Prognostic value of novel serum biomarkers, including C-reactive protein to albumin ratio and fibrinogen to albumin ratio, in COVID-19 disease: A meta-analysis

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Abstract
With COVID-19 still hovering around and threatening the lives of many at-risk patients, an effective, quick, and inexpensive prognostic method is required. Few studies have shown fibrinogen to albumin ratio (FAR) and C-reactive protein to albumin ratio (CAR) to be promising as prognostic markers for COVID-19 disease. However, their implications remain unclear. This meta-analysis aimed to elucidate the prognostic role of FAR and CAR in COVID-19 disease. A systematic literature search was undertaken using PubMed and Embase till April 2022. Inverse variance standardised mean difference (SMD) was calculated to report the overall effect size using random effect models. The generic inverse variance random-effects method was used to pool the area under the curve (AUC) values. All statistical analyses were performed on Revman and MedCalc Software. A total of 23 studies were included. COVID-19 non-survivors had a higher CAR on admission compared with survivors (SMD = 1.79 [1.04, 2.55]; p < 0.00001; I² = 97%) and patients with a severe COVID-19 infection had a higher CAR on admission than non-severe patients (SMD = 1.21 [0.54, 1.89]; p = 0.0004; I² = 97%). Similarly, higher mean FAR values on admission were significantly associated with COVID-19 mortality (SMD = 0.55 [0.32, 0.78]; p < 0.00001; I² = 82%). However, no significant association was found between mean FAR on admission and COVID-19 severity (SMD = 0.54 [-0.09, 1.18]; p = 0.09; I² = 91%). The pooled AUC values found that CAR had a good discriminatory-power to predict COVID-19 severity (AUC = 0.81 [0.75, 0.86]; p < 0.00001; I² = 80%) and mortality (AUC = 0.81 [0.74, 0.87]; p < 0.00001; I² = 86%). FAR had a fair discriminatory-power to predict COVID-19 severity (AUC = 0.73 [0.64, 0.82]; p < 0.00001; I² = 89%). Overall, CAR was a good predictor of both severity and mortality associated with COVID-19 infection. Similarly, FAR was a satisfactory predictor of COVID-19 mortality but not severity.

Abbreviations: AUC, area under the curve; CAR, C-reactive protein to albumin ratio; COVID-19, coronavirus disease-2019; FAR, fibrinogen to albumin ratio.
INTRODUCTION

The SARS-CoV-2 virus was first reported in December of 2019 in Wuhan, China. With minimal data on its mode of transmission as well as disease severity, it quickly spread throughout the world and was eventually declared a pandemic on 11 March 2020, by the World Health Organisation (WHO).\(^1\) As of 20 May 2022, the total number of confirmed cases was more than 521 million, while more than 6.27 million people have died worldwide.\(^2\) The case fatality rate (CFR), which is defined by the WHO as the proportion of individuals diagnosed with a disease who die from that disease and is, therefore, a measure of severity among detected cases, varies widely from country to country. A mortality analysis done by John Hopkins showed that as of 27 May 2022, CFR for COVID-19 in Yemen was found to be as high as 18.2%, while in the UK and the USA, it was 0.8% and 1.2%, respectively.\(^3\)

While the natural history of COVID-19 usually has mild-to-moderate respiratory and gastrointestinal symptoms, essentially any system of the body can be affected. With the possibility of numerous clinical presentations as well as a relatively wide incubation period of 5–14 days, it is imperative that clinicians realise the severity of their patient’s conditions well in time. Numerous prognostic markers have been utilised which include demographics (age, smoking, and male sex), comorbidities, physical examination factors (low blood pressure, hypoxaemia, tachycardia, tachypnea, dyspnoea, abdominal pain, fever, fatigue, myalgias, and anorexia), laboratory tests (leucocytosis, leukocytopenia, thrombocytopenia, elevated blood lactate, elevated plasma creatinine, elevated blood C-reactive protein (CRP), elevated blood procalcitonin, elevated blood lactate dehydrogenase (LDH), elevated erythrocyte sedimentation rate (ESR), elevated blood B-type natriuretic peptide (BNP), deranged liver function tests, and deranged renal function tests), radiological parameters (consolidations, pleural or pericardial effusions) and high sequential organ failure assessment (SOFA) score.\(^4\)

Fibrinogen is an acute-phase reactant produced by the liver. Its plasma levels increase in pro-inflammatory and hypercoagulable states.\(^5\) Fibrinogen-related coagulation dysfunction has also been closely associated with tumour angiogenesis, invasion, and metastasis.\(^6\) CRP is also an acute-phase reactant produced by the liver that serves as an early marker of infection and inflammation. Its levels rise rapidly and give the highest peak in 48 hours from the disease onset. Its half-life is about 19 h and its concentration decreases when the inflammatory stages end. Likewise, albumin is also produced by hepatocytes. Pro-inflammatory cytokines like tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6) inhibit albumin production. The decrease in plasma albumin level can be directly correlated with the degree of inflammation and poor nutritional status. Likewise, fibrinogen-to-albumin ratio (FAR) and C-reactive protein-to-albumin ratio (CAR) have emerged as prognostic immune biomarkers in various diseases like solid tumours, leukemias, ST-segment elevation myocardial infarction, and septicemias.\(^6\) Emerging evidence suggests that FAR and CAR are promising prognostic markers for COVID-19 disease. However, the quest for an effective, quick, and inexpensive prognostic method is still underway. Therefore, we conducted this meta-analysis to elucidate the prognostic value of the CAR and FAR in assessing the mortality and severity of COVID-19 disease.

METHODS

The current systematic review and meta-analysis was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.\(^7\)

Search strategy

A rigorous literature search was conducted using PubMed and Embase till April 2022. The MedRxiv and SSNR preprint servers were also screened. We utilised a combination of keywords, including ‘COVID-19,’ ‘SARS-CoV-2,’ ‘coronavirus,’ ‘Fibrinogen to albumin ratio,’ and ‘C-reactive protein to albumin ratio.’ For more eligible studies, we checked the reference lists of the included articles manually. Duplicate citations were eliminated and all remaining articles were examined by their titles and abstracts to appraise eligibility. The detailed search strategy is provided in Supplementary Table 1.

Eligibility criteria

All observational studies and case series were included if they met the following inclusion criteria: (a) articles assessing FAR or CAR as a prognostic markers in COVID-19 patients; (b) studies with a sample size of ≥10 patients. These studies were included irrespective of the age, gender, and ethnicity of the study population. The exclusion criteria were pre-determined as follows: (a) if no data regarding mean FAR or CAR at baseline was available; (b) duplicate publications; (c) letters to the editor, case reports, commentaries, reviews, and posters.
2.3 | Study selection and quality assessment

Two authors reviewed the titles and abstracts of the retrieved articles. Based on the preset eligibility criteria, both authors screened the studies independently. Any conflicts of judgement were resolved by discussion with the study lead (Sawai Singh Rathore). The risk of bias assessment and quality appraisal of included studies was performed using the Newcastle-Ottawa Scale (NOS). Two investigators (Sawai Singh Rathore and Kinza Iqbal) independently employed the NOS for evaluating the individual quality of each study. The following sections were rated: low bias risk (8–9 points), moderate bias risk (5–7 points), and high bias risk (0–4 points) (Table 1).

2.4 | Data extraction and statistical analysis

The data extraction for each study was carried out by two authors and was cross-checked to eliminate errors. From each study, several details were retrieved, including the name of the first author, country of origin, study design, sample size, median age, female sex proportion, comorbidities, the definition of severity, mean CAR at baseline, the area under the curve (AUC), cut-off value, sensitivity, and specificity. The utility of a risk prediction model to differentiate between patients who will develop an outcome (in this case, COVID-19 mortality/ severity) compared to those who will not is defined as discrimination (measured using the C-statistic i.e. the AUC of the receiver operating characteristic curve). C-statistic values range from 1.0 (perfect agreement between model-estimated risk and observed events) to 0.5 (random concordance). We utilised the following cut-off values of AUC for the discrimination ability of the prognostic markers (i) 0.81–0.90 = good discrimination; ii) 0.71–0.80 = fair discrimination; (iii) 0.61–0.70 = modest/poor discrimination; and (iv) 0.50–0.60 = very poor/almost no association. The generic inverse variance method was used to pool the AUC values using the random-effects model.

ReviewManager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and MedCalc® Statistical Software version 19.6.4 (MedCalc Software Ltd.; https://www.medcalc.org; 2021) were used for all statistical analyses. Results for outcome analysis were presented as standardised mean difference (SMD) with 95% confidence intervals (CIs) and pooled using the inverse variance random-effects model. The I² statistics were used to assess the heterogeneity of effect size estimates across these studies with I² (low heterogeneity: I² ≤ 25%; moderate: 25%–50%; high >75%). Probability values less than 0.05 were considered statistically significant in all cases. A leave-one-out sensitivity analysis was also carried out to assess the effects of individual studies on the statistical results. Publication bias was explored using funnel plots. Quality of evidence for the primary and secondary outcomes was rated as high, moderate, low, and very low using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group approach (Supplementary Table 2).

3 | RESULTS

3.1 | Literature search and baseline characteristics

Of the 821 articles obtained from the initial literature search, 525 non-duplicate studies were screened based on the titles and abstracts to assess relevance. Subsequently, the full texts of 54 potentially eligible articles were reviewed. After exclusions, 23 studies with a total of 7774 participants remained and were ultimately included in the analysis. The process of study selection is summarised in Supplementary Figure 1 using the PRISMAflowchart. Sixteen studies reported the association of CAR with COVID-19 outcomes, four studies included FAR, and three studies included both CAR and FAR. Table 1 outlines the study characteristics of the included articles, while Table 2 summarises the optimal cut-off, the area under the curve (AUC), sensitivity, and specificity of CAR and FAR for predicting COVID-19 mortality and severity.

3.2 | Quality assessment and publication bias

The methodological quality and risk of bias assessment of the included papers identified 18 high-quality and five moderate-quality studies (Table 1). As a result, all studies were considered suitable for quantitative analysis. The funnel plots of publication bias are shown in Supplementary Figure 2.

3.3 | Results of the meta-analysis

3.3.1 | C-reactive protein to albumin ratio (CAR)

Mortality

A total of eight studies (N = 2138 participants) explored the prognostic value of mean CAR on admission in predicting COVID-19 mortality. Pooled estimates revealed that COVID-19 non-survivors had a higher CAR on admission compared with survivors (SMD = 1.79 [1.04, 2.55]; p < 0.00001; I² = 97%) (Figure 1a). Therefore, higher CAR values on admission were significantly associated with COVID-19 mortality. Meta-analysis of the AUC values reported by 8 studies (N = 1912 patients) revealed that CAR had a good discriminatory-power to predict COVID-19 mortality (AUC = 0.81 [0.74, 0.87]; p < 0.00001; I² = 86%) (Figure 2a).

Severity

In all, 11 studies (N = 2972 participants) assessed the relation between mean CAR on admission and COVID-19 severity. Severe COVID-19 patients had higher mean CAR on admission compared those who had mild to moderate COVID-19 disease (SMD = 1.21 [0.54, 1.89]; p = 0.0004; I² = 97%) (Figure 1a). Thus, our results showed that higher mean CAR values on admission were significantly related to the development of severe COVID-19 disease. On pooling the AUC values reported across 8 studies (N = 1548 patients), we
| Study               | Type of study              | Sample size | Mean/median age | Female gender (%) | Hypertension (%) | Cardiovascular disease (%) | Diabetes (%) | Chronic pulmonary disorders (%) | Chronic kidney disease (%) | Obesity (%) | Smoking (%) | NCOS |
|---------------------|---------------------------|-------------|-----------------|-------------------|------------------|----------------------------|--------------|---------------------------------|---------------------------|--------------|--------------|------|
| Cekic et al.        | Retrospective             | 590         | 65.63 ± 14.9    | 40                | 52               | 22                         | 32           | 10                              | -                         | -            | -            | 8    |
| Abdulmecit et al.   | Retrospective             | 386         | 71.2 ± 12.9     | 45.9              | 57.8             | 43.8                       | 34.5         | 31.1                            | 11.7                      | -            | 40.7         | 7    |
| Acehan et al.       | Retrospective             | 613         | 59.04 ± 19.5    | 41.6              | 39.3             | 9                          | 21.5         | 14.5                            | 9                         | -            | -            | 8    |
| Gemcioglu et al.    | Retrospective             | 301         | 45 (245)        | 46.5              | 20.9             | 8                          | 13           | 5.3                             | 1.7                       | 1.3          | 5.3          | 8    |
| Küçükceran et al.   | Retrospective             | 717         | -               | 48.3              | 36.3             | 19.1                       | 27.5         | 16.5                            | -                         | -            | -            | 7    |
| Torun et al.        | Retrospective             | 188         | -               | 50.5              | 54.3             | 28.2                       | 34           | 13.8                            | -                         | -            | -            | 6    |
| Kuluçtürk et al.    | Retrospective             | 400         | -               | -                 | -                | -                          | -            | -                               | -                         | -            | -            | 7    |
| Karakoyun et al.    | Retrospective             | 197         | 54              | 45.2              | 44.2             | 16.2                       | 24.4         | 8.6                             | 6.1                       | -            | -            | 7    |
| Saylık et al.       | Retrospective             | 176         | 61.4            | 69                | 176              | 23                         | 30           | 17                              | 4                         | 12           | 28           | 8    |
| Kalyon et al.       | Retrospective              | 639        | 73              | 58.9              | 71.1             | 36                         | 44           | 21.7                            | 8                         | 57.1         | -            | 6    |
| Wang X et al.       | Retrospective        | 90          | -               | -                 | -                | -                          | -            | -                               | -                         | -            | -            | 8    |
| Xue et al.          | Retrospective             | 114         | 63              | 43.8              | 3242             | 14.91                      | 14.04        | 8.77                            | -                         | -            | -            | 8    |
| Bahadırlı et al.    | Retrospective             | 273         | 52              | 53.8              | 38.8             | 36.2                       | 13.2         | 33.7                            | 6.6                       | -            | -            | 7    |
| Kalabin et al.      | Retrospective             | 75          | 62.9            | 34.67             | 66.67            | 20                         | 40           | 8                               | 14.67                     | -            | -            | 6    |
| Wang H et al.       | Retrospective             | 61          | 53              | 49.2              | 19.7             | 6.6                        | 9.8          | -                               | -                         | -            | -            | 8    |
| Li et al.           | Retrospective             | 557         | 62              | 46.7              | 48               | 13.5                       | 21.9         | 8                               | -                         | -            | -            | 7    |
| El-Shabrawy et al.  | Retrospective            | 116         | 36              | 48.5              | 121              | 2                          | 8.1          | 5.1                             | -                         | -            | 6.1          | 7    |
| Deniz et al.        | Retrospective            | 1077        | 57.5            | 48.3              | -                | -                          | -            | -                               | -                         | -            | -            | 8    |
| Vehbi et al.        | Retrospective            | 105         | 63.2            | 62.9              | 25.7             | 10.5                       | 20           | 114.3                           | 6.7                       | -            | -            | 6    |
| Ağksarı et al.      | Retrospective            | 223         | 59.70 ± 19.01   | 47.1              | 46.2             | 18.8                       | 27.4         | 10.8                            | -                         | -            | -            | 7    |
| Az et al.           | Retrospective            | 540         | 48              | 44.1              | 15.2             | 6.1                        | 15.4         | 3.3                             | 2                         | -            | -            | 6    |
| Ozdemir et al.      | Retrospective            | 281         | -               | 48.8              | 48               | 26                         | 40.6         | 14.2                            | 29.9                      | -            | 27.4         | 8    |
| Tocoglu et al.      | Descriptive study        | 55          | 74 (64–80)      | 34.5              | 70.9             | 34.5                       | 38.2         | -                               | -                         | -            | -            | 8    |
found that the CAR had a good discriminatory power to predict COVID-19 severity \( (\text{AUC} = 0.81 \, [0.75, 0.86]; \ p < 0.00001; \ I^2 = 80\%) \) (Figure 2b).

### 3.3.2 | Fibrinogen to albumin ratio (FAR)

#### Mortality

Overall, five studies \( (N = 2778 \text{ participants}) \) assessed the link between mean FAR on admission and COVID-19 mortality. There was a significantly higher mean FAR in COVID-19 non-survivors compared with survivors. Therefore, a higher mean FAR on admission was significantly associated with COVID-19 mortality \( (\text{SMD} = 0.55 \, [0.32, 0.78]; \ p < 0.00001; \ I^2 = 82\%) \) (Figure 1c). The pooled AUC values found that the FAR had a fair discriminatory power to predict COVID-19 severity \( (3 \text{ studies}; \ N = 2023 \text{ participants}; \ \text{AUC} = 0.73 \, [0.64, 0.82]; \ p < 0.00001; \ I^2 = 89\%) \) (Figure 2c).

#### Severity

Only three studies \( (N = 865 \text{ participants}) \) reported the mean FAR on admission of severe and non-severe COVID-19 patients. There was no significant difference between the mean FAR on admission in patients who had severe COVID-19 infection versus those who had mild-moderate COVID-19 disease \( (\text{SMD} = 0.54 \, [-0.09, 1.18]; \ p = 0.09; \ I^2 = 91\%) \) (Figure 1d). Only two studies reported the area under the curve (AUC) values for the ability of FAR to predict COVID-19 severity; therefore, it was not meta-analysed (Table 2).

#### Leave-one-out sensitivity analysis

Sensitivity was calculated by systematically eliminating one study at a time to establish the robustness of the results. It did not lead to significant changes in the SMD estimates in both severity and mortality outcomes for the CAR ratio group, consistent with the robustness of
the result that a high mean CAR at the time of admission in COVID-19 patients is associated with increased severity and mortality due to disease despite high heterogeneity. For FAR, in severity outcome, removing Torun et al. led to the significant effects, indicating this study as a cause of heterogeneity. No change was seen in the mortality outcome for FAR analysis (Supplementary Table 3).

4 | DISCUSSION

In this study, we investigated the prognostic value of CAR and FAR in assessing the mortality and severity of COVID-19 disease. Fibrinogen, albumin, and CRP are all acute-phase reactants. Although it has been reported that albumin, CRP, and fibrinogen abnormalities are prognostic markers in patients with COVID-19, changes in their levels are not observed simultaneously in the patients. For this reason, the use of CAR and FAR could better correlate with these protein levels and have great potential as prognostic factors in patients with COVID-19.

In our meta-analysis, higher mean values of FAR on admission correlated significantly with mortality associated with COVID-19 disease, with an AUC of 0.81. FAR had a fair discriminatory power to predict COVID-19 mortality. However, there was no significant difference between FAR levels on admission in patients with a severe COVID-19 infection compared with mild-to-moderately infected patients \( (p = 0.9) \). Similarly, higher mean CAR value on
admission correlated significantly with the development of severe COVID-19 disease, with an AUC value of 0.81. Higher mean CAR value on admission also correlated significantly with COVID-19 mortality, with an AUC value of 0.81. CAR had a good discriminatory power to predict COVID-19 severity as well as mortality.

C-reactive protein (CRP) is an acute-phase reactant produced by the liver in response to inflammation. It is usually secreted under the influence of cytokines such as interleukin-6 and tumour necrosis factor-alpha. While an elevated CRP titre is uncommon with viral infections, it has proven to be a reliable marker of morbidity and mortality associated with COVID-19 disease. In one study, each 50-unit increase in CRP increased the odds of death by almost 42% (OR = 1.42, 95% CI: 1.25–1.60), and for each 100-unit increase in CRP, the odds increased two-fold (OR = 2.01, 95% CI: 1.57–2.56), while controlling for BMI, comorbidities, and age. In another retrospective analysis of 275 COVID-19 patients, patients with CAR values of ≥1.59 and <11.19 had a higher frequency of comorbidities such as hypertension, chronic obstructive pulmonary disease (COPD), and coronary artery disease (CAD); and in-hospital mortality was 12.6 times higher than the reference group (patients with CAR value of <0.29).

Hypoalbuminemia in patients with COVID-19 infection has been definitively described in the literature. Yet, its role as a predictor of outcomes associated with COVID-19 infections has yet to be assessed robustly. Decreased albumin levels can result in upregulation of ACE2 receptors that increase COVID-19 infections since albumin has the ability to downregulate ACE2 receptors. Mechanisms for the drop in serum albumin levels are not clearly known. Inflammatory cytokine-induced decrease in the synthesis of albumin by the liver has been postulated. However, the median time from onset of COVID-19 illness to hospital admission is usually low (<2 weeks), which is smaller than the half-life of serum albumin (3 weeks), suggesting that hypoalbuminemia might be less likely to result from decreased albumin synthesis in severe COVID-19. For the same reason, it can be assumed that poor nutrition may not be the likely cause of the development of hypoalbuminemia. Inflammation-induced increase in capillary permeability is likely a better explanation for COVID-19 induced hypoalbuminemia. In a
retrospective cohort study with 299 patients, serum albumin level <3.5 g/dl at presentation independently increased the risk of death in COVID-19 by at least 6-fold.\textsuperscript{38} Therapeutic efficacy of albumin in sepsis and cirrhosis demonstrates that it can act through a modulatory effect on inflammation and oxidative stress in addition to the plasma volume expansion.\textsuperscript{39} Albumin treatment has been shown to improve oxygenation in ARDS by a meta-analysis.\textsuperscript{40}

Studies have found that an increased FAR could result from cytokine storms induced by the COVID-19 virus invasion.\textsuperscript{41} Our study found that FAR values on admission are statistically significantly associated with COVID-19 mortality. Similar results have been arrived upon in previous studies.\textsuperscript{42} Yet, there are multiple possible explanations for FAR on admission to be an unreliable indicator of COVID-19 severity. Fibrinogen is an acute-phase reactant, hence its levels are expected to rise with an ongoing COVID-19 viraemia. However, while fibrinogen levels increase in the early stage of inflammation, they tend to peak and then decrease in the later stages when the disease is severe. Hence, values obtained at the time of admission have a very high likelihood of being falsely normal. It is also a known fact that a COVID-19 infection is a hypercoagulable state in itself.\textsuperscript{5} In severe cases, when the imbalance in coagulation pathways increases substantially, patients might develop disseminated intravascular coagulation (DIC), which is marked by consumptive thrombocytopenia, and elevated fibrin-degradation products, and a low fibrinogen level. However, its plasma levels can remain elevated for prolonged periods despite ongoing consumption in DIC. Hence, hypofibrinogenemia for diagnosis of DIC carries very low sensitivity.\textsuperscript{43} Hypercoagulation has also been associated with hypoalbuminemia.\textsuperscript{44} Meta-analysis results also demonstrated that increased CRP levels and decreased levels of albumin (a negative acute-phase reactant) were among the most common laboratory findings. The mechanism for hypoalbuminemia in COVID-19 has not been explained extensively, though there have been some explanations - increased capillary permeability, causing albumin to seep into the interstitial space,\textsuperscript{39} or decreased albumin synthesis from the liver due to suppression by circulating cytokines.

The limitations of our meta-analysis include exclusion of discharged COVID-19 patients in the study, failure to evaluate treatment protocols, and failure to selectively remove those patients who were on anticoagulants. The FAR and CAR levels were recorded only once on admission, which limited the capability to assess the change in their values over time. Moreover, we could not evaluate all the nutritional parameters of the patients, such as BMI due to the unavailability of this data.

5 | CONCLUSION

With COVID-19 still hovering around and threatening the lives of many at-risk patients and with the availability of limited healthcare capacity, early prediction of COVID-19 severity and mortality is crucial. To assess the prognosis of COVID-19 patients, an effective, quick, and inexpensive method is required. Overall, CAR was a good predictor of both severity and mortality associated with COVID-19 infection, while FAR had a fair discriminatory-power to predict COVID-19 severity. Both CAR and FAR can be easily calculated from routinely measured laboratory parameters in COVID-19 patients. For this reason, these may be simple and useful indexes that can be used for predicting adverse outcomes in COVID-19 patients.
36. Güney BC, Taştan YO, Doğantekin B, et al. Predictive value of CAR for in-hospital mortality in patients with COVID-19 pneumonia: a retrospective cohort study. *Arch Med Res.* 2021;52(5):554-560. https://doi.org/10.1016/j.arcmed.2021.02.006

37. Liu BC, Gao J, Li Q, Xu LM. Albumin caused the increasing production of angiotensin II due to the dysregulation of ACE/ACE2 expression in HK2 cells. *Clin Chim Acta.* 2009;403(1-2):23-30. https://doi.org/10.1016/j.cca.2008.12.015

38. Huang J, Cheng A, Kumar R, et al. Hypoalbuminemia predicts the outcome of COVID-19 independent of age and co-morbidity. *J Med Virol.* 2020;92(10):2152-2158. https://doi.org/10.1002/jmv.26003

39. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enter Nutr.* 2019;43(2):181-193. https://doi.org/10.1002/jpen.1451

40. Uhlig C, Silva PL, Deckert S, Schmitt J, de Abreu MG. Albumin versus crystalloid solutions in patients with the acute respiratory distress syndrome: a systematic review and meta-analysis. *Crit Care.* 2014;18(1):R10. Published 2014 Jan 9. https://doi.org/10.1186/cc13187

41. Bi X, Su Z, Yan H, et al. Prediction of severe illness due to COVID-19 based on an analysis of initial Fibrinogen to Albumin Ratio and Platelet count. *Platelets.* 2020;31(5):674-679. https://doi.org/10.1080/09537104.2020.1760230

42. Çekiç D, Arman ME, Genç AC, et al. Predictive role of FAR ratio in COVID-19 patients. *Int J Clin Pract.* 2021;75(12):e14931. https://doi.org/10.1111/ijcp.14931

43. Venugopal A. Disseminated intravascular coagulation. *Indian J Anaesth.* 2014;58(5):603-608. https://doi.org/10.4103/0019-5049.144666

44. Chi G, Gibson CM, Liu Y, et al. Inverse relationship of serum albumin to the risk of venous thromboembolism among acutely ill hospitalized patients: analysis from the APEX trial. *Am J Hematol.* 2019;94(1):21-28. https://doi.org/10.1002/ajh.25296

**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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