



ORIGINAL ARTICLE

Predictive Value of Fibrinogen / Albumin Ratio for In-hospital Mortality in COVID-19 Patients

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ABSTRACT

Background: Fibrinogen Albumin Ratio (FAR) is being tested as a novel marker for many inflammatory diseases. Many studies have linked the high FAR level to the severity of illness and mortality. This study aimed to evaluate the FAR's potential application in COVID-19 patients as a predictor of illness severity and in-hospital mortality, that may improve management of COVID-19 patients. **Methods:** This prospective cohort study was conducted at COVID-19 Isolation Unit, Zagazig University hospitals, Egypt. WBCs, CRP, ferritin, albumin, fibrinogen, fibrinogen to albumin ratio and assessment of the outcome by in hospital death and the length of hospital stay were done for all patients. **Results:** Between the first and seventh days, there was a substantial change in fibrinogen and FAR that significantly increased on 7th day while albumin significantly decreased on 7th day. Critically ill patients had FAR that was greater than moderate and severe patients, as well as severe patients than moderate patients. A mean LOS was 11.7 ± 2.9 days and 68% of them were survived. There was a sizable distinction between survivors and non-survivors in terms of fibrinogen on 7th day and FAR on 1st and 7th days that were lower in survivors compared to non-survivors. Additionally, there were differences between albumin levels in survivors and non-survivors on 1st and 7th days. The fibrinogen on 7th day, albumin 1st and 7th days, FAR 1st and 7th days could be used to predict mortality. **Conclusions:** In COVID-19 patients, the fibrinogen to albumin ratio can be used to predict mortality.

Keywords: Mortality; COVID-19; Fibrinogen to albumin ratio.

INTRODUCTION

Coronaviruses which are described as a single-stranded mRNA virus that can cause each or both of upper and lower respiratory tract infections. A novel coronavirus (SARS-Cov-2) outbreak began in China in December 2019 and in March 2020, the World Health Organization declared the outbreak to be the COVID-19 pandemic [1]. By December 2022, there were over 645 million confirmed COVID-19 cases worldwide as a result of the outbreak [2].

Coagulopathy and the associated problems are known to manifest in COVID-19, and most patients have laboratory findings of coagulopathy, including elevated levels of D-dimer, LDH, and fibrinogen [3].

A procoagulant protein called fibrinogen is generated in the liver and its blood levels rise in numerous inflammatory conditions. The fibrinogen to albumin ratio (FAR) level is better than fibrinogen or albumin alone in assessment of disease severity. Because the increase in coagulation markers is linked to clinical deterioration and mortality in COVID-19, albumin is a negative acute-phase reactant protein and low levels are associated with the severity of the disease. The goal of this work is to evaluate the use of the FAR as a predictor of disease severity and in-hospital mortality in COVID-19 [4].

METHODS

This prospective cohort study was conducted at COVID-19 Isolation Unit of Zagazig University Hospitals in Egypt from March 2022 to August 2022.

Cases who are mild, severe, or critically ill [5] that were admitted to an isolation facility and had a COVID-19 diagnosis confirmed by positive PCR results were included [6].

Individuals who had significant comorbidities that were previously recognized were excluded from the study, such as cancer, chronic liver disease, chronic renal failure and autoimmune illnesses.

All participants were subjected to complete medical history taking, which includes: age, sex, symptoms since commencement (fever, cough, dyspnea, anosmia, etc.), smoking history and length of COVID-19 infection. Associated comorbidities e.g. DM, cardiovascular diseases etc. Complete clinical examination. All patients were subjected to clinical examination, oxygen saturation and ABGs, medical imaging including: non contrast CT chest or X- ray, conventional laboratory investigations as CBC which was done on automated cell counter, model XN 2000 (Sysmex, Japan) along with checking for a differential leucocytic count on Giemsa-stained peripheral blood smears.

Inflammatory biomarkers CRP, Ferritin were done by using immunoassay Cobas e 411 immunoassay analyzers (Roche diagnostic Germany). Assessment of Fibrinogen to Albumin (FAR) ratio: on admission and on day 7, D-Dimer and Fibrinogen were done on automated coagulation analyzer, model CS 2100 system (Siemens, AG, Germany), Albumin was done on Cobas C311 / sol analyzers (Roche diagnostic Germany). The FAR was computed by dividing the fibrinogen concentration by the albumin concentration using the statistical software SPSS. All the patients underwent the conventional Egyptian protocol in their treatment [7]. Outcome of the study included, in-hospital death and length of hospital stay. According to in-hospital mortality, patients were divided into two groups, survivors and non-survivors.

Ethical consideration

All participants in the study gave their informed consent in writing, and the local institutional review

board (Ethical Committee) gave its approval (IRB) dated 9.1.2022.

Statistical Analysis

With SPSS software version 18 (USA), data were examined. Data presented as a mean \pm SD. The paired student's t-test for parametric data was used for the statistical comparisons. Comparisons between three groups were done using one way ANOVA followed by Tukey's test. To assess the relationship between the variables, Pearson correlation was used. Receiver operating characteristic (ROC) curve analysis was performed to predict the value of various variables as diagnostic and prognostic markers. The degree of significance was determined at $P < 0.05$.

RESULTS

The present study included 38 patients, their mean age was 51.4 ± 7.3 , 55.3% of patients were male 44.7 % female, that 40% of patients had DM, 32% had HTN, 15.8% had cardiovascular diseases, 13% had respiratory diseases (7.8 % COPD, 2.6 % Br asthma, 2.6 % ILD), 2.6% neurological disease and 29% were smokers (Table 1).

The mean CRP, serum ferritin, D-dimer and WBCs was 81.1 ± 45.9 , 401.1 ± 264.6 , 0.9 ± 0.45 and 6.9 ± 2.46 respectively (Table 2).

There was significant difference between 1st and 7th day regarding fibrinogen and FAR that increased on 7th day while albumin significantly decreased on 7th day (Table 3).

Table (4) showed that FAR was significantly higher in critically ill patients than moderate and severe patients and also higher in severe patients than moderate patients.

The mean LOS was 11.7 ± 2.9 days and 68% of them were survived (Table 5).

There was significant difference between both groups regarding fibrinogen on 7th day and FAR on 1st and 7th day that were higher in non survivors than survivors. Also there was significant difference between both groups regarding albumin on 1st and 7th day, that were lower in non survivors than survivors and LOS that were higher in non survivors than survivors (Table 6).

The fibrinogen on 7th day, albumin 1st and 7th day, FAR 1st and 7th day could be used for prediction of mortality (Table 7, figure 1-3).

Table (1): Demographic data, Co-morbidities and smoking among studied population

Demographic data and Comorbidities	Overall patients (N=38)
Age	51.4 ± 7.3
Gender	
Male	21 (55.3%)
Female	17 (44.7%)
Diabetes mellitus (DM)	15 (40%)
Systemic hypertension (HTN)	12 (32%)
Cardiovascular diseases	6 (15.8%)
Respiratory diseases	5 (13%)
Chronic obstructive pulmonary disease(COPD)	3 (7.8 %)
Bronchial asthma (BA)	1(2.6 %)
Interstitial lung disease (ILD)	1 (2.6 %)
Neurological disease	1 (2.6%)
Smokers	11 (2.6 %)

Data are represented as mean ± SD or Number (%).

Table (2): Inflammatory biomarkers on 1st day among the studied population.

Variables	1 st day
CRP	81.1 ± 45.9
Serum Ferritin (ng/ml)	401.1 ± 264.6
D- Dimer (mg/l)	0.9 ± 0.45
WBCs	6.9 ± 2.46

Data are represented as mean ± SD. Data are analyzed using paired student t test.

Table (3): Albumin, fibrinogen and FAR on 1st and 7th days among the studied population.

Variables	1st day	7th day	T	P
Albumin	3.95 ± 0.58	3.73 ± 0.68	2.5	0.01*
Fibrinogen (mg/dl)	422.4 ± 150.5	476.8 ± 103.9	2.43	0.02*
Fibrinogen to Albumin ratio (FAR)	122.2 ± 4.7	125.1 ± 52.1	-2.2	0.04*

Data are represented as mean ± SD. Data are analyzed using paired student t test.

Table 4: Comparison between moderate, severe and critically ill cases regarding FAR on 7th day.

Variables	Moderate	Severe	Critically ill	F	P
FAR on 7 th day	105.4 ± 12.5	135.8 ± 15.8	171.5±22.5	107.7	<0.0001

Data are represented as mean ± SD.

P1& P2 & P3 = 0.0001

P1: between moderate and severe

P2: between moderate and critically ill.

P3: between severe and critically ill.

Table (5): Length of hospital stay (LOS) and survival among the studied population

Variables	Overall patients (N=38)
LOS	11.7 ± 2.9
Survival rate	26 (68%)

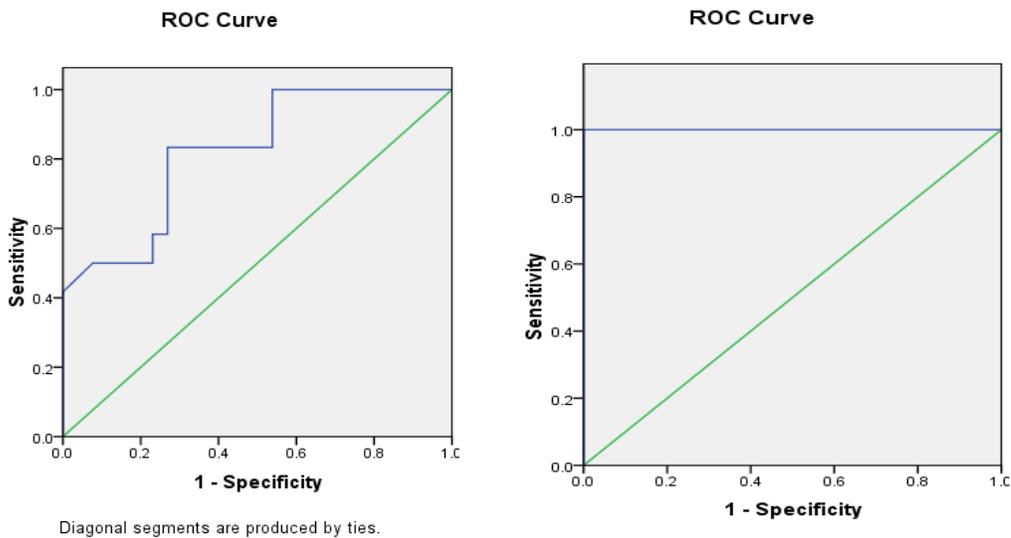
Data are represented as mean ± SD or Number (%).

Table (6): Relation between survivors and non survivors regarding fibrinogen, albumin, FAR and LOS.

		Non survivors (N=12)	Survivors (N=26)	t	P
1 st day	Albumin	3.4 ± 0.37	4.1 ± 0.51	-4.5	<0.0001*
7 th day		2.9 ± 0.14	4.09 ± 0.49	-7.8	<0.0001*
1 st day	Fibrinogen (mg/dl)	505.9 ± 117.2	463.4 ± 96.7	1.17	0.24
7 th day		609.4 ± 58.1	336.2 ± 86.9	9.8	<0.0001*
1 st day	FAR	146.8 ± 31.4	110.8 ± 20.4	4.2	<0.0001*
7 th day		177.7 ± 21.9	93.2 ± 19.2	21.5	<0.0001*
	LOS	19.2 ± 2.9	10.5 ± 2.2	10.6	<0.0001*

Table (7): Roc curve of fibrinogen, and albumin and FAR for prediction of mortality.

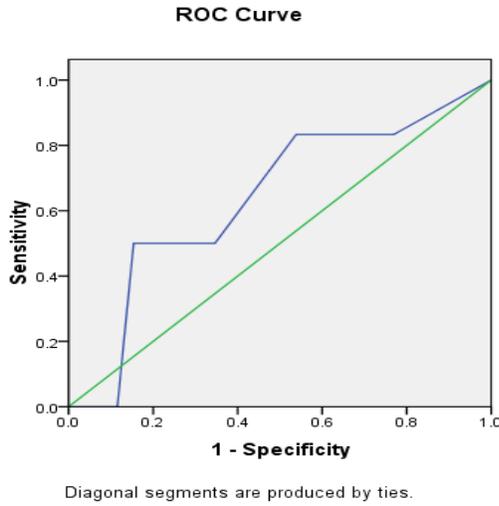
		AUC	P value	Cut off	sensitivity	Specificity
Fibrinogen	at 1 st day	0.6	0.28	412	75%	65%
	at 7 th day	0.98	0.000	305	100%	53%
Albumin	at 1 st day	0.9	0.000	3.2	66%	61%
	at 7 th day	0.8	0.000	2.8	75%	55%
FAR	at 1 st day	0.82	0.002*	108.5	100%	58%
	at 7 th day	1	0.000	88.9	100%	78%



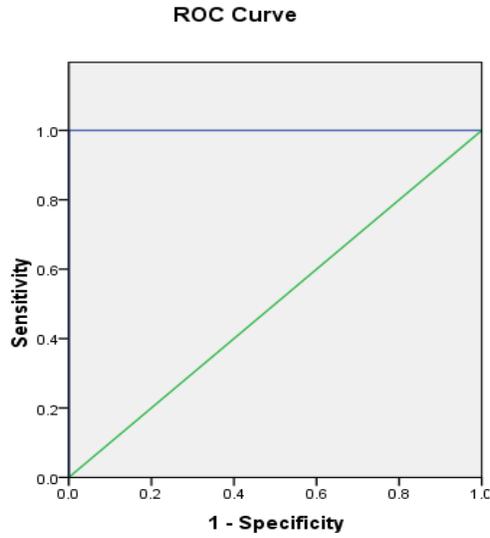
Roc curve of fibrinogen on 1st day

Roc curve of fibrinogen on 7th day

Figure (1): ROC curve of fibrinogen on 1st and 7th day for prediction of mortality.

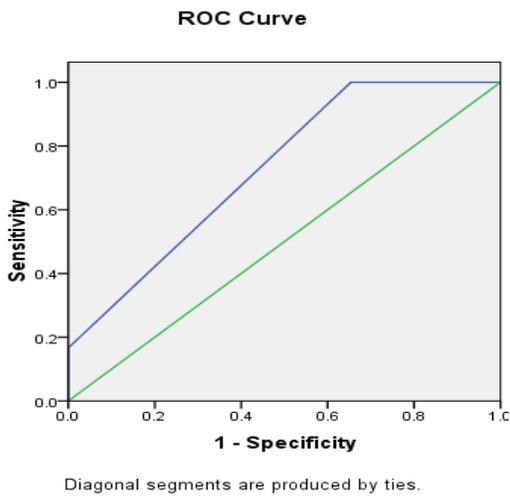


Roc curve of albumin on 1st day

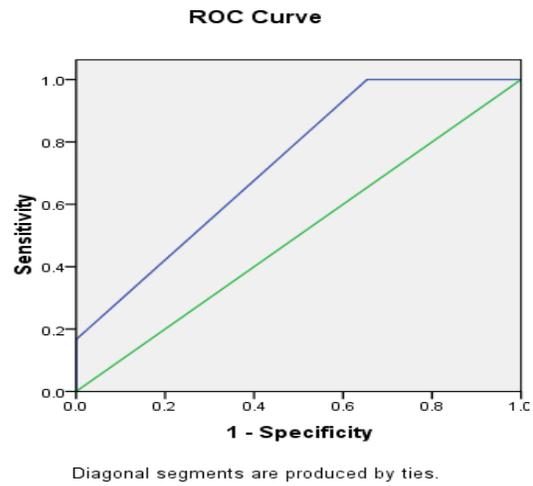


Roc curve of albumin on 7th day

Figure (2): ROC curve of albumin on 1st and 7th day for prediction of mortality.



Roc curve of FAR on 1st day



Roc curve of FAR on 7th day

Figure (3): ROC curve of FAR on 1st and 7th day for prediction of mortality.

DISCUSSION

COVID-19 is one of the most dangerous viral diseases in the world that causes both morbidity and mortality. The most effective defenses against viral illnesses are virus-specific vaccinations and antiviral medications. Broad-spectrum COVID-19 medications however, are still being tested. During the second week of their illness, some patients who have radiographic evidence of pneumonia and have clinical or laboratory indicators of deterioration are admitted to hospitals [8].

Hospitalized COVID-19 patients represent management challenges in isolation units, to hasten the prognosis of COVID-19 patients and the measures mortality prediction that should be applied fast and readily are required. Hospitalized COVID-19 patients frequently have hypercoagulation, which results in high D-dimers and fibrinogen levels which predicts how severe the condition will be [9]. D-dimer, albumin and fibrinogen have been utilized in several studies to predict the severity and death in those patients [10]. Determining the Fibrinogen to Albumin ratio (FAR) as a predictor of disease severity and in-hospital mortality in COVID-19 patients was the purpose of the current study.

All COVID-19 patients hospitalized in Zagazig University Hospitals Isolation Units (29 patients in the ICU and 9 patients in the Ward) were included in this prospective cohort analysis, which found that the mean age was 51.4 ± 7.3 , 55.3% 40% of patients had diabetes mellitus (DM), 15.8% had cardiovascular disease, 13% had respiratory disease, 32% had high blood pressure, 2.6% had neurological disease, and 29% smoked. Of patients, 44.7% were male and 45.3% were female (Table 1).

Küçükceran et al. [11] who examined the predictive usefulness of FAR in COVID-19 patients discovered that, overall, 495 patients (69%) had at least one comorbidity in their medical history, with hypertension being the most prevalent (260 patients, 36.3%). 167 patients (23.3%) were admitted to the intensive care unit out of a total of 550 hospitalized patients (76.7%).

In the present study, the mean CRP, serum ferritin, D-dimer and WBCs on time of admission was 81.1 ± 45.9 , 401.1 ± 264.6 , 0.9 ± 0.45 and 6.9 ± 2.46 respectively (Table 2).

Fibrinogen is an active component of the coagulation cascade and an acute-phase reactant that is secreted by the liver. The epithelial-

endothelial barrier loses its integrity in response to SARS, allowing fluids and proteins, including serum albumin, to move from the intravascular to the extravascular compartments. On the other hand, hypoalbuminemia, which is brought on by hypoxaemia and causes the recruitment of immune cells and the production of inflammatory mediators that cause endothelial dysfunction, does the opposite. Hence, hypoalbuminemia may be employed in COVID-19 patients as a marker of the severity of epithelial-endothelial damage [12].

In the present study, there was a significant variation in FAR between the first and seventh days. Study the FAR ratio in connection to the progression of the disease, which was higher in critically ill cases than severe and higher in severe cases than in moderate cases (Table 3, Table 4).

In consist with this result Bi et al. [13] found that FAR levels in patients with severe disease were much greater than those in the non-severe group, according to researchers who evaluated the prediction of severe illness based on fibrinogen to albumin ratio.

In addition Li et al. [14] and Zhang Xiao [15] have demonstrated that in disorders characterized by inflammation and thrombosis, the fibrinogen-albumin ratio (FAR) is related with poor clinical outcomes. Moreover, Afşin et al. (16) have also mentioned how crucial FAR is for foretelling COVID-19 disease severity.

Çekiç et al. [17] demonstrated that patients who passed away had significantly higher fibrinogen to albumin ratios (p value was ($p < 0.001$)).

According to this study, the average length of stay was 11.7 ± 2.9 days, and 68% of them survived (Table 5).

Also, Küçükceran et al. [11] revealed that the average hospital stay was 9 days (5–14).

Also Atlas et al. [18] who examined the impact of the fibrinogen-to-albumin ratio (FAR) on ICU mortality in COVID-19 patients and found that 80.7% of patients had worse outcomes. The average hospital stay was 12.7 days, and the average length of stay in the ICU was 8.8 days.

The current investigation demonstrated a significant difference in fibrinogen on the seventh day, FAR on the first and seventh days and LOS, which was higher in non survivors than in survivors, between those who survived and those who did not. Albumin levels on the first and seventh days were also significantly different

between the two groups, with non-survivors having lower levels than survivors (Table 6).

In agreement with these results, Küçükceran et al. [11] demonstrated that the non-survivor group's median fibrinogen value was substantially greater than that of the group that survived ($p < 0.001$). In comparison to the survivor group, the median albumin value in the non-survivor group was substantially lower ($p < 0.001$). Also, it revealed that the non-survivors' FAR levels were substantially greater ($p < 0.001$).

Moreover, ÇİÇEKLI et al. [19] who looked at the FAR in COVID-19 patients found that in non-surviving patients as opposed to surviving patients, the FAR values were greater ($p = 0.001$) and the albumin levels were lower ($p = 0.001$). Regarding FAR, there was a considerable variation between the groups ($p < 0.001$). Also ÇİÇEKLI et al. [19] revealed that FAR was considerably higher in patients whose hospital stays lasted longer than a week compared to those whose stays lasted less time ($p = 0.001$). Longer hospital stays the more severe COVID-19 infections and enhanced coagulation cascade are all possible causes of these outcomes.

Also Altuntaş et al. [20] who examined the connections between COVID-19 patients over the age of 65 presenting to the emergency room of a tertiary teaching hospital and their FAR values and their mortality and disease severity found that patients' laboratory values were calculated using the values at the time of initial presentation. Analyzing the lab's measurements showed that fibrinogen ($p = 0.001$) and FAR ($p = 0.001$) were statistically significant in separating patients who had death from those who did not.

The study of Küçükceran et al. [11] demonstrated that the non-survivor group's median FAR value was substantially higher than the survivor group's ($p < 0.001$).

And in line with these earlier research, there was that of Altuntaş et al. [20] who demonstrated that the FAR values in the mortality group were higher than those in the non-fatal group ($p = 0.001$).

Atlas et al. [18] found that 78 patients (76.5%) died, while 24 patients (23.5%) survived their time in the ICU and were transferred to the regular wards. Their FAR scores were noteworthy ($P = 0.001$). The FAR levels of the non-survivors were significantly higher ($p < 0.05$).

According to this study's ROC curve analysis, albumin on the first and seventh days, fibrinogen

on the seventh day and FAR on the seventh day could all be used to predict death (Table 7).

In line with this study, Küçükceran et al. [11] ran ROC analysis to evaluate the FAR's ability to predict in-hospital COVID-19 mortality. The FAR cut-off value of 112.33 was determined to have an AUC value of 0.703 and to have the following characteristics: 71.4% sensitivity, 64% specificity, 29.7% PPD, and 91.3% NPD.

In addition, Atlas et al. [18] demonstrated that ROC curve analysis revealed that FAR was successful in predicting mortality in COVID-19 patients. The FAR's AUCs were 0.989.

Also, Altuntaş et al. [20] indicated that the cut-off value for FAR was 14.4, demonstrating 75.0% sensitivity and 69.0% specificity, and that the area under the AUC value for FAR was 0.731 (95% confidence interval; 0.659-0.802, $p = 0.001$).

Ulloque-Badaracco et al. [21] found that a total of 3693 participants were included in nine researches that evaluated this connection. The AUC ranged from 0.654 to 0.989, while the cut-off was between 0.111 and 0.15. According to the meta-analysis, patients with high FAR values on the COVID-19 had a greater probability of dying (OR: 2.05; 95%CI 1.66-2.54; $p = 0.001$). With a total of 2897 patients, eight researches evaluated this connection. The area under the curve (AUC) was between 0.629 and 0.838, while the cut-off was between 0.088 and 0.15. According to the meta-analysis, COVID-19 patients with high FAR values had a higher probability of developing a serious illness (OR: 2.41; 95% CI 1.41-4.12; $p < 0.001$).

The main limitation in this study is the small number of cases due to shrinkage of pandemic in that period.

We recommended application of FAR in the conventional laboratory workup for following up in-hospital COVID-19 patients. To get at outcomes that are more strongly supported by evidence, additional research with a bigger sample size is advised.

Conclusions:

In COVID-19 patients, the fibrinogen to albumin ratio can be used to predict mortality.

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