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Estimation of Serum Pre-Albumin in COVID-19 Egyptian Patients

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a newly emerged pathogen with high morbidity and mortality. Laboratory testing is essential in assessing disease severity. Pre-albumin (PAB) is used as a marker of nutrition and found as a negative acute phase protein, decreased markedly in Coronavirus disease 2019 (COVID-19) patients. The aim of the paper measures the serum PAB level in Egyptian patients infected with COVID-19 and correlate its level with clinical, lab biomarkers severity and outcome. The study was conducted at Al-Zahraa University Hospital and the National Research Institute of Tropical Medicine Cairo from March 2021 to August 2021. This study included 90 patients aged above 18 years, divided into 3 groups according to severity (mild, moderate, and severe), each group involved 30 patients who were further classified according to outcome into survived and non-survivors. Serum PAB is markedly decreased in severe COVID-19 patients in comparison to mild and moderate groups with a cut of point between mild and moderate is ≤ 164.2 with a sensitivity of 66.67 and a specificity of 96.5 and cut off point between moderate and severe groups ≤ 130with sensitivity of 55.17and specificity of 76.67. Serum PAB levels decreased in non-survivor patients in comparison to surviving patients. There was a negative correlation between serum PAB and inflammatory markers. Serum PAB is a negative acute phase protein that significantly decreased in severe COVID-19 patients and un-survived patients. It can be used as a marker for covid-19 severity. A single use of PAB could achieve a modest prediction performance for the prognosis of COVID-19. When combined with other conventional laboratory indicators, PAB could produce a better performance.

Keywords: Covid-19, Pre-Albumin, Transthyretin, Biomarker.

1. Introduction

The COVID-19 epidemic was declared a Public Health Emergency of International Concern by the World Health Organization in January 2020 [1]. Within a month of the outbreak in Wuhan, the SARS-CoV-2 virus extended rapidly all over China [2]. It was highly contagious and spread worldwide. In Egypt, from January 2020 to November

2021, there have been 340,269 confirmed cases of COVID-19 with 19,249 deaths, reported to WHO [3]. Since the outbreak of COVID-19, extensive attention has been raised to combat the spread of the virus. To date, no therapeutics have been established to be effective against COVID-19. Different technologies have been applied in vaccine preparation at least 14 vaccines have reached clinical application and/or have been authorized for use against SARS-CoV-2 [3]. If herd immunity among different nations is achieved at a desirable level in the post-vaccination period, the COVID-19 pandemic could be stopped by the end of 2021 [4]. Several inflammatory biomarkers have been implicated in severe COVID-19, suggesting an immunochemical profile consistent with the so-called "cytokine storm" [5]. It is important to note that proinflammatory cytokines appear to be not solely biomarkers, but also causative factors in COVID-19 progression and mortality. Biochemical markers of inflammation including ferritin, CRP, and erythrocyte sedimentation rate (ESR) have all been implicated in severe COVID-19 and can be useful in assessing disease severity [6]. The protein PAB, also known as transthyretin, is a negative acute phase-reactant produced in the liver that acts as a transport protein for thyroxine and is used as a marker of nutrition [7]. Serum PAB exhibited a significant change in the early stage of SARS-CoV-2 infection which decreased markedly. Combined with common symptoms and epidemiology, PAB could act as a surrogate biomarker for the early triage of COVID-19 [8]. The aim of the paper measures the serum PAB level in Egyptian patients infected with covid-19 and correlate its level with clinical, lab biomarkers severity and outcome of the patients.

2. Patients and Methods

The study was conducted at Al-Zahraa University Hospital and the National Research Institute of Tropical Medicine Cairo from March 2021 to August 2021. This study included 90 patients aged above 18 years, divided into 3 groups according to severity (mild, moderate, and severe). Mild cases were symptomatic with lymphopenia or leucopenia with no radiological signs of pneumonia. Moderate cases have pneumonic manifestation with lymphopenia or leucopenia. Severe cases: RR ≥30, SaO2 < 92 on room air, Pa o2 / fi o2 ratio <300, chest radiology showing more than 50 % lesion or progressive lesion within 24 to 48 hours. Each group involved 30 patients who were further classified into survived and non-survivors. Inclusion criteria**:** Patients were diagnosed with Covid-19 by signs and symptoms, Computed tomography (CT) chest findings, and polymerase chain reaction (PCR) for SARS-CoV-2. Exclusion criteria were chronic liver and kidney disease.

2.1 Laboratory Investigation

Complete blood count (CBC), liver function tests (LFTs) including alanine transaminase (ALT) & aspartate aminotransferase (AST), kidney function test including serum creatinine and blood urea nitrogen, prothrombin time (PT), international normalized ratio (INR), and inflammatory markers including serum ferritin, dehydrogenase (LDH), C-reactive protein (CRP), D-Dimer and serum PAB measured by enzyme-linked immunoassay (ELISA).

2.2 Ethical Considerations

The study was done after approval from the local ethics and research committee. Written informed consent was taken from all participants after an explanation of the study.

2.3 Statistical Analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) vs. 23.

Mann-Whitney test, Student's t-test, Kruskal Wallis test, and Fisher's exact test were used to compare groups. P-value < 0.05 was considered statistically significant, P-value > 0.05 is non-significant and P < 0.001 is highly significant. P1 is a comparison of groups I & II (mild vs moderate), P2 is a comparison of groups I & III (mild vs severe), and P3 comparison of groups II & III (moderate vs severe).

3. Results

Demographic data show a highly significant increase in age in Group III in comparison to the other groups while there is no statistically significant difference between the studied groups regards to gender or smoking (Table 1). As regards lymphocytic count, and lymphocytic / Neutrophil ratio: There is a highly significant decrease in group III in comparison to group I & II, while as regard WBCs: There is a significant increase in group III in comparison to group I and group II. As regards albumin there is a statistically highly significant decrease in group III in comparison to group I and group II. As regards PT and INR, there is a highly significant increase in group III in comparison to group I and group II. As regards ALT and AST, there is a statistically significant increase in group III and group II in comparison to group I, as regards urea, there is a statistically highly significant increase in group III & II in comparison to group I (Table 2). There is a highly significant increase of D-dimer, LDH, ferritin, and CRP levels in group III in comparison to group I & II. While there is a highly statistically decrease of PAB level in group III in comparison to group I & II (Table 3). There is a statistically significant relation between outcome and PAB level, the level of PAB is lower in non-survivors than in survived cases (Table 4). There is a statistically highly significant positive correlation between PAB level and absolute lymphocytic count while there is statistically highly significant negative correlation between PAB level and (D-dimer, LDH, ferritin, and CRP). There was statistically negative correlation between pre albumin level and (urea, PT and INR). (Table 5).

The best cut off point between mild and moderate is ≤ 164.2 with sensitivity of 66.67 and specificity of 96.55 and The best cut off point between moderate and sever groups is ≤ 130 with sensitivity of 55.17and specificity of 76.67.(table 6).

Table (1): Demographic data in the studied groups

		Group I (Mild)	Group II (Moderate)	Group III (Sever)	Test value	P-value	P1	P2	P3
		No. = 30	No. = 30	No. = 30					
Age	Mean ± SD	46.60 ± 13.06	54.53 ± 12.95	57.93 ± 12.03	6.303•	0.003 HS	0.018 S	0.001 HS	0.302 NS
	Range	25 – 75	33 – 81	30 – 81					
Gender	Female	13 (43.3%)	15 (50.0%)	12 (40.0%)	0.630*	0.730 NS	–	–	–
	Male	17 (56.7%)	15 (50.0%)	18 (60.0%)					
Smoking	Non-smoker	22 (73.3%)	25 (83.3%)	25 (83.3%)	1.250*	0.535 NS	–	–	–
	Smoker	8 (26.7%)	5 (16.7%)	5 (16.7%)					

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), P1: Mild Vs moderate P2: Mild Vs severe P3: Moderate Vs severe

Table (2): Comparison of complete blood picture, liver function and kidney function test among the studied groups.

		Severity			Test value	P-value	P1	P2	P3
		Group I (mild)	Group II (moderate)	Group III (sever)					
		No. = 30	No. = 30	No. = 30					
Hb	Mean ± SD	13.16 ± 1.59	12.04 ± 1.58	12.33 ± 2.15	2.708	0.072	–	–	–
	Range	9.5 – 15.5	8 – 14.7	7.2 – 16.8		N. S			
Wbcs	Median (IQR)	7.6 (4.7 – 10.6)	6.05 (4.9 – 7.8)	10 (6.4 – 12.5)	8.331	0.016	0.277	0.069	0.005
	Range	1.8 – 15.2	3.7 – 19	2.5 – 33		S	N. S	N. S	S
Lymph	Median (IQR)	1.1 (1 – 1.2)	0.8 (0.7 – 1.1)	0.7 (0.5 – 0.9)	30.042	0.000	0.001	0.000	0.005
	Range	0.6 – 1.5	0.5 – 2	0.3 – 1.2		H. S	H. S	H. S	S
Neutrophil	Median (IQR)	4.1 (3.2 – 6.3)	4.4 (3.7 – 6.2)	3.75 (2.8 – 8.1)	0.080	0.961	–	–	–
	Range	0.2 – 14	0.9 – 15	0.2 – 32		N. S			
L/N ratio	Median (IQR)	0.25 (0.16 – 0.38)	0.19 (0.16 – 0.24)	0.14 (0.09 – 0.26)	7.124	0.028	0.155	0.017	0.078
	Range	0.07 – 5.5	0.05 – 0.75	0.02 – 3.5		S	N. S	S	N. S
Plt	Mean ± SD.	271.90 ± 85.30	242.00 ± 106.06	272.37 ± 105.12	0.921	0.402	–	–	–
	Range	64 – 432	122 – 651	86 – 475		N. S			
Albumin	Mean ± SD	4.00 ± 0.24	3.95 ± 0.37	3.50 ± 0.35	21.495	< 0.001	0.526	0.000	0.000
(g \ dl)	Range	3.5 – 4.5	3 – 4.5	2.6 – 4.2		H. S	N. S	H. S	H. S
ALT	Median (IQR)	20.5 (15 – 33)	31 (24 – 48)	35 (21 – 52)	10.321	0.006	0.003	0.009	0.965
(U \ L)	Range	11 – 64	17 – 135	10 – 114		H. S	H. S	H. S	N. S
AST (U \ L)	Median (IQR)	27 (22 – 35)	42 (25 – 58)	42 (31 – 58)	11.509	0.003	0.006	0.002	0.959
	Range	15 – 53	15 – 139	17 – 235		H. S	H. S	H. S	N. S
PT	Mean ± SD	12.30 ± 0.27	13.84 ± 1.44	15.57 ± 2.52	28.252	< 0.001 H.S	0.001 H. S	0.000 H. S	0.000 H. S
	Range	12 -12.9	12.6-17	1 -2.6					
INR	Mean ± SD	1.08 ± 0.11	1.12 ± 0.14	1.37 ± 0.33	15.342	< 0.001 H. S	0.510 N. S	0.000 H. S	0.000 H. S
	Range	1-1.4	1-1.4	1-2.6					
Urea	Median (IQR)	25(17-37)	40.5(24-56)	46(34-67)	14.684	<.001	.010	0.000	0.287
(mg /dl)	Range	11-107	17-112	23-92		H. S	S	H. S	N. S
Creat (mg/dl)	Median (IQR)	75(.6-1)	8(.7 -1)	9(,6-1,2)	1.435	488 N. S			
	Range	3 -2.7	4 -3.2	4-8					

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), P1: Mild Vs moderate P2: Mild Vs severe P3: Moderate Vs severe.

Table (3): Results of inflammatory markers and PAB level among the studied groups.

		Severity			Test value	P-value	P1	P2	P3
		Group I mild	Group II moderate	Group III sever					
		No. = 30	No. = 30	No. = 30					
D-dimer (microgram \ml)	Median (IQR)	0.4 (0.3 – 0.5)	1.2 (0.7 – 1.5)	1.2 (0.55 – 1.55)	29.723	< 0.001 HS	0.000 HS	0.000 HS	0.889 NS
	Range	0.2 – 1.2	0.2 – 2.3	0.1 – 3.8					
LDH (U\L)	Median (IQR)	196.5 (123 – 248)	234 (197 – 325)	479 (241 – 540)	24.372	< 0.001 HS	0.010 S	0.000 HS	0.003 HS
	Range	67 – 340	128 – 976	128 – 1276					
Ferritin (MICRO \LITER)	Median (IQR)	131 (95 – 215)	354.5 (295 – 465)	498 (365 – 797)	30.457	< 0.001 HS	0.000 HS	0.000 HS	0.009 HS
	Range	58 – 1953	107 – 2000	165 – 1731					
CRP (ml \L)	Median (IQR)	7 (3.8 – 13)	14 (9 – 17)	20 (12 – 47)	20.596	< 0.001 HS	0.001 HS	0.000 HS	0.053 NS
	Range	1.8 – 156	6 – 48	6 – 192					
Pre albumin (ng\ml)	Median (IQR)	207.2(181.4– 242.2)	156 (132.8 –181.7)	126.7 (122.3 – 160)	30.236	0.000 HS	0.000 HS	0.000 HS	0.033 S
	Range	150.1 – 402	114.3 – 498.1	88.7 – 285.2					

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), P1: Mild Vs moderate P2: Mild Vs severe P3: Moderate Vs severe.

Table (4): Comparison of the PAB level in survived & non-survived groups.

PAB (ng \ml)	Survived	non-survivors	Test value	P-value	Sig.
	No. = 79	No. = 11			
Median (IQR)	170.4 (133.4 − 222.5)	124 (118.3 − 181.7)	-2.050	0.040	S
Range	88.7 – 498.1	88.7 – 286			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS), P1: Mild Vs moderate P2: Mild Vs severe P3: Moderate Vs severe

Table (5): Correlation between pre albumin level and other markers

	Pre albumin	
	r	P-value
Hb	0.178	0.098 (NS)
WBCs	0.035	0.744 (NS)
Lymph	0.439**	0.000 (HS)
Neutrophil	0.055	0.608 (NS)
L/N ratio	0.189	0.077 (NS)
Plt	0.151	0.159 (NS)
.D-dimer	-0.349**	0.001 (HS)
LDH	-0.430**	0.000 (HS)
Ferriten	-0.368**	0.001 (HS)
CRP	-0.260*	0.018 (NS)
Albumin	0.276**	0.009 (H.S)
PT	-0.391**	0.000 (H.S)
INR	-0.211*	0.050 (S)
Urea	-0.435**	0.000 (H.S)

P-value >0.05: Non-significant (NS); P-value <0.05: *Significant (S); P-value< 0.01: **highly significant (HS)

Table (6): Cut off point between mild and moderate groups.

Group	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Mild and moderate	≤ 164.2	0.785	66.67	96.55	95.2	73.7
Moderate and sever	≤ 130	0.662	55.17	76.67	69.6	63.9

4. Discussion

PAB is used as a marker of nutrition found as a negative acute phase protein, used as a marker for COVID-19 severity. Our results regarding lymphocytopenia was in agreement with Fan et al who reported lymphocytopenia among most COVID-19 patients on admission and leucopenia [9]. The predominance of lymphopenia in COVID-19 suggests that the virus might act on lymphocytes, particularly T lymphocytes, inducing a reduction of CD4. The mechanism of lymphopenia seems to be due to the cytotoxic action of the virus and the collective characteristics of severe patients which are more likely to be older and have underlying diseases which make them more susceptible to endothelial dysfunction and its correlated lymphopenia [10]. There was a statistically significant increase in ALT and AST levels in group III and group II in comparison to group I. This is in agreement with Sultan et al who found that ALT and AST abnormalities were observed in 13.2% and 8.5% of patients at admission, respectively, and in 29.4% and 17.5% of patients at peak hospitalization, respectively. Hepatic dysfunction in COVID-19 could be related to an uncontrolled immune reaction, sepsis, or drug-induced liver injury, besides the direct cytopathic effect of the virus [11]. In line with our findings, Siddiqi et al reported that there is a significant elevation of inflammatory cytokines and biomarkers, such as interleukin, CRP, ferritin, PCT, and D-dimer [12]. We also found that an elevated D-dimer is associated with increased severity of COVID-19 infection, which can be explained as COVID-19 infection could induce the dysfunction of the hemostatic system, leading to a hypercoagulable state, a condition that commonly encounter in sepsis [13]. We found a high statistical decrease in PAB levels in severe cases in comparison to mild & moderate cases. This can be explained as PAB is a well-known negative acute-phase reactant, therefore its serum concentrations typically decrease during acute inflammatory processes [14].

6. Conclusion

Serum PAB, is a negative acute phase protein, decreased markedly in severe COVID-19 and non-Survived patients. low serum ALB and PAB levels can be used as predictive indicators of malnutrition, severe type of COVID-19 and may be used for prognostic prediction of COVID 19. We recommended further studies on a large number of patients contain control group to validate the results.

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