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Original Article

Levels of Plasma C-reactive protein, Albumin and Pre-Albumin in Nigerian COVID-19 Patients

Ganiyu Olatunbosun Arinola[1], Fabian Victory Edem[1], Temitope Oluwagbenga Alonge[2,3]

[1]Department of Immunology, College of Medicine, University of Ibadan, Ibadan, Nigeria
[2]Department of Surgery, College of Medicine, University of Ibadan, Ibadan, Nigeria
[3]Infectious Diseases Centre, Olodo, Ibadan, Nigeria

Abstract

Aim: COVID-19 is a new viral, rapidly infectious and inflammatory disease, with no treatment currently.However, no study reported combination of high sensitive C-reactive protein (a marker of inflammation), albumin and prealbumin (markers of nutritional status) in the prognosis of COVID-19 among Nigerian COVID-19 patients. We assessed plasma levels of hsCRP, albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in newly admitted COVID-19 patients and COVID-19 patients at discharge.

Material and Methods: Albumin, pre-albumin and C-RP levels were determined in the plasma of confirmed cases of COVID-19 recruited form one Infectious Diseases Center, Ibadan, Nigeria using ELISA. hsCRP-albumin ratio and hsCRP-prealbumin ratio were calculated. All these parameters were compared in both groups of patients and controls.

Results: hsC-RP level was significantly higher in newly admitted COVID-19 patients compared with discharged COVID-19 patients or COVID-19 free control ($p<0.05$). There were no significant differences in plasma levels of albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in both groups of COVID-19 patients compared with control ($p>0.05$).The mean values of plasma hsC-RP, albumin and prealbumin in most COVID-19 patients (89%, 100% and 91% respectively) were within normal reference ranges. hsC-RP were significantly increased in newly admitted COVID-19 patients who were females, above 40 years of age and stayed above 10 days of hospital admission ($p<0.05$ in each case).

Conclusion: PlasmahsC-RP levelmight be a useful prognostic marker of COVID-19. Also COVID-19 in this group of patients exhibited low grade inflammation.

Keywords: COVID-19; inflammatory factors; nutrititional indicators; prognosis

INTRODUCTION

Worldwide, new SARS-COV 2 disease (COVID-19) is a health emergency because itrapidly spread with highfatality and asymptomatic patients are sources of infection (1-3). COVID-19 is divided into 4 types, namely, mild, moderate, severe and critical with severe patients havinghigher mortality rate and longer hospitalization times (4). Thus, prompt identification of early warning signs of progression or severity of COVID-19 may assist in timely initiation of interventions, reduce mortality, improve the cure rate and shorten the hospital admission (5).

The immunopathological processes and eradication strategies of COVID-19 are still in the exploratory stage. The main pathological changes of COVID-19 are lung damage and immune system malfunctions (6). COV attachment to lung epithelial cells through S protein and entrance into cells lead to formation of dsRNA of COV during CoV replication in host cell cytoplasm (7). The host innate immune system detects dsRNA (a Pathogen Associated Molecular Patterns, PAMPs) of COV using Pattern Recognition Receptors (PRRs). This is followed by NF-kB activation which promotes the synthesis of type I IFNs and other proinflammatory cytokines (8). Examples of PRRs involved in human immune response to CoV are Toll-like receptors TLR 2, TLR 4, mannose receptor, scavenger receptor; mannose-binding lectin and C-reactive protein (9). Thus, emphasising the importance of determining the levels of C-RP at different stages of COVID-19.

Serum C-reactive protein (C-RP) and hsCRP are acute-phase proteins synthesized by the liver following cytokine stimulation, infection or inflammation. However, hs C-RP detect lower levels of C-RP (10). The relatively short half-life (approximately 19 hours) of C-RP makes it a useful monitor for infections and inflammatory diseases. In addition, laboratory tests for C-RP are easily available and less costly than cytokine tests (10). C-RP functions to activate the Complement System enhance phagocytosis

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Corresponding Author: Ganiyu Olatunbosun Arinola, Department of Immunology, College of Medicine, University of Ibadan, Ibadan, Nigeria **E-mail:** drarinolaog64@yahoo.com

and an important index for the diagnosis or assessment of severe pulmonary infectious diseases (11). Matsumoto et al reported that C-RP level was raised in severe pneumonia (12). High C-RP levels have been related to prognosis and mortality in critically ill patients (13,14). A large prospective clinical trial demonstrated significantly less cardiovascular risk for patients with hsCRP less than 2.0 mg/L (15). The authors also added that more aggressive treatment strategies may be warranted in subjects with risk of cardiovascular diseases with hsCRP of 3.0 mg/L or those with acute inflammation having hs hsCRP above 10 mg/L (15).

Albumin and prealbumin are among recommended factors to assess the nutritional status but prealbumin was suggested to bemore important (16,17) and a fall in serum prealbuminfor over 6 month was independently associated with increased death risk (18). Albumin was associated with the treatment outcome of cancers and inflammatory diseases (3,8). Previous studies also found that the albumin level was significantly lower in patients with severe COVID-19 (19) while low serum albumin was linked with poor prognosis and high mortality (20). Inter-relation between inflammation and malnutrition was established as malnutrition lead to production of factors of inflammation (21). Several unique characteristics found in severe COVID-19 include lymphopenia, high C-reactive protein (C-RP) level, hypoalbumineamia and underlying co-morbid diseases (22-24). hsCRP-albumin ratio, a combination of markers for systemic inflammation and nutritional status, has been extensively studied as an independent prognostic marker in patients with infection, malignancy, and other diseases (12-21). Based on this knowledge, we hypothesised that the ratio of hsCRP-albumin or hsCRP-prealbumin ratio could be used as a predictive marker for recovery of Nigerian COVID-19 patients. However, none of the above studies was conducted in Nigerian COVID-19 patients. In the present study, we evaluated the association between hsC-RP, hsCRP-albumin ratio or hsCRP-prealbumin ratio as tools to assess the length of hospitalisation or prognostication in Nigerian patients with COVID-19.

MATERIALS and METHODS

Confirmed cases of COVID-19 were recruited from an Infectious Diseases Center, Ibadan, Nigeria. At admission and discharged, the plasma levels of albumin, prealbumin and hsC-RP were determined using ELISA as previously carried out (25) while hsCRP-albumin and hsCRP-prealbumin were calculated. Data were represented as mean±SD and differences between these were calculated using Student-t test. Proportions were compared using Chi-square analysis while correlation was done using Spearmans' Rank test. $p<0.05$ was taken as significant.

ELISA procedure for the determination of plasma levels of albumin, prealbumin and hs C-RP

Venous blood samples were collected from all subjects in 10ml Vacutainer lithium heparin tubes. Blood samples were spun at 1500 x g for 15minutes to obtain the plasma which were frozen and stored at -80^{0}C until. Samples were analyzed for the levels of albumin, prealbumin and hs C-RP based on the method described by the manufacturer. The manufacturer of hs CRP is CalbiotechInc, USA having analytical sensitivity = 0.005 mg/L and detection range = 0.005-0.1 mg/L while the manufacturer for albumin (analytical sensitivity = 1.900 ng/ml and detection range = 6.25 ng/ml - 200 ng/ml) and pre-albumin (analytical sensitivity = 0.415 ng/ml and detection range = 3.125 ng/ml - 100 ng/ml) is Immunology Consultants Laboratory Inc, USA. Fifty (50) µl per well of appropriate sample dilution buffer, antigen standard cocktail or experimental samples was pipetted into microtiter plates. This was incubated at room temperature (25-27°C) for 120 minutes. The ELISA immunoplate was washed 3 times with 350µl/well of washing buffer. One hundred (100) µl per well of detection antibodies was added. This was incubated at room temperature for 60 minutes. The immunoplate was re-washed 3 times with 350µl/well of washing buffer. One hundred (100) µl/well of diluted Avidin-HRP conjugate was added, after which the plate was incubated at room temperature for 30 minutes avoiding light rays. The plate was washed 4 times and 100µl per well of developing solution was added. The reaction was stopped with 100µl/well of Stop Solution and absorbance optical density (O.D) was read at 450nm within 30 minutes following the addition of stop solution. The average absorbance value of each O.D was plotted against corresponding values to plot a standard curve. The average absorbance of each plasma sample was used to determine corresponding albumin, pre-albumin and C-RP value by interpolating from the curve.

RESULTS

The mean plasma level of hsC-RP was significantly increased while the mean plasma levels of albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio were similar in newly admitted COVID-19 patients compared with COVID-19 free control (Table 1). All the levels are within normal reference ranges(hsC-RP=0-5mg/L, Albumin=3.5-5.5g/dL, Prealbumin=15-36mg/dL). The mean levels of hsC-RP, albumin, prealbumin, hsCRP-albumin and hsCRP-prealbumin were similar in discharged COVID-19 patients compared with COVID-19 free control (Table 2). The mean level of C-RP was significantly increased while the levels of albumin, prealbumin, hsCRP-albumin and hsCRP-prealbumin were similar in newly admitted COVID-19 patients compared with discharged COVID-19patients (Table 3). hsC-RP was significantly increased in newly admitted COVID-19 patients above 40years of age compared with patients below 40years of age (Table 4) and in those that were female COVID-19 patients (Table 5). Four each of both COVID-19 patients had values of hsC-RP above the normal reference ranges (Table 6). Only mean level of hsC-RP was significantly increased in COVID-19 patients with hospital admission above 10days compared with those having hospital stay

below 10days (Table 7). Table 8 shows that hsC-RP levels were significantly correlated with ages of newly admitted COVID-19 patients.

Table 1. Comparison of mean levels of hsCRP, albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in newly admitted COVID-19 patients and COVID-19 free control

Variables	COVID (Newly admitted) (n=35)	Control (n=20)	t-value	P-value
hsCRP (mg/L)	4.83±0.72	3.54±0.74	24.434	0.001*
Albumin (g/dL)	5.28±0.02	5.31±0.04	-0.812	0.420
Prealbumin(mg/dL)	21.77±1.34	23.95±1.55	-1.464	0.149
hsCRP-Albumin ratio	0.77±0.14	0.69±0.14	0.349	0.728
hsCRP-Prealbumin ratio	0.20±0.04	0.18±0.03	0.745	0.460

*Significant at p<0.05, Normal ranges: hsCRP =0-5mg/L, Albumin=3.5-5.5g/dL, Prealbumin=15-36mg/dL

Table 2. Comparison of mean levels of hsCRP albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in COVID-19 patients on discharge and control

Variables	COVID (At discharge) (n=35)	Control (n=20)	t-value	P-value
hsCRP (mg/L)	3.60±0.65	3.54±0.74	0.053	0.958
Albumin (g/dL)	5.26±0.03	5.31±0.04	-1.000	0.322
Prealbumin(mg/dL)	23.32±1.47	23.95±1.55	-0.696	0.490
hsCRP-Albumin ratio	0.68±0.12	0.69±0.14	-0.048	0.962
hsCRP-Prealbumin ratio	0.18±0.04	0.18±0.03	0.541	0.591

*Significant at p<0.05, Normal ranges: hsCRP=0-5mg/L, Albumin=3.5-5.5g/dL, Prealbumin=15-36mg/dL

Table 3. Comparison of mean levels of hsCRP albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio o in newly admitted COVID-19 patients and COVID-19 patients at discharge

Variables	COVID (At discharge) (n=35)	Control (n=20)	t-value	P-value
hsCRP (mg/L)	4.83±0.72	3.60±0.65	6.833	0.006*
Albumin(g/dL)	5.28±0.02	5.26±0.03	0.737	0.466
Prealbumin(mg/dL)	21.77±1.34	23.32±1.47	-0.891	0.379
hsCRP-Albumin ratio	0.97±0.14	0.68±0.12	1.139	0.263
hsCRP-Prealbumin ratio	0.20±0.04	0.18±0.04	0.495	0.624

*Significant at p<0.05, Normal ranges: hsCRP=0-5mg/L, Albumin=3.5-5.5g/dL, Prealbumin=15-36mg/dL

Table 4. Comparison of mean levels of hsCRP, albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in newly admitted COVID-19 patients below or above 40years of age

Variables	<40years (n=22)	≥40years (n=13)	t-value	P-value
hsCRP	3.26±0.80	6.47±1.90	-10.708	0.002*
Albumin	5.26±0.03	5.31±0.02	-0.957	0.347
Prealbumin	20.19±1.39	22.08±2.77	-0.649	0.522
hsCRP-Albumin ratio	0.63±0.16	1.22±0.36	-1.751	0.091
hsCRP-Prealbumin ratio	0.18±0.05	0.32±0.11	-1.397	0.174

*Significant at p<0.05

Table 5. Comparison of mean levels of hsCRP, albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in newly admitted male and female COVID-19 patients

Variables	Male (n=21)	Female (n=14)	t-value	P-value
hsCRP	3.51±1.06	4.60±1.19	-2.682	0.042
Albumin	5.28±0.02	5.26±0.04	0.527	0.603
Prealbumin	21.96±2.03	19.24±1.31	1.110	0.277
hsCRP-Albumin ratio	0.67±0.20	0.88±0.23	-0.701	0.489
hsCRP-Prealbumin ratio	0.18±0.06	0.24±0.06	-0.705	0.487

*Significant at p<0.05

Table 6. Comparison of proportions of newly admitted COVID-19 patients, COVID-19 patients at discharge and controls having levels of hsCRP, albumin and prealbumin within or outside normal reference ranges

Variables	COVID (Newly Admitted)	COVID (At Discharge)	Control	P'	P''
hsCRP					
Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0.037*	0.037*
Normal	31 (88.6)	31 (88.6)	36 (100.0)		
Elevated	4 (11.4)	4 (11.4)	0 (0.0)		
Albumin					
Decreased	0 (0.0)	0 (0.0)	0 (0.0)	1.000	1.000
Normal	35 (100.0)	35 (100.0)	36 (100.0)		
Elevated	0 (0.0)	0 (0.0)	0 (0.0)		
Prealbumin					
Decreased	1 (2.9)	1 (2.9)	0 (0.0)	0.593	0.386
Normal	32 (91.4)	30 (85.7)	34 (94.4)		
Elevated	2 (5.7)	4 (11.4)	2 (5.6)		

P' Diagnosis vs Control, P'' Discharge vs Control, *Significant at p<0.05 Normal ranges: hsCRP =0-5mg/L, Albumin=3.5-5.5g/dL, Prealbumin=15-36mg/dL

Table 7. Comparison of mean levels of hsCRP, albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in COVID-19 patients with hospital admission of above or below 10days

Variables	DOA<10days (n=21)	DOA≥10days (n=14)	t-value	P-value
hsCRP	2.62±1.01	4.01±1.03	-3.451	0.030*
Albumin	5.24±0.05	5.29±0.02	-0.957	0.348
Prealbumin	19.04±1.58	20.91±1.65	-0.719	0.479
hsCRP-Albumin ratio	0.51±0.20	0.76±0.20	-0.794	0.434
hsCRP-Prealbumin ratio	0.15±0.07	0.21±0.06	-0.585	0.564

Table 8. Correlation of age with levels of hsCRP, albumin, prealbumin, hsCRP-albumin ratio and hsCRP-prealbumin ratio in newly admitted COVID-19 patients

Correlating pair	COVID (At diagnosis) (n=35)
Age	r, p
hsCRP	0.373, 0.040*
Albumin	0.022, 0.909
Prealbumin	0.125, 0.518
hsCRP-Albumin ratio	0.357, 0.057
hsCRP-Prealbumin ratio	0.316, 0.095

*Significant at p<0.05

DISCUSSION

COVID-19 is prevalent in many countries worldwide and identification of early warning signs for the severity or the timely initiation of intervention is urgently needed (1-3). COVID-19 is divided into 4 types (mild, moderate, severe and critical) and patients with severe or critical cases have a higher mortality rate and longer hospitalisation period, this call for early prognosis to shorten the hospital stay duration (4). Early monitoring of key indicators to guide appropriate management strategies are essential to improve case fatality. It is widely reported that "inflammatory cytokine storm"is the only cause of COVID-19progression (5,9).

C-reactive protein is a reliable biomarker used in clinical practice and it is increasingly expressed in the presence of infection, trauma, tissue necrosis, cancer, and several types of inflammatory diseases (12-14). Albumin and prealbumin reflect nutritional state andthey arenegative acute phase reactants associated with inflammatory diseases or early warning signs of disease progression (16,18). Lower albumin levels were observed in critically ill patients than in severely ill patients (16,18,26). Albumin is a negative indicator of systemic inflammatory response due to increased catabolism or down-regulation of hepatic synthesis or increased capillary permeability can result in the escape of albumin to the interstitial space (27,28). Decreased level of albumin was revealed to be significantly related to poor patient survival (18) or in severe COVID-19 patientswith higher risk of mortality (29,30). Normal levels of albumin in most COVID-19 patients considered for this study might be indicative of reduced catabolism or low capillary leakage of albumin. Therefore, explaining high survival rate of COVID-19 patients in Infectious Diseases Centerconsidered for this study.

The role of albumin in the progression of COVID-19 remains unknown (26) but we hypothesized that plasma albumin level at admission might not serve as a predictive factor for COVID-19 outcomes because the mean level of albumin in newly admitted COVID-19 patients was similar to the levels in discharged COVID-19 patients or control. This might be due to low level inflammation, normal synthentic hepatic function and adequate nutritional status of COVID-19 patients admitted in this center. This adequate level of albumin in COVID-19 patients which indicates normal nutritional status is in support of erroneous belief that COVID-19 is a disease of "well-to-do" people. Since the levels of albumin and prealbumin were similar in both groups of Nigerian COVID 19 patients compared with control, and the levels of albumin and prealbumin were within normal reference ranges. It may be conjectured that COVID-19 patients in this Infectious Diseases Centre were not in critical condition when admitted. This may also be supported by the fact that no death of COVID-19 patients had been reported in this center since it commenced operation in March 2020 coupled with short stay in admission by these patients (6-19 days). Albumin is synthesized in the liver with a serum half-life of approximately 21 days (31), thus it is likely that the level of albumin in the patients during admission was maintained till discharged (maximum of 14 days), thus explaining thesimilarity in the mean levels of albumin among COVID-19 patients at admission and on discharge.

High sensitive CRP is a sensitive systemic marker of inflammation and tissue damage. It has been reported that C-RP binds to ligands exposed on SARS-COV 2 to activate Complement pathways, eventually exacerbating tissue damage and leading to more severe disease(9). Li et al (9) reported that an increase in the C-RP level can be used as an indicator of COVID-19 progression and a meta-analysis also showed that concentrations of C-RP remained high in patients who died of COVID-19 (32). Recently, C-RP was shown to have more relevance than other inflammatory markers for assessing the severity of COVID-19 (19,23,29,30). For example, in 56.4% of the non-severe cases had hsCRP value higher or equal than 5 mg/L, however, in severe cases, the percentage was 81.5% (33,34). The elevated levels of hsC-RP in newly admitted COVID-19 patients compared with control in this study might be due to formation of C-RP as innate immune response to dsRNA of proliferating SARS-COV 2. The implication of this is that cardiovascular effect is imminent if COVID-19 patients are not properly managed. Also, the elevated levels of hsC-RP in newly admitted COVID-19 patients compared with discharged COVID-19 patients could be related to the gradual or slow reduction of SARS-COV 2 reaction products or persistence of SARS-COV 2

despite cure of symptoms. Moreover, the half-life of C-RP is 19 days (10) and the maximum stay of COVID-19 patients in the present center was 14 days. It is possible that the low inflammation still persist in COVID-19 patients when discharged. However, only 4 (11.4%) COVID-19 patients had hs C-RP values above normal reference ranges; therefore it is likely that these 4 patientswere experiencing COVID-19 induced cardiovascular complications.

The hsCRP-albumin ratio or hsCRP-prealbumin ratio reflects the balanced relationship between the severity of the inflammatory reaction and nutritional status. Studies showed that the hsCRP:albumin ratio was predictive of disease progression and mortality in patients with gastric cancer, pancreatic cancer and non-small-cell lung cancer (35,36). hsCRP-albumin ratio or hsCRP-prealbumin ratio were similar in both groups of COVID-19 patients compared with control. Also, mean hsCRP-albumin ratio or hsCRP-prealbumin ratio were similar when COVID-19 patients of different ages, genders and hospital stay were compared. This indicated non-usefulness of hsCRP-albumin ratio or hsCRP-prealbumin ratio in the prognosis and differentiation of COVID-19 in patients from this center.

Plasma hsCRP level was found in this study to be higher in female COVID-19 patients. Gender differences in plasma levels of hsCRP were shown to be higher in healthy women than men (37,38) due to gender differences in both visceral and subcutaneous fat or estrogen, which is known to increase levels of hsC-RP (39). Therefore, determination of the , influence of hormones on COVID-19 severity is desirable. The aging process is characterised by an increase in the concentration of several inflammatory biomarkers especially hsCRP. The age-related increase of inflammatory markers was associated with composition modifications (39). Thus, higher mean plasma hsCRP in COVID-19 patients above 40 years compared with those below 40years is expected.

LIMITATIONS

The limitations of this current study are: small sample size, lack of critically ill COVID-19 patients in Intensive Care Unit of the Center and need to conduct a large-scale multicentre study.

CONCLUSION

Elevated hsCRP level could be a valuable marker to predict the possibility of progression from mild to severe COVID-19. This could help health care workers identify those patients at an early stage for prompt management. Also, COVID-19 in this group of patients was mild with low grade inflammation.

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