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Study of the value of serum amyloid a for predicting the severity and recovery of COVID 19

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Abstract
Background: One of the acute-phase reactants that may rise by a factor of up to a thousand during inflammation is serum amyloid A (SAA). It served as a helpful measure of illness severity in individuals infected with the COVID-19 virus. This study was out to assess SAA's effectiveness in predicting the course and prognosis of COVID-19.
Methods: This case control study was carried out on 60 patients aged from 23 to 55 years old, both sexes, polymerase chain reaction (PCR) confirmed COVID-19 patients and 20 healthy individuals. Patients were subdivided into two groups: Group (1): 20 apparently healthy subjects and Group (2): 60 PCR confirmed COVID 19 patients which sub-classified to: (mild, moderate and severe cases.
Results: The SAA level was positively correlated with CRP (r= 0.714, P= 0.001), serum ferritin (r= 0.738, p< 0.001), D. Dimer (r= 0.477, P= 0.039), and IL6 (r= 0.832, P< 0.001), and negatively correlated with total protein (r= -0.607, P = 0.006). This indicates that SAA is positively correlated with these variables. With a sensitivity of 89.57% and a specificity of 68.19%, the cutoff SAA for COVID-19 patients is more than 126.03 mcg/ml. Patients with mild symptoms or no symptoms at all had much lower SAA levels than those with moderate or severe COVID-19 symptoms, and vice versa; patients with severe symptoms also had significantly higher SAA levels than those with moderate symptoms.
Conclusions: Elevated levels of the SAA protein, an indicator of inflammation, are associated with more serious disease. The sensitivity, specificity, and accuracy of SAA in predicting the severity of COVID-19 are all improved when measured in conjunction with other inflammatory markers. This method provides the best possible disease-specific operational characteristics, which doctors may use to make better judgments in a pinch.

Keywords: SAA, Predicting, Severity, Recovery, COVID19

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was the progenitor of the highly infectious and lethal coronavirus disease 19 (COVID-19), which in turn caused a global pandemic and an enormous number of deaths [1, 2].

COVID-19 pandemic has affected almost all countries and territories worldwide. Wuhan, China was where the first pandemic was initially detected in December 2019. Several countries have advised their nationals to take caution. Public health precautions have included actions including regular handwashing, mask-wearing, social distancing, and avoiding large gatherings. To prevent the transmission of the virus and bring the curve to a more manageable level, measures such as lockdowns and keeping inside have been implemented [3].

SARS-CoV-2 may spread via direct routes such as droplet and human-to-human transmission, as well as through indirect contact via infected items and airborne infection [4]. Upon entry into the body, SARS-CoV-2 begins its infection process. The host's innate and adaptive immunity initiate effective antiviral responses by producing proinflammatory cytokines like interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α from macrophages and monocytes. This process also involves activating T cells, CD4, and CD8+ T cells, crucial for managing viral replication, restricting virus spread, reducing inflammation, and eliminating infected cells [5].

Hepatocytes produce and release acute-phase proteins (APP) such C-reactive protein (CRP) and serum amyloid A (SAA) in response to circulating cytokines, primarily IL-6 [6].

SAA proteins are acute-phase reactants that may rise *in vivo* quantities by up to 1000-fold during inflammation [7].
Recent studies indicate that SAA might serve as a valuable marker for assessing disease severity in COVID-19 patients. Patients with decreasing SAA levels tended to have a more favorable prognosis than those with increasing levels. Patients with elevated levels of SAA in the beginning are more likely to have worse chest computed tomography (CT) scans [8].
This study aimed to assess the utility of SAA in predicting the severity and recovery of COVID-19.

Patients and Methods
This case-control research included 60 patients, aged 23 to 55 years, of both sexes, who were proven to have COVID-19 by PCR testing, as well as 20 healthy persons. The research was conducted with clearance from the Ethical Committee of Tanta University Hospitals in Tanta, Egypt, under approval: 35060/11/21. Patient permission was acquired after providing them with detailed information.
Exclusion criteria were patients with other types of coronaviruses, other inflammatory diseases, any disease affect level of SAA, acute underlying illness and with severe liver failure or malignancy.

Patients were further subdivided into two groups
Group (1): 20 apparently healthy subjects, non-medicated and showed no evidence of any pathological conditions. They were 14 males and 6 females with age ranged from 23-51 years.

Group (2): 60 PCR confirmed COVID 19 patients. They were 39 males and 21 females with age ranged from 25-55 years. Patients were subclassified according to MOHP (Ministry of health and population) to: [Group 2A (Mild cases): 9 patients with no pneumonia, no hypoxia with normal CT imaging, Group 2B (Moderate cases): 32 patients with pneumonia without hypoxia, positive CT imaging and O_2 saturation > 92% and Group 2C (Severe cases): 19 patients with pneumonia and hypoxia, O_2 saturation < 92% respiratory rate > 30 breath/min and lung infiltration > 50%].
All patients completed history taking, clinical examination, and several laboratory investigations including complete blood count (CBC), indicators of severity such as CRP, serum ferritin, D-dimer, interleukin (IL6), liver and renal function tests, and assessment of SAA levels.

Samples collection
The treatment was performed under sterile conditions upon the arrival of each patient. Each person had 8 cubic centimeters of venous blood collected using a disposable sterile plastic syringe. The sample was divided as follows: 2 ml of blood was collected in an EDTA tube and well mixed for a complete blood count. 4 ml of blood was collected in a regular tube and then spun at 3000 RPM for 20 minutes to isolate the serum. Afterward, the serum was divided into two portions, with one portion stored at -20 degrees Celsius until the analysis of SAA. 2 ml of blood was collected in a sodium citrate tube with a composition of 1.6 ml blood and 0.4 ml citrate. The sample was centrifuged at 3000 RPM for 20 minutes to isolate the plasma for D-Dimer analysis.

Measurement of serum (SAA) using ELISA technique
The (SAA) ELISA assay is an enzyme immunoassay for measurement of SAA in human serum supplied by Bioassay Technology Laboratory. No sample or standard was put to the blank well. 50 microliters of standard solution were introduced to the standard wells. 40 microliters of the sample were put to the test wells.10 microliters of anti-SAA antibody were applied to the test wells. 50µl of Streptavidin-HRP was applied to both the standard and test wells. The sealing membrane was then sealed, gently shaken, and incubated for 60 minutes at 37 ºC. A washing solution was made by diluting it 25 times with distilled water for future use. The membrane was delicately removed and the liquid was emptied. Shaken, the rest of the water was blown away. 50 microliters of substrate solution A and 50 microliters of substrate solution B were added to each well, mixed gently, and left to incubate at 37 ºC, away from light, for 10 minutes. To halt the reaction, 50µl of Stop Solution was applied to each well; the color of the liquid quickly became yellow. Last but not least, after 10 minutes of adding the stop solution, the optical density (OD) was measured under a 450 nm wavelength, with the blank well serving as the reference point. The concentration of the standards and their related OD values were used to create the standard curve linear regression equation. The concentration of the samples was then determined by applying the OD values of the samples to this regression equation.

Statistical analysis
Statisticians at IBM© in Chicago, IL, USA, used SPSS v27 to analyze the data. To determine whether the data distribution was normal, the Shapiro-Wilks test and histograms were used. Mean and standard deviation (SD) were used to display quantitative parametric data, which were evaluated using an ANOVA (F) test with a Tukey post hoc test. The Kruskal-Wallis test, in conjunction with the Mann Whitney test for group comparisons, was used to examine quantitative non-parametric data. The data was presented using interquartile range (IQR) and median. The Chi-square test was used to analyze qualitative variables, which were presented as frequency and percentage (%). The link between many variables was examined using Pearson's moment correlation equation. Evaluation of diagnostic precision by means of sensitivity, specificity, PPV, and NPV and other statistical measures. Statistical significance was determined by a two-tailed P value that was lower than 0.05.

Results
There was no statistically significant difference in sex and age between patient groups with varying illness severity and the control group ($p > 0.05$). The results of the patient cohorts. The death rates were 0% in the mild group, 31.3% in the intermediate group, and 73.7% in the severe group. The death rate in the severe group was substantially greater than in the other categories. The recovery rates were 100% in the mild group, 68.8% in the intermediate group, and 26.3% in the severe group. The recovery rate in severe group was significantly lower than of other groups. Table 1

Table 1: Statistical analysis of the results in relation to the patient and control groups' mean sex and age

		Control (n = 20)	Mild (n = 9)	Moderate (n = 32)	Severe (n = 19)	P
Age (years)		37.30±8.31	35.0±5.74	37.72±7.69	41.47±7.89	0.157
Sex	Male	14(70.0%)	7(77.8%)	21(65.6%)	11(57.9%)	0.739
	Female	6(30.0%)	2(22.2%)	11(34.4%)	8(42.1%)	
Outcomes	Survived	--	9(100.0%)	22(68.8%)	5(26.3%)	0.001*
	Death	--	0(0.0%)	10(31.3%)	14(73.7%)	

There was no significant difference between patient group with different disease severity and control group regarding Hb level, RBCs count, platelet count and albumin levels. The levels of total lipids and blood urea were found to be significantly higher in COVID-19 patients experiencing severe symptoms compared to those with mild or moderate symptoms and the control group. Similarly, the neutrophil percentage was found to be significantly higher in the mild, moderate, and severe disease groups than in the control group. On the other hand, the lymphocytic percentage and total protein levels were significantly lower in the mild, moderate, and severe disease groups than in the control group. Compared to the control group and patients with mild symptoms, individuals with moderate to severe COVID-19 symptoms had significantly higher levels of creatinine and liver enzymes (ALT and AST). The total bilirubin levels of COVID-19 patients with severe symptoms were significantly higher than those of patients with mild to moderate symptoms, the control group, and those without symptoms at all. Patients with severe COVID-19 symptoms had far higher direct bilirubin levels than those with mild or moderate symptoms, and this trend was consistent across all illness severity categories when compared to the control group. COVID-19 individuals with severe symptoms exhibited significantly elevated blood urea levels compared to those with minor symptoms. Table 2

Table 2: Comparison of several study groups based on laboratory parameters

	Control (n = 20)	N=60			P
		Mild (n = 9)	Moderate (n = 32)	Severe (n = 19)	
Hb (g/dl)	12.74±0.90	12.63±1.66	12.41±1.68	11.76±2.46	0.340
RBCs ($\times10^9$/ul)	4.63±0.46	4.44±0.53	4.63±0.74	4.38±1.01	0.628
HCT (%)	40.0±4.29	39.07±3.14	38.75±5.79	36.97±8.51	0.474
MVC (fl)	84.92±6.95	84.92±4.44	84.13±6.57	84.42±7.23	0.975
MCH (pg)	28.26±2.26	28.22±1.34	27.16±2.39	26.52±3.02	0.107
MCHC (%)	33.30±0.67	32.69±1.23	32.58±2.39	31.37±3.28	0.071
PLT ($\times10^3$)	255.0(197.5-295.0)	190.0(181.0 – 240.0)	205.5(123.5 – 289.5)	230.0 (120.0 – 305.0)	0.317
TLC ($\times10^3$)	7.70±1.98	6.60±1.81	9.75±4.09	14.05±4.86	<0.001*
p_0		0.882	0.222	<0.001*	
Sig. bet. grps.		p_1=0.120, p_2<0.001*, p_3=0.001*			
SEG (%)	63.20±4.56	79.33±5.15	78.13±9.10	81.37±6.87	<0.001*
p_0		<0.001*	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.971, p_2=0.900, p_3=0.420			
ALT (u/l)	22.40±7.39	26.33±7.48	52.16±20.53	149.4±135.1	<0.001*
p_0		0.519	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.007*, p_2<0.001*, p_3=0.071			
AST (u/l)	10.0 – 30.0	23.0 – 39.0	22.0 – 115.0	30.0 – 320.0	<0.001*
p_0		0.079	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.028*, p_2=0.002*, p_3=0.151			
Total bilirubin (mg/dl)	0.66±0.20	0.58±0.16	0.76±0.36	1.75±3.32	0.014*
p_0		0.328	0.603	0.014*	
Sig. bet. grps.		p_1=0.152, p_2=0.003*, p_3=0.027*			
Direct bilirubin (mg/dl)	0.19±0.04	0.28±0.07	0.39±0.22	1.04±2.14	<0.001*
p_0		0.031*	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.355, p_2=0.012*, p_3=0.020*			
Total protein (g/dl)	6.75±0.49	6.71±0.46	6.78±0.36	6.07±0.79	<0.001*
p_0		0.999	0.997	0.001*	
Sig. bet. grps.		p_1=0.989, p_2=0.019*, p_3<0.001*			
Albumin (g/dl)	3.73±0.30	3.72±0.33	3.93±0.48	3.64±0.54	0.116
Urea (mg/dl)	25.90±5.40	35.44±7.89	64.28±47.88	96.58±66.23	<0.001*
p_0		0.047*	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.119, p_2=0.006*, p_3=0.073			
Creatinine (mg/dl)	0.71±0.19	0.88±0.16	1.29±1.02	1.84±1.38	<0.001*
p_0		0.104	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.213, p_2=0.044*, p_3=0.231			

CRP levels significantly increased in COVID-19 patients with moderate and severe symptoms compared to the control group. CRP levels were significantly elevated in individuals with severe symptoms in comparison to those with mild and moderate symptoms. COVID-19 individuals with moderate and severe symptoms showed statistically significant elevations in serum ferritin and SAA levels compared to those with mild symptoms and the control group. Levels were notably elevated in individuals with severe symptoms in comparison to those with mild

symptoms. Statistically significant elevation in D. dimer levels was seen in COVID-19 patients with moderate and severe symptoms compared to the control group. Additionally, D. dimer levels were notably greater in patients with severe symptoms than in those with mild symptoms. Statistically significant rise in IL6 levels was seen in patient groups with varying illness severity (mild, moderate, severe) and the control group. IL6 levels were notably greater in patients with severe symptoms compared to those with mild and moderate symptoms. Table 3

Table 3: Comparison of several study groups based on CRP, serum ferritin, D. dimer, IL6, and SAA levels.

	Control (n = 20)	Patients (n = 60)			p
		Mild (n = 9)	Moderate (n = 32)	Severe (n = 19)	
CRP (mg/dl)	3.95±1.10	30.33±21.13	68.91±34.34	166.7±43.43	<0.001*
p_0		0.054	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.061, p_2<0.001*, p_3<0.001*			
Serum ferritin (Mcg/L)	46.18±20.15	87.58±41.26	282.1±68.44	677.1±312.8	<0.001*
p_0		0.916	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.009*, p_2<0.001*, p_3<0.001*			
D. dimer (g/L)	0.33±0.15	0.53±0.34	1.30±2.16	3.12±4.48	<0.001*
p_0		0.141	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.151, p_2=0.040*, p_3=0.319			
IL6 (pg/ml)	10.09±4.14	78.67±29.27	95.33±19.78	150.7±34.23	<0.001*
p_0		<0.001*	<0.001*	<0.001*	
Sig. bet. grps.		p_1=0.230, p_2<0.001*, p_3<0.001*			
SAA (mcg/ml)	18.31±8.66	58.02±25.15	134.0±37.08	242.5±57.58	<0.001*
p_0		0.052	<0.001*	<0.001*	
Sig. bet. grps.		p_1<0.001*, p_2<0.001*, p_3<0.001*			

SAA had significant positive correlation with CRP level (r= 0.714, P= 0.001), serum ferritin level (r= 0.738, p< 0.001), D. Dimer level (r= 0.477, P= 0.039) and IL6 level (r= 0.832, p< 0.001)and had significant negative correlation with total protein level (r= -0.607, P =0.006) while there was no correlation with age, Hb concentration, RBCS count, platelet count, total leucocytic count, leucocytic differential count, ALT level, AST level, total bilirubin level, direct bilirubin level, albumin level, blood urea level, creatinine level. Table 4

Table 4: Correlation between SAA with laboratory investigations in severe group

	N=19	
SAA (mcg/ml) vs.	**r**	**p**
Age (years)	0.009	0.969
Hb(g/dl)	-0.266	0.270
RBCs (/ul)	-0.192	0.431
HCT	-0.247	0.308
MVC	-0.191	0.433
MCH	-0.125	0.611
MCHC	-0.039	0.875
PLT ($\times 10^3$)	0.264	0.275
TLC ($\times 10^3$)	0.244	0.313
SEG	0.285	0.236
Lymph (/ul)	-0.315	0.189
ALT (u/l)	0.189	0.439
AST (u/l)	0.156	0.524
Total bilirubin (mg/dl)	0.093	0.706
Direct bilirubin (mg/dl)	0.097	0.692
Total protein (g/dl)	-0.607*	0.006*
Albumin (g/dl)	-0.452	0.052
Urea (mg/dl)	0.103	0.674
Creatinine (mg/dl)	0.330	0.168
CRP (mg/dl)	0.714*	0.001*
Serum ferritin (Mcg/L)	0.738*	<0.001*
D. dimer (g/L)	0.477*	0.039*
IL6 (pg/ml)	0.832*	<0.001*

The cut off SAA for COVID 19 patients is > 126.03 mcg/ml with a sensitivity of 89.47% and a specificity of 68.29%, AUC is 0.915 in the ROC curve analysis with 56.7% PPV, 93.3% NPV and the accuracy is 75%. The cut off CRP for COVID 19 patients is >96 mg/dl with a sensitivity of 73.68% and a specificity of 87.80%, AUC is 0.897 in the ROC curve analysis with 73.7% PPV, 87.8% NPV and the accuracy is 83.33%.

The cut off serum ferritin for COVID 19 patients is >281.03 Mcg/L with a sensitivity of 94.74% and a specificity of 78.05%, AUC is 0.942 in the ROC curve analysis with 66.7% PPV, 97.0% NPV and the accuracy is 83.34%. While the cut off IL6 for COVID 19 patients is >103.7 pg/ml with a sensitivity of 84.21% and a specificity of 68.29%, AUC is 0.918 in the ROC curve analysis with 55.2% PPV while NPV is 90.0% and the accuracy is 73.33%.

After combination between SAA and CRP, the ROC curve analysis shows that AUC = 0.940, sensitivity = 90.2%, specificity = 90.2%, PPV= 80.95%, NPV= 94.87% and accuracy = 90%. While After combination between SAA and ferritin, the ROC curve analysis shows that AUC = 0.938, sensitivity = 78.95%, specificity = 100%, PPV= 100%, NPV= 91.11% and accuracy = 93.33%. Figure 1

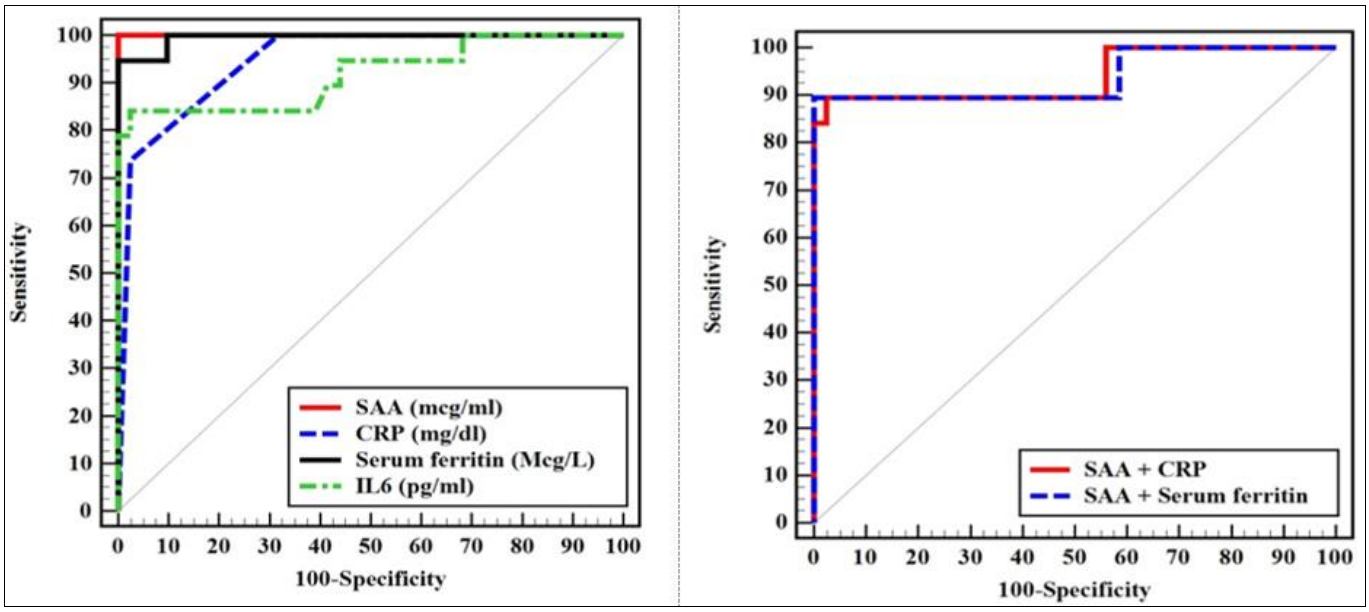

Fig 1: ROC curve for SAA, CRP, serum ferritin and IL6 to predict severe patients from non-severe (mild + moderate)

Discussion

This RNA virus, which resembles a crown, is known as SARS-CoV-2. Its size ranges from 60 to 140 nanometers in diameter. A ridge and a concave surface characterize one side of it. More contacts with ACE2 are made, and the binding interface is bigger. COVID-19's causal agent, SARS-CoV-2, triggered a worldwide epidemic that killed millions of people three years ago [9, 10].

SAAs are significant acute-phase reactants originating from the liver. Inflammation-associated cytokine-peptide hormones secreted by endothelial cells, lymphocytes, and activated monocytes and macrophages primarily regulate their production. The acute-phase response is a synchronized reaction to tissue injury, infection, and inflammation, where acute phase proteins mainly function to restore equilibrium in the body. During substantial inflammation, major acute-phase proteins (APP) may rise by up to 1000 times compared to non-inflammatory settings [11].

The study showed that patients with severe symptoms had higher CRP levels than those with mild or moderate symptoms and the control group. The same results seen by Chen *et al.* [12] reported that Patients with moderate-severe SARS-CoV-2 pneumonia had elevated CRP levels compared to those with a mild illness.

Serum ferritin levels were significantly greater in the moderate-to severe-symptom group compared to the control group and those with mild symptoms, according to this research. The outcome was consistent with Rasyid *et al.* [13] showed that elevated Serum ferritin was an independent predictor of severe SARS-CoV-2 disease.

In this investigation, D. dimer levels were significantly greater in the patient group experiencing moderate to severe symptoms compared to the control group, and in patients with severe symptoms, they were even higher than in patients with milder symptoms He *et al.* [14] confirmed that D-dimer levels had predictive value for patient prognosis, as they were noticeably greater in patients who did not survive compared to those who did. A higher D-dimer score suggested a more critical patient state, and some patients with this consequence also had additional major health issues. Inflammatory reactions to viral infections, endothelial cell dysfunction leading to increased thrombin production, and hypoxia causing coagulation disorders through increased viscosity and the transcription factor-dependent signaling pathway are all potential causes of elevated D. dimer levels in COVID-19 patients [15].

Results showed that IL6 levels were greater in the illness severity group compared to the control group, and that patients with severe symptoms had higher levels than those with mild or moderate symptoms. According to Coomes *et al.*[16] observed that There was a strong correlation between increased IL-6 levels and negative clinical outcomes, and these levels were shown to be much higher in the context of complex COVID-19 illness.

Levels of SAA were significantly higher in patients with severe symptoms than in those with mild or moderate symptoms and the control group. This discovery aligns with the research conducted by Zinellu *et al.* [17]. Increased levels of Serum Amyloid A (SAA) were shown to be strongly linked to more severe disease outcomes, such as clinical assessment, acute respiratory distress syndrome (ARDS) development, and a greater risk of death in COVID-19 patients. The research found that 40% of COVID-19 patients admitted to hospitals died. The mortality rate among individuals with severe symptoms was 73.7%, which was greater than that of those with mild and moderate symptoms. The recovery rate for patients with severe symptoms was 26.3%, which was lower than the rates for other categories. the result was supported by Mahendra *et al.* [18] reported that mortality rate was higher among severe cases than other ones.

Regarding to these results, SAA levels and mortality rate were significantly higher in COVID-19 with severe symptoms than in patients with mild or moderate symptoms and the recovery rate was significantly lower in patients

with severe symptoms than in patients with milder ones. Zhang *et al*. [15] reported that severe COVID-19 symptoms was shown to influence patients' improvement during follow-up and associated with poor outcome.

The present study showed that SAA had a positive correlation with CRP, serum ferritin, D. dimer, and IL6 in COVID 19 patients and this agree with Abdelhakam *et al*. [19] reported that the SAA level was positively correlated with CRP and ferritin levels in patients with COVID 19.

In this study also showed that SAA had a negative correlation with total protein levels. ROC curve was used to analyze the efficiency of SAA, CRP, ferritin and IL6 for predicting severe COVID-19. The accuracy of SAA was higher than the accuracy of IL6 but lower than the accuracy of CRP and ferritin, demonstrating that CRP and ferritin were more efficient in predicting the severity of COVID 19 than SAA and IL6. The second ROC curve was used to estimate the prognostic value of single and combined biomarkers in discriminating between severe and mild COVID 19 patients. After combination between SAA and CRP the accuracy became higher than the accuracy of any single biomarker and after combination between SAA and ferritin the accuracy for them also became higher than the accuracy of each one individually. This means that the combination of these acute phase reactants may be more useful for risk stratification and clinical monitoring of COVID 19 patients than the single biomarker. Combining inflammatory biomarkers has significant potential to improve the classification of COVID-19 patients at arrival. Improved patient triage will enhance the efficient allocation of medical resources [20].

Limitations of this study included that the sample size was relatively small. We excluded patients who had other types of coronaviruses, inflammatory diseases, any disease affect level of SAA levels, acute underlying illness and Patients with severe liver failure or malignancy. Short term follow-up. High cost of ELISA kit.

Conclusions

Elevated levels of the SAA protein, an indicator of inflammation, are associated with more serious disease. The sensitivity, specificity, and accuracy of SAA in predicting the severity of COVID-19 are all improved when measured in conjunction with other inflammatory markers. This method provides the best possible disease-specific operational characteristics, which doctors may use to make better judgments in a pinch.

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Conflict of Interest: Nil.

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