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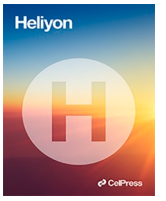

Research article

# Predictive value of hematocrit, serum albumin level difference, and fibrinogen-to-albumin ratio for COVID-19-associated acute respiratory failure

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A R T I C L E I N F O

*Keywords:*
COVID-19
qCSI (quick COVID-19 severity index)
Fibrinogen-to- albumin ratio
Hematocrit
Serum albumin levels difference

A B S T R A C T

*Background:* Acute respiratory failure is the main clinical manifestation and a major cause of death in patients with COVID-19. However, few reports on its prevention and control have been published because of the need for laboratory predictive indicators. This study aimed to evaluate the predictive value of hematocrit level, serum albumin level difference, and fibrinogen-to-albumin ratio for COVID-19-associated acute respiratory failure.

*Material and methods:* A total of 120 patients with COVID-19 from the First Affiliated Hospital of Anhui Medical University were selected between December 2022 and March 2023. Patients were divided into acute respiratory failure and non-acute respiratory failure groups and compared patient-related indicators between them using univariate and multivariate logistic regression analyses. Receiver operating characteristic analysis was performed to determine the discrimination accuracy.

*Results:* In total, 48 and 72 patients were enrolled in the acute respiratory failure and non-acute respiratory failure groups, respectively. The Quick COVID-19 Severity Index scores, fibrinogen-to-albumin ratio, hematocrit and serum albumin level difference, fibrinogen, and hematocrit levels were significantly higher in the acute respiratory failure group than in the non-acute respiratory failure group. A Quick COVID-19 Severity Index >7, fibrinogen-to-albumin ratio >0.265, and hematocrit and serum albumin level difference >12.792 had a 96.14 % positive predictive rate and a 94.06 % negative predictive rate.

*Conclusion:* Both fibrinogen-to-albumin ratio and hematocrit and serum albumin level difference are risk factors for COVID-19-associated acute respiratory failure. The Quick COVID-19 Severity Index score combined with fibrinogen-to-albumin ratio, and hematocrit and serum albumin level difference predict high and low risks with better efficacy and sensitivity than those of the Quick COVID-19 Severity Index score alone; therefore, these parameters can be used collectively as a risk stratification method for assessing patients with COVID-19.

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## 1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic is a lethal viral outbreak caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The clinical presentations of COVID-19 are heterogenous, including fever, cough, expectoration, chest tightness, shortness of breath, and diarrhea. Approximately 10 % of patients with COVID-19 worldwide exhibit long-term infection [1]; some patients may develop persistent post-COVID-19 syndrome [2], which poses unprecedented challenges to healthcare systems and the global economy. Owing to the rapid and effective transmission of SARS-CoV-2, the COVID-19 pandemic has affected millions of people and caused hundreds of thousands of deaths [3]. While most patients with COVID-19 develop mild-to-moderate symptoms, up to 20 % of patients rapidly progress to respiratory failure [4–6]. Patients with COVID-19 who have severe or critically severe illness are prone to multiple organ failure, which increases their risk of death [7].

China has been severely affected by the COVID-19 pandemic, especially between the end of 2022 and the beginning of 2023. Studies conducted in China during the early stages of the pandemic have shown that severe disease and unfavorable prognosis were associated with comorbidities such as hypertension, diabetes, obesity, asthma, chronic obstructive pulmonary disease (COPD), and advanced age [8,9]. Data from studies in Italy showed that more than two-thirds of those who died of COVID-19 had diabetes [10], and that COVID-19 and diabetes were associated with aggravated inflammatory reactions [11]. One study showed that 85 % of patients with COVID-19 and obesity required mechanical ventilation and 62 % died [12]. Given the millions of confirmed cases worldwide, a thorough understanding of the risks and protective factors associated with COVID-19 is crucial to prevent disease transmission, progression, and unfavorable patient outcomes.

Current evidence suggests that the risk factors for COVID-19 in adults include: demographic factors such as advanced age, male sex, and ethnicity; and the presence of underlying diseases such as cardiovascular diseases, hypertension, and COPD [13]. Although rapid diagnostic techniques continue to improve [14], acute respiratory failure (ARF) remains a major life-threatening condition; early identification of high-risk patients is critical to implement evidence-based prevention strategies that improve patient outcomes. Quick COVID-19 Severity Index (qCSI) and CURB-65 (consciousness, uremia, respiratory rate, blood pressure, age $\geq$65 years) scores can be used to predict the progression to respiratory failure within 24 h. A retrospective study of 1,919 patients with COVID-19 confirmed that the qCSI score was more convenient than the CURB-65 score for screening the severity of COVID-19 severity in the emergency department [15–17], albeit with low sensitivity and specificity. Identifying rapid, easily accessible, reliable, highly sensitive, and affordable biomarkers is crucial to assess and treat COVID-19.

Currently, the laboratory indicators for evaluating disease severity are not fully understood. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios can predict the severity of COVID-19 [18]; however, they these parameters are not impractical in patients with granulocytopenia caused by immunosuppression. Hematocrit and serum albumin level differences (HCT-ALB) can predict poor prognosis in patients with infectious diseases, although no relevant research has been conducted on However, its predictive capability in patients with COVID-19 is unknown. The fibrinogen-to-albumin ratio (FAR) is a novel inflammatory marker associated with mortality in patients with sepsis, cardiovascular disease, cancer, or ischemic stroke, and is especially useful for guiding risk stratification and developing personalized treatment in patients with acute coronary syndrome [19]. Several researchers have suggested that elevated FAR is associated with the severity of COVID-19 and risk of death [20]. However, its utilization as a risk stratification biomarker for COVID-19 pneumonia and for predicting prognosis remains to be confirmed.

The COVID-19 pandemic is characterized by high mortality and uncertain disease progression; identifying the relationships of FAR and HCT-ALB with COVID-19-associated ARF is crucial to rapidly and accurately evaluate disease progression. In this study, we aimed to identify the high-risk factors that for predicting COVID-19-associated ARF within 24 h in patients with early-stage disease—so that emergency doctors can accurately grade and treat and improve the survival rate of patients with COVID-19.

## 2. Material and methods

### 2.1. General material

Consecutive patients who had been diagnosed with COVID-19 using reverse transcription-PCR from a nasopharyngeal swab were treated in the intensive care unit and the general ward of the First Affiliated Hospital of Anhui Medical University in China between December 2022 and February 2023. Patients were classified into non-ARF ($n$ = 72) and ARF groups ($n$ = 48) according to their requirement of high-flow noninvasive ventilation or invasive mechanical ventilation. This study included 74 males and 46 females. The average age of patients with ARF was 68.142 $\pm$ 15.701 years, and that of patients without ARF was 60.967 $\pm$ 18.674 years.

### 2.2. Clinical data collection

We analyzed clinical and laboratory data, including age, sex, body mass index (BMI), chronic underlying disease, and 28-day survival. At admission, the patients underwent the following: pulmonary computed tomography (CT); detection of SARS-CoV-2 RNA; and routine tests for levels of hematocrit (HCT), plasma fibrinogen (FIB), blood urea nitrogen (BUN), alanine transaminase, aspartate transaminase, and serum albumin (ALB). The qCSI indexes [17] included respiratory rate, oxygen flow rate, and $SpO_2$; the values of these parameters were at their worst within 4 h of admission.

We defined ARF as $PO_2 < 60$ mmHg with or without $PCO_2 > 50$ mmHg, and requiring high-flow, noninvasive, or invasive mechanical ventilation within 24 h of admission. The following patients were excluded: (1) patients who had received antiviral treatment; (2) those of age <18 years; (3) those who underwent massive fluid infusion; (4) those with ARF caused by cardiogenic pulmonary

edema, pleural effusion, or atelectasis; (5) those requiring oxygen at >6 L/min; and (6) those with ARF within 4 h of admission.

This study adhered to the ethical standards of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. This compliance underscores our commitment to ethical research practices.

### 2.3. Sample size estimation and statistical methods

According to previous clinical data, the mortality rates of patients with COVID-19-associated ARF and those without were 52.4 % and 15 %, respectively. In this study, a statistical power of 0.8 and a types I error probability of 0.05 were set; the absolute differences in detectable mortality were calculated for 20 patients in the ARF group and 30 patients in the non-ARF group (on a ratio of 1–1.5).

Statistical analyses were performed using SPSS statistical software (version 22; IBM Corporation, Armonk, NY, USA) and GraphPad Prism (version 8.0.2; GraphPad Software, USA). Measurement data conforming to a normal distribution were expressed as mean ± standard deviation (x ± s). In contrast, non-normal measurement data are expressed as median and interquartile intervals (M [P25 and P75]), and count data are expressed as frequencies or percentages. Variables were explored in a univariate analysis using Pearson's chi-square or Fisher's exact tests for categorical variables and Student's *t*-test or Mann–Whitney *U* test for continuous variables; variables with a *P*-value <0.05 were considered statistically significant.

## 3. Results

### 3.1. Baseline characteristics

A total of 120 patients with COVID-19 were enrolled, of whom 72 and 48 were classified into the non-ARF and ARF groups, respectively. The ARF group had a higher proportion of male patients (70.8 % vs 55.6 %) and patients with type 2 diabetes (37.5 % vs 13.9 %), those with immunosuppression (31.2 % vs 13.9 %), and those with renal dialysis disease (22.9 % vs 11.1 %). The ARF group exhibited greater age, higher qCSI scores, and higher mortality than the non-ARF group. Moreover, the ARF group exhibited elevated serum FIB levels, higher FAR, increased HCT and HCT-ALB, and lower serum ALB levels than the non-ARF group. We observed no significant differences in BMI; serum levels of BUN, hypersensitive-*c*-reactive-protein (Hs-CRP), and procalcitonin (PCT); and prevalence of heart disease, hypertension, and COPD between the two groups (Table 1).

### 3.2. Risk factors for ARF

ARF in patients with COVID-19 was used as the dependent variable (yes = 1; no = 0). Variables with a *P*-value <0.05 in the univariate analysis (Table 2) were used as independent variables to establish a multifactor analysis model. Further multiple regression

**Table 1**
Basic characteristics of patients with COVID-19.

| Characteristic | ARF (n = 48) | non-ARF (n = 72) | *P*-value |
|---|---|---|---|
| Sex (male/female) | 34/14 | 40/32 | 0.022 |
| Age (years) | 68.142 ± 15.701 | 60.967 ± 18.674 | 0.006 |
| BMI (kg/m$^2$) | 18.523 ± 5.701 | 20.34 ± 3.215 | 0.532 |
| Respiratory rate (breaths/min) | 27.134 ± 4.461 | 21.892 ± 3.235 | 0.036 |
| Oxygen flow rate (L/min) | 4.154 ± 0.862 | 2.081 ± 0.501 | 0.041 |
| Pulse oximetry (%) | 93.778 ± 1.516 | 95.035 ± 1.204 | 0.052 |
| Heart disease; n (%) | 5 (10.4) | 7 (9.7) | 0.654 |
| Hypertension; n (%) | 10 (20.8) | 16 (22.2) | 0.553 |
| Diabetes (type 2/type 1); n | 18/4 | 10/5 | <0.001 |
| COPD; n (%) | 12 (25.0) | 17 (23.6) | 0.627 |
| ISP; n (%) | 15 (31.3) | 10 (13.9) | 0.003 |
| Renal dialysis; n (%) | 11 (22.9) | 8 (11.1) | 0.027 |
| FIB (g/L) | 9.933 ± 3.315 | 5.523 ± 1.775 | 0.003 |
| HCT | 46.824 (30.704,55.720) | 38.457 (30.646,45.320) | 0.013 |
| ALB (g/L) | 26.054 ± 5.061 | 30.553 ± 4.822 | 0.036 |
| BUN (μmol/L) | 11.564 (6.463, 20.753) | 10.260 (7.729, 15.154) | 0.135 |
| AST (u/L) | 36.253 ± 6.713 | 33.263 ± 5.081 | 0.082 |
| ALT (u/L) | 38.503 ± 7.601 | 35.708 ± 4.431 | 0.152 |
| PCT (ng/mL) | 1.228 (0.160,2.750) | 0.830 (0.042,2.305) | 0.106 |
| hs-CRP (mg/L) | 94.210 (40.652,180.725) | 80.037 (20.107,120.065) | 0.052 |
| FAR | 0.464 ± 0.148 | 0.258 ± 0.174 | 0.023 |
| HCT-AlB | 14.234 ± 2.168 | 9.340 ± 1.843 | <0.001 |
| qCSI scores | 6.958 ± 2.457 | 4.652 ± 2.243 | 0.004 |
| In-hospital mortality; n (%) | 25 (50.083 %) | 10 (13.888 %) | <0.001 |

BMI, body mass index; FAR, fibrinogen-to-albumin ratio; FIB, fibrinogen; ALB, albumin; HCT, hematocrit; HCT-ALB, hematocrit and serum albumin level difference; qCSI, Quick COVID-19 Severity Index; ALT, alanine transaminase; AST, aspartate transaminase; PCT, procalcitonin; Hs-CRP, hypersensitive-*c*-reactive-protein; ISP, immunosuppressed patients: systemic lupus erythematosus, rheumatoid arthritis, malignancy, transplantation, and immunosuppressive therapy.

**Table 2**
Assignment table.

| Variable | Assignment |
|---|---|
| Age | Continuous variables |
| FAR | Continuous variables |
| FIB | Continuous variables |
| ALB | Continuous variables |
| HCT | Continuous variables |
| HCT-ALB | Continuous variables |
| qCSI scores | Continuous variables |
| Diabetes | Yes = 1, No0 = 0 |
| Immune system diseases | Yes = 1, No0 = 0 |
| Renal dialysis | Yes = 1, No0 = 0 |

FAR, Fibrinogen-to-albumin ratio; FIB, fibrinogen; ALB, albumin; HCT, hematocrit; HCT-ALB: hematocrit and serum albumin levels difference; qCSI, Quick COVID-19 Severity Index.

analysis of the variables showed that serum FIB levels, HCT-ALB, FAR, and qCSI scores were independent risk factors, and serum ALB level was a protective factor against ARF in patients with COVID-19 ($P < 0.05$; Table 3).

### 3.3. Analysis of correlation between independent predictors and qCSI scores

Serum FAR levels, HCT-ALB, and FIB positively correlated with qCSI scores ($rs = 0.766$,0.740 and 0.551, respectively; $P < 0.0001$) (Fig. 1A–C), whereas ALB levels negatively correlated with qCSI scores ($rs = -0.523$; $P < 0.0001$) (Fig. 1 D).

### 3.4. Receiver operating characteristic curve analysis of predictive indicators in patients with COVID-19 complicated with ARF

The predictors of ARF were used to draw receiver operating characteristic (ROC) curves (Table 4 and Fig. 2). The areas under the curves of FIB, ALB, FAR, HCT-ALB, qCSI, and qCSI + FAR + HCT-ALB were 0.805, 0.614, 0.840, 0.814, 0.756, and 0.916, respectively. The sensitivities were 68.72 %, 21.23 %, 91.42 %, 68.92 %, 60.54 %, and 91.50 %, respectively, while the specificities were 88.53 %, 58.04 %, 75.41 %, 83.33 %, 80.62 %, and 81.05 %, respectively. The cutoff values of FIB, ALB, FAR, HCT-ALB, and qCSI scores were 6.452, 30.156, 0.265, 12.792, and 7, respectively. The positive predictive values were 23.34 %, 34.67 %, 78.09 %, 83.54 %, 67.87 %, and 96.14 % while the negative predictive values were 76.70 %, 67.45 %, 69.49 %, 67.97 %, 52.05 %, and 94.06 %.

## 4. Discussion

COVID-19 is an acute respiratory infectious disease caused by SARS-CoV-2. Researchers have extensively studied the origin, pathogenesis, diagnosis, and treatment of the disease over the past two years; however, no specific antiviral drug has been established yet. Patients with COVID-19 lack typical clinical manifestations, and the disease can progress rapidly to respiratory failure, septic shock, coagulopathy, and bleeding. Progression to severe or critically severe disease can result in concurrent multiple organ failure, which increases the risk of death [7]. In clinical practice, early identification of patients with ARF prevents disease progression and improves prognosis.

In this study, patients with COVID-19 and ARF were significantly older than those without ARF. Therefore, an advanced age is a risk factor for severe and critical COVID-19 pneumonia [21]. Greater age is associated with increased susceptibility to COVID-19 pneumonia [22]. Older patients with COVID-19 are prone to poor outcomes because of the following reasons: (1) they often have more

**Table 3**
Univariate and multivariate logistic regression analyses of independent predictors for COVID-19–associated ARF.

| Variables | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | OR | 95%CI | *P*-value | OR | 95%CI | *P*-value |
| FAR | 1.739 | 1.209–3.377 | 0.023 | 1.835 | 1.092–2.897 | <0.001 |
| Age | 2.925 | 1.095–12.425 | 0.002 | 3.045 | 1.307–10.504 | 0.053 |
| HCT | 1.415 | 1.043–4.742 | 0.034 | 1.653 | 1.223–3.625 | 0.082 |
| FIB (g/L) | 5.023 | 1.625–8.349 | 0.006 | 4.659 | 1.307–6.874 | 0.009 |
| ALB (g/L) | 0.882 | 0.730–0.974 | 0.046 | 0.760 | 0.557–0.893 | 0.006 |
| HCT-ALB | 6.305 | 2.624–8.721 | 0.017 | 8.652 | 2.624–9.721 | <0.001 |
| qCSI | 3.230 | 0.876–6.408 | 0.006 | 2.986 | 1.097–10.524 | <0.001 |
| Diabetes | 1.758 | 0.883–3.308 | 0.113 | – | – | 0.140 |
| Immune system diseases | 2.205 | 0.681–7.093 | 0.105 | – | – | 0.421 |
| Renal dialysis | 1.684 | 0.647–2.745 | 0.058 | – | – | 0.332 |

FAR, fibrinogen-to-albumin ratio; FIB, fibrinogen; ALB, albumin; HCT, hematocrit; HCT-ALB, hematocrit and serum albumin level difference; qCSI, Quick COVID-19 Severity Index; CI, confidence interval; OR, odds ratio.

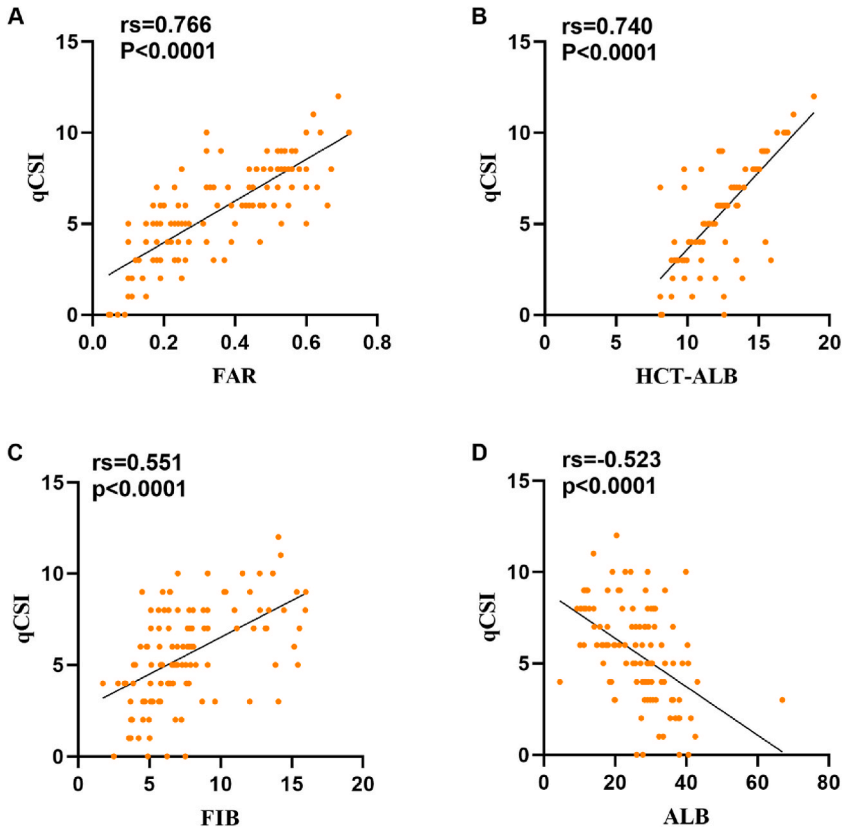


**Fig. 1.** Analysis of the relationship between (A) FAR, (B) HCT-ALB, (C) FIB, (D) ALB levels and qCSI scores FIB, fibrinogen; HCT-ALB, hematocrit and serum albumin level difference; FAR, fibrinogen-to-albumin ratio; ALB, albumin; qCSI, Quick COVID-19 Severity Index.

**Table 4**
Analysis of the predictive value of independent predictors on ARF.

| Variables | AUC | Cut point | Specificity (%) | Sensitivity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|
| FIB | 0.805 | 6.452 | 88.53 | 68.72 | 23.34 | 76.07 |
| ALB | 0.614 | 30.156 | 58.04 | 21.23 | 34.67 | 67.45 |
| FAR | 0.840 | 0.265 | 75.41 | 91.42 | 78.09 | 69.49 |
| HCT-ALB | 0.814 | 12.792 | 83.33 | 68.92 | 83.54 | 67.97 |
| qCSI scores | 0.756 | 7 | 80.62 | 60.54 | 67.87 | 52.05 |
| qCSI + FAR + HCT-ALB | 0.916 | – | 81.05 | 91.50 | 96.14 | 94.06 |

AUC, area under the receiver operating characteristic curve; FAR, fibrinogen-to-albumin ratio; FIB, fibrinogen; ALB: albumin; HCT-ALB, hematocrit and serumalbumin level difference; qCSI, Quick COVID-19 Severity Index.

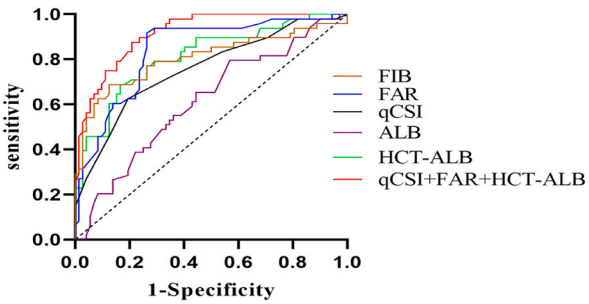


**Fig. 2.** ROC curves predicting acute respiratory failure in patients with COVID-19.

comorbidities and decreased organ reserve function; (2) their immune system is weaker against chronic proinflammatory states associated with infectious diseases and aging, and persistently low innate immune activation may increase tissue damage from infection; and (3) they demonstrate elevated levels of proinflammatory cytokines, which leads to disease development [23].

Among patients with COVID-19, men are more likely to be seriously affected and more probable to develop ARF during disease progression. Men account for 61 % of patients with severe COVID-19 [24] and are at a higher risk of death from the disease than women [25]. Immunity in men is weakened by genetic and hormonal factors [23], and normal plasma testosterone levels may promote SARS-CoV-2 entry into host cells and its systemic transmission [26,27]. In addition, infection-prone lifestyle factors (such as smoking) can increase the levels of angiotensin-converting enzyme 2 (ACE2) in the pulmonary vascular endothelia, which may predispose patients with COPD to rapid COVID-19 progression [28]. These factors may explain increased COVID-19 severity in male patients.

Diabetes is one of the most common comorbidities among critically ill patients with COVID-19; patients with diabetes and COVID-19 often present with serious symptoms and rapidly progressing disease [29]. Our findings indicate that diabetes is a high-risk factor for early respiratory failure in patients with COVID-19. The inflammatory response is more amplified in patients with SARS-CoV-2 and diabetes than in those without diabetes; consequently, proinflammatory cytokines (TNF-α,IL-1β,IL-6, IL-8, and IFN-γ) are released in the blood in large quantities [30]. A cytokine storm is particularly significant in patients with type 2 diabetes [31,32]. SARS-CoV-2 enters alveolar cells via ACE2, triggering the release of inflammatory factors that activate macrophages in alveolar tissue. The induction factors and chemokines released by macrophages cause mononuclear cells to accumulate in the lung tissue. Extreme infiltration of inflammatory cells induces cytokine storms, leading to acute lung injury and acute respiratory distress syndrome [33]. Additionally, patients with diabetes and COVID-19 experience excessive activation of the coagulation system, microthrombus formation, and stagnation of pulmonary circulation, which result in decreased oxygenation. Jon et al. proposed that patients with type 2 diabetes are at high risk of severe COVID-19 and therefore increase the ICU occupancy rate [34]. Patients with type 2 diabetes exhibit high levels of ACE2 receptors, which may extend the cell-binding period of SARS-CoV-2 and increase the viral load and infection severity [35]. Our study found that patients with type 2 diabetes are more likely to be infected with COVID-19 and develop ARF than those with type 1 diabetes. Future studies are required to confirm increased mortality due to COVID-19 in patients with type 2 diabetes.

The incidence of COVID-19 in patients with long-term kidney disease is extremely high, especially in those undergoing dialysis and kidney transplantation because of impaired immune function. Compared with the general population, patients with COVID-19 have a greater risk of admission and death [36]. Moreover, this study revealed that the presence of renal failure is a high-risk factor for progression to severe COVID-19.

FIB, which promotes platelet aggregation, increases plasma viscosity, and causes red blood cell aggregation, is a reactive protein whose levels increase during the acute phase of systemic inflammation [37]; serum FIB levels may reflect the severity of the systemic inflammatory response [38]. A meta-analysis revealed that elevated FIB levels were a risk factor for poor outcomes in patients with COVID-19 [39,40]. The current study found that FIB is a high-risk factor for ARF in patients with COVID-19 infection. Fibrinogen is a precursor of fibrin and is involved in thrombus formation. Increased serum FIB levels can cause formation of microthrombi, which is directly associated with ARF.

Albumin, the most abundant plasma protein synthesized in the liver, accounts for 40%–60 % of total plasma protein. It not only maintains colloid osmotic pressure in blood vessels but also has antioxidant, anti-inflammatory, anticoagulant, and antiplatelet aggregation activities [41]. Serum albumin can bind to various inflammatory mediators such as lipopolysaccharide and other bacterial antigens and alleviate endodermatitis by inhibiting the adhesion of inflammatory cells to endothelial cells [42,43]. In patients with severe infections, circulating serum ALB levels decrease with progressive inflammation [43]. The amino acid Cys-34 in albumin may cause antithrombotic effects by binding to nitric oxide and forming *S*-nitroso albumin. Hypoproteinemia not only aggravates the inflammatory response but also causes endothelial dysfunction, weakens antithrombotic effects, and increases blood viscosity [44]. Violi et al. reported that in patients with severe SARS-CoV-2 infection, serum ALB levels may be associated with hypercoagulability, which leads to disease progression and increased mortality [45]; therefore, serum ALB level may be an independent predictor of poor prognosis in patients with COVID-19 [46]. Hu et al. proposed that the interaction between the SARS-CoV-2 surface spike protein (S1) and ACE2 receptor contributes to viral particle penetration and replication in host cells [47]. Due to the high expression of ACE2 in the lungs, SARS-CoV-2 is more likely to infect large numbers of cells in the lungs and cause respiratory distress. In addition, albumin may be further oxidized into human non-mercaptoalbumin, which induces activated white blood cells in the lungs to synthesize inflammatory cytokines to regulate platelets and promote inflammation [48] and result in a cytokine storm, leading to ARF. Studies have shown that in patients with acute respiratory distress syndrome, after 24 h of albumin treatment, arterial blood gas parameters appear to improve. The ratio of oxygen partial pressure to inhaled oxygen fraction, which persists for at least seven days [49], may be related to albumin-specific binding of the SARS-CoV-2 S1 subunit and subsequent downregulated expression of the ACE2 receptor. Cekic et al. found that the integration of serum levels of ALB and FIB with the FAR value correlated with the severity of COVID-19 pneumonia at a higher predictive value than those of serum levels of ALB or FIB alone [50]. Moreover, this study found that FAR can effectively predict the progression of COVID-19 pneumonia with respiratory failure with a prediction efficiency that was better than that of ALB and FIB as independent laboratory indicators. The increase in FAR can not only reflect the uncontrolled inflammatory response and disturbed coagulation function but also has higher sensitivity and accuracy in predicting acute respiratory failure complicated by single FIB and ALB, with fewer influencing factors and more clinical practical value. Therefore, FAR can be used as a biomarker of acute respiratory failure in COVID-19.

Patients with COVID-19 demonstrate high metabolism, and most exhibit gastrointestinal dysfunction with impaired liver function, which increases albumin consumption and synthesis disorders and decreases serum albumin levels. Inflammatory factors damage the endothelium, which increases capillary leakage. This results in serum albumin and massive fluid spill, and reduced effective blood volume. Since the diameter of red blood cells is larger than that of the endothelium (6–7 nm in diameter) [51,52], the red blood cells

cannot pass through the endothelium, which results in increased HCT value. Differences in HCT and serum ALB levels are associated with poor outcomes in patients with sepsis [53]. No relevant research has been conducted on the infection of COVID-19 with HCT-ALB, however, our study found that in patients with COVID-19, HCT-ALB is an independent risk factor for ARF and is positively correlated with qCSI score. In patients with a high qCSI score, the difference between HCT and ALB significantly increased, and the increased HCT-ALB may be related to an uncontrolled inflammatory factor storm. When HCT-ALB was >12.792, the positive prediction rate for ARF was as high as 83.54 %; its accuracy, sensitivity, and positive predictive value was higher when combined with FAR and qCSI scores. In clinical practice, we found that the qCSI score may produce bias in statistical outcomes owing to the discontinuity of monitoring indicators with lower sensitivity. Combining the qCSI score with laboratory indicators can not only reduce bias and improve diagnostic sensitivity and specificity but also has advantages of being fast, cheap, easy to obtain, and having greater clinical value. For patients with COVID-19 whose qCSI score is > 7, FAR is > 0.265, and HCT-ALB is > 12.792, the probability of developing ARF is as high as 96.14 %. In these patients, even if respiratory distress is not clearly present or lung lesions are not apparent, early treatment involving antivirals, anticoagulants, conscious prone position, and even immunomodulatory drugs such as glucocorticoids and IL-6–receptor blockers, should be initiated. If patients exhibit persistent respiratory distress even with medication, they should be moved to the intensive care unit early and initiated on lung protective ventilation therapy. The COVID-19 pandemic has resulted in an extreme shortage of medical resources, which has caused considerable pressure on emergency medical workers. The results in this study indicate that preliminary screening of patients using the qCSI score and FAR and HCT-ALB laboratory indicators enables more accurate hierarchical diagnosis and treatment and rational use of medical resources, which will be of considerable help for emergency departments and for further diagnosis and treatment of COVID-19.

Our study has some limitations. First, the nutritional status and anemia of the patients were not adequately assessed; and second, this was a single-center and retrospective study, and despite multifactor analysis, confounding and bias factors were difficult to control. Additionally, the sample size of our study was small. To generalize the results of our study, multicenter prospective studies with larger numbers of cases should be conducted.

## 5. Conclusion

Both the FAR and HCT-ALB can predict ARF in patients with COVID-19. The qCSI score combined with FAR and HCT-ALB has a higher accuracy and sensitivity than the qCSI score alone in predicting low risk and can be widely used in the emergency department to classify the degree of risk in patients with COVID-19.

Future studies should expand this research in several directions. External validation is required to assess the prospective robustness and usefulness of the evaluation indicators. Moreover, we intend to conduct multicenter, large-sample studies to understand the inflammatory storm and its relationship with early ARF in immunosuppressed patients with COVID-19.

## Ethical approval statement

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University, Hefei, China. Ethics Approval Number: Quick-PJ 2023-9-31. All procedures complied with the hospital's ethical standards, and all patients provided informed consent and agreed to the public disclosure of data and images.

## Data availability statement

Raw data supporting the conclusions of this study will be available upon request from the authors.

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## CRediT authorship contribution statement

**Peipei Liang:** Writing – review & editing. **Zhijian Wei:** Supervision. **Ran Li:** Writing – review & editing. **Enze Zhou:** Writing – review & editing. **Zheng Chen:** Data curation.

## Declaration of competing interest

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

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