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REVIEW

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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]; $p < 0.00001$; $I^2 = 97\%$) 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]; $p = 0.0004$; $I^2 = 97\%$). Similarly, higher mean FAR values on admission were significantly associated with COVID-19 mortality (SMD = 0.55 [0.32, 0.78]; $p < 0.00001$; $I^2 = 82\%$). However, no significant association was found between mean FAR on admission and COVID-19 severity (SMD = 0.54 [−0.09, 1.18]; $p = 0.09$; $I^2 = 91\%$). The pooled AUC values found that CAR had a good discriminatory-power to predict COVID-19 severity (AUC = 0.81 [0.75, 0.86]; $p < 0.00001$; $I^2 = 80\%$) and mortality (AUC = 0.81 [0.74, 0.87]; $p < 0.00001$; $I^2 = 86\%$). FAR had a fair discriminatory-power to predict COVID-19 severity (AUC = 0.73 [0.64, 0.82]; $p < 0.00001$; $I^2 = 89\%$). 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.

KEYWORDS
C-reactive protein to albumin ratio, CAR, COVID-19, FAR, fibrinogen to albumin ratio, prognostic marker

1 | 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, thrombocytopaenia, 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.

2 | 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]

2.1 | 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.

2.2 | 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).[8] 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.[9] 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 I^2 statistics were used to assess the heterogeneity of effect size estimates across these studies with I^2 (low heterogeneity: $I^2 \leq 25\%$; 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).[10,11]

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.[12–34] 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,[12–27] four studies included FAR,[28–31] and three studies included both CAR and FAR.[32–34] 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]; $p < 0.00001$; I^2 = 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]; $p < 0.00001$; I^2 = 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; I^2 = 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

TABLE 1 Baseline characteristics of included studies

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 (24.5)	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
Kuluöztürk et al.	Retrospective	400	-	41.25	-	-	-	-	-	-	-	7
Karakoyun et al.	Retrospective	197	54	45.2	44.2	16.2	24.4	8.6	6.1	-	-	7
Saylik et al.	Retrospective	176	61.4	69	176	23	30	17	4	12	28	8
Kalyon et al.	Retrospective case-control	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	32.42	14.91	14.04	8.77	-	-	-	8
Bahadirli 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 cohort study	116	36	48.5	12.1	2	8.1	5.1	-	-	6.1	7
Deniz et al.	Retrospective cohort study	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
Açıksarı 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

TABLE 2 Cut-off, area under the curve (AUC), sensitivity, and specificity of C-reactive protein to albumin ratio (CAR) and Fibrinogen to albumin ratio (FAR) in predicting COVID-19 severity and mortality

Study	Outcome	AUC (CIs)	Optimal cut-off value	Sensitivity %	Specificity %
Fibrinogen to albumin ratio (FAR)					
Acehan et al.	Mortality	0.668 (0.594–0.742)	11.1078	62.3	57.5
Cekic et al.	Mortality	0.808 (0.771–0.844)	0.13	74.9	74.6
Küçükceran et al.	Mortality	0.703 (0.656–0.749)	>112.33	71.4	64
Gemcioglu et al.	Severity	0.766	0.102	65.31	77.91
Torun et al.	Severity	0.737 (0.663–0.81 1)	113.5	69.6	65.8
C-reactive protein to albumin ratio (CAR)					
Acehan et al.	Mortality	0.790 (0.728–0.852)	2.1561	73.6	68.4
Açıksarı et al.	Mortality	0.81 (0.75–0.86)	0.34	-	-
Kalyon et al.	Mortality	0.781 (0.708–0.853)	23	70.69	72.65
Ozdemir et al.	Mortality	0.807 ± 0.025	56.62	71.1	71.4
Saylik et al.	Mortality	0.778 (0.656, 0.621)	20.75	82.3	72.8
Tocoglu et al.	Mortality	0.721 (0.530–0.912)	1.37	73.8	72.7
Bahadirli et al.	Mortality	0.725 (0.635–0.815)	0.91	78.57	61.22
El-Shabrawy et al.	Mortality	0.955 (0.917–0.993)	-	-	-
Bahadirli et al.	Severity	0.729 (0.662–0.797)	0.74	86.79	56.82
Deniz et al.	Severity	0.85	1.89	81	86
El-Shabrawy et al.	Severity	0.922 (0.862–0.981)	8.9	82.4	90.9
Gemcioglu et al.	Severity	0.765	6.25	68.32	75.49
Karakoyun et al.	Severity	0.718(0.649–0.779)	0.9	69.1	70.8
Li et al.	Severity	0.866 (0.822–0.911)	1.843	91.1	78
Torun et al.	Severity	0.841 (0.784–0.899)	7.54	82.6	66.7
Vehbi et al.	Severity	0.70 (0.58–0.81)	1	76.5	76.1
Wang X et al.	Severity	0.812 (0.709–0.914)	0.296	76.7	80.4
Xue et al.	Severity	0.81 (0.73–0.88)	0.71	82.76	80.36

Abbreviations: AUC, Area under the curve; CI, confidence intervals.

found that the CAR had a good discriminatory-power to predict COVID-19 severity (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 ($N = 2778$ 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 (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 studies; $N = 2023$ participants; AUC = 0.73 [0.64, 0.82]; $p < 0.00001$; $I^2 = 89\%$) (Figure 2c).

Severity

Only three studies ($N = 865$ 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 (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).

3.3.3 | 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

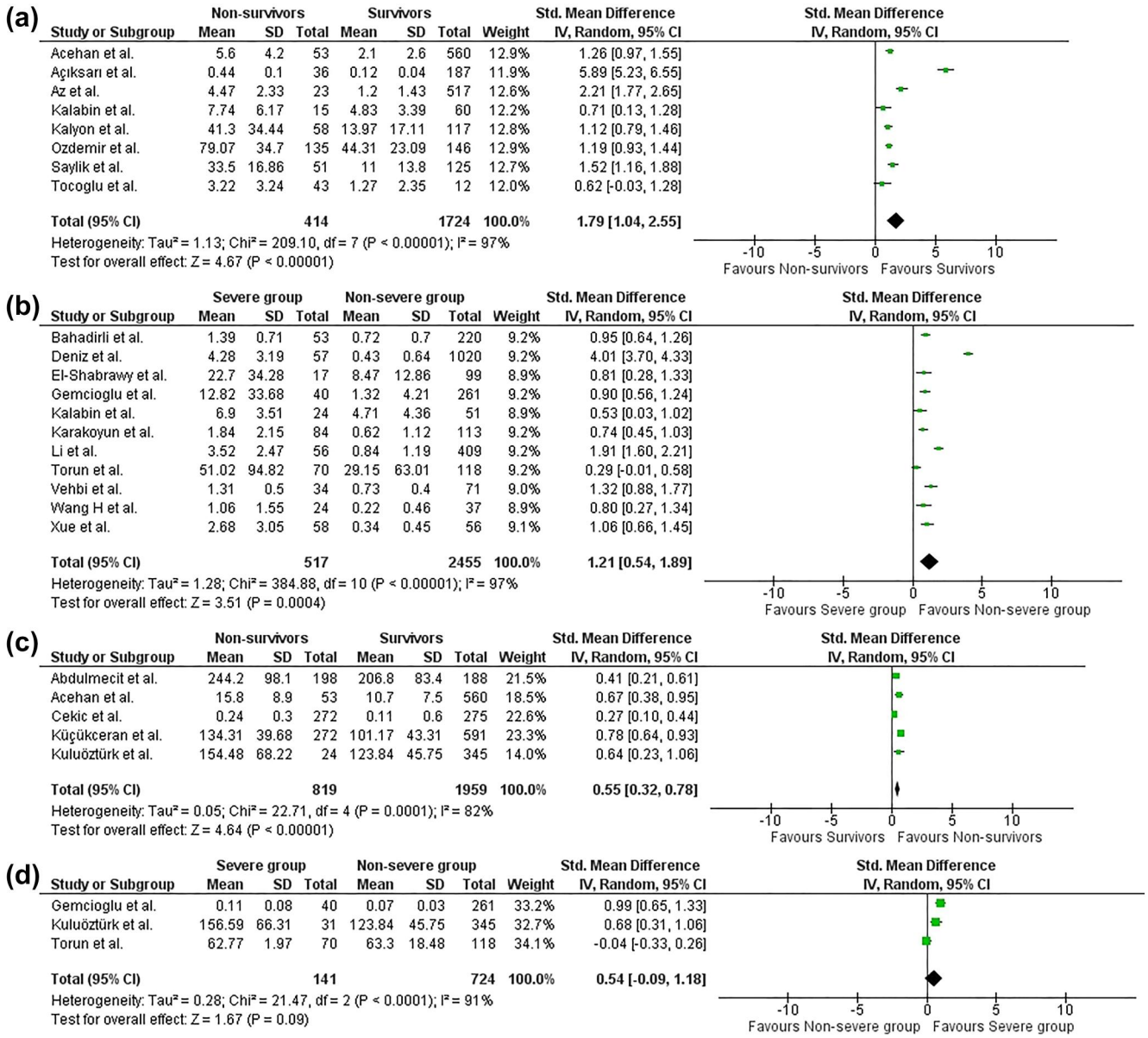

FIGURE 1 Pooled results of the association between: (a) Mean C-reactive protein to albumin ratio (CAR) and COVID-19 mortality; (b) Mean C-reactive protein to albumin ratio (CAR) and COVID-19 severity; (c) Mean Fibrinogen to albumin ratio (FAR) and COVID-19 mortality; (d) Mean Fibrinogen to albumin ratio (FAR) and COVID-19 severity. Std. Mean difference, Standard mean difference; IV, inverse variance, SD, Standard deviation, CI, Confidence interval

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.[34] 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.[31] 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 value 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

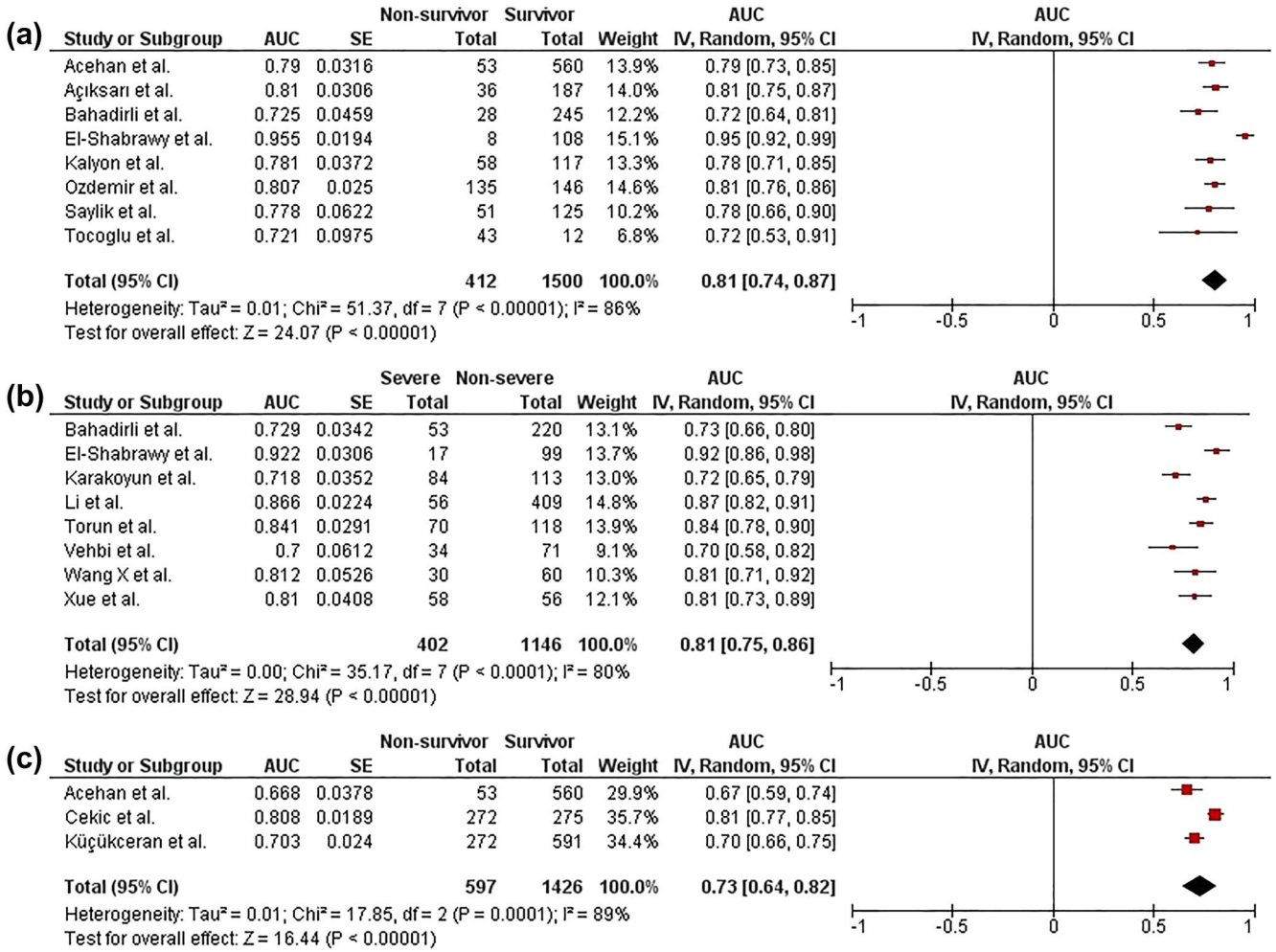

FIGURE 2 Pooled results of Area under the curve (AUC): (a) Predictive value of C-reactive protein to albumin ratio (CAR) in COVID-19 mortality; (b) Predictive value of C-reactive protein to albumin ratio (CAR) in COVID-19 severity; (c) Predictive value of fibrinogen to albumin ratio (FAR) in COVID-19 mortality. AUC, area under the curve; IV, inverse variance, SE, Standard error, CI, Confidence interval

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.[35] 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).[36]

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.[37] 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.[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.[39] Albumin treatment has been shown to improve oxygenation in ARDS by a meta-analysis.[40]

Studies have found that an increased FAR could result from cytokine storms induced by the COVID-19 virus invasion.[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.[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 late 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.[5] In severe cases, when the imbalance in coagulation pathways increases substantially, patients might develop disseminated intravascular coagulation (DIC), which is marked by consumptive thrombocytopaenia, 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.[43] Hypercoagulation has also been associated with hypoalbuminemia.[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,[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.

AUTHOR CONTRIBUTIONS

Sawai Singh Rathore conceived the study and draughted the research protocol. Sawai Singh Rathore, Sharvi Obero, and Keshav Bhattar provided a critical review of and approved the study design. Kinza Iqbal, Guadalupe Abigail Benítez-López, Felipe Velasquez-Botero, Jonathan Hilliard, Chinelo Chioma Madekwe, and Khalil Khalil conducted the database searches. Sawai Singh Rathore, Kinza Iqbal, Guillermo Andrés Moreno Cortes, and María Alejandra Nieto-Salazar made the primary selection of eligible papers, including data extraction. Sawai Singh Rathore, Sharvi Obero, Chinelo Chioma Madekwe and Thomas C. Flowers checked the study selection process and data extraction. Sawai Singh Rathore and Kinza Iqbal analysed the data. All authors contributed to the interpretation of the analysis. Sawai Singh Rathore, Sharvi Obero, Kinza Iqbal, Keshav Bhattar, and Guadalupe Abigail Benítez-López wrote the manuscript. All authors provided a critical review and approved the final manuscript.

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CONFLICT OF INTEREST

Authors have no potential conflict of interest to declare.

DATA AVAILABILITY STATEMENT

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

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