and kidney disease status on the association between COVID-19 severity and serum irisin levels. Moreover, the serum irisin concentration is negatively correlated with disease severity in patients with Parkinson's disease,[29] coronary artery disease,[30] and obstructive sleep apnoea.[31] Overall, irisin participates in the pathogenesis of COVID-19 and can be used to evaluate COVID-19 severity in patients with many diseases.

Previous investigations have indicated that irisin measurements can help with disease diagnosis. Additionally, a growing number of studies have shown that the expression level of irisin is strongly correlated with the prognosis of many systemic diseases. A clinical trial revealed that a low serum irisin concentration can predict poor short-term outcomes in patients with stroke.[32] Moreover, higher serum irisin levels are strongly related to insulin resistance in patients with acne vulgaris.[33] Furthermore, decreased serum irisin levels are associated with a lower event-free survival rate in coronary artery disease patients after percutaneous coronary intervention.[34] Consequently, we believe that the serum irisin concentration may be used to assess the clinical outcomes of patients with COVID-19. The relationship between serum irisin levels and COVID-19 prognosis was subsequently evaluated during hospitalization. Our results revealed that the number of deaths increased within one month of hospitalization. Logistic regression analysis confirmed that low serum irisin levels upon admission increased the risk of death in COVID-19 patients. However, a prospective study revealed that the level of serum irisin at admission is similar between cured COVID-19 patients and patients who died.[15] This conclusion was inconsistent with our research. However, that study included only 59 COVID-19 patients. The large difference in sample sizes may have caused the different results. Therefore, the results of the present study strongly demonstrate that a lower level of serum irisin at admission predicts death within one month in hospitalized COVID-19 patients.

In summary, the results of the present study indicated that the serum irisin level is negatively correlated with the severity and prognosis of COVID-19 patients. However, several limitations exist in this research. First, this was a small sample study, and these findings need to be confirmed in a larger sample. Second, all the samples were obtained from the Second Affiliated Hospital of Anhui Medical University. Additional patients should be recruited from multiple hospitals and medical centers. Third, the circulating level of serum irisin was only measured in COVID-19 patients. The local expression of irisin in lung tissues is not known. Fourth, the mechanism by which SARS-CoV-2 infection causes a decrease in irisin in COVID-19 patients could not be measured in the present epidemiological study. The specific mechanism should be analyzed in animal and cellular experiments. Fifth, the previous studies have confirmed liver diseases, heart diseases,[35] kidney diseases,[36] and exercise[37] can affect the expression of irisin. Therefore, the current study cannot fully overcome the influence of other confounding factors on the level of serum irisin in COPVID-19 patients. The above results demonstrated that serum irisin concentration was inversely correlated with disease severity and risk of death among COVID-19 patients. In addition, many animal experiments have shown that supplementation with irisin can alleviate neuroinflammation and neuronal apoptosis,[38] liver inflammation,[39,40] acute lung injury,[41] type 1 diabetic cardiomyopathy,[42] and so on. These data suggest that irisin supplementation may attenuate COVID-19 or other inflammatory lung diseases. However, this investigation was only an observational study. More animal and cellular experiments can address these questions and reveal the exact role of irisin in COVID-19 patients.

Conclusions

This prospective cohort study revealed a negative correlation between serum irisin levels and the severity of COVID-19. Low serum irisin levels upon admission increase the risk of poor prognosis in COVID-19 patients. These results show that irisin is involved in the pathological process of COVID-19, indicating that serum irisin levels can be used as a biomarker for disease assessment and death prediction in COVID-19 patients. The current results should be further replicated and verified in another cohort.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Approval for this research was obtained from the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (YX2021-147). All patient data were confidential, and we complied with the Declaration of Helsinki.

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Author Contributions

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