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Correlation of Plasma Albumin Status with Markers of Hepato-biliary Dysfunction and Systemic Inflammation Among COVID-19 Patients

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Abstract: *Background*: Several studies have reported profound altered serum albumin level status among patients with COVID-19 disease. Hence, the current study aimed to evaluate the plasma albumin status levels and to establish the relationship between serum albumin level status and markers of hepato-biliary dysfunction and systemic inflammation among COVID-19 patients of African origin. *Methods*: This was a retrospective study of pre-treatment data obtained from patients with confirmed real-time reverse transcription-polymerase chain reaction COVID-19 disease in Eleme COVID-19 treatment center, Port Harcourt, Southern Nigeria. Data were obtained from each patients' case notes, medical review charts, nurses' vital signs/medication charts, laboratory records, and archived data from the electronic medical records using trained research assistants at the treatment center. The data extraction was done using validated data collection templates. Data analysis was done using standard protocols. *Results*: Among the 473 studied cases, 112 (23.7%) had normal plasma albumin status while 361 (76.3%) had low plasma albumin status. Among the low plasma albumin status subgroups, 57.6% and 42.4% had clinically insignificant and clinically significant low plasma albumin status levels, respectively. No difference was observed in the mean plasma levels/activities of all the markers of hepato-biliary dysfunctions between the subjects with normal and low albumin status levels and also between the clinically insignificant and clinically significant low plasma albumin status subgroups ($p>0.05$). However, a statistically significant difference was observed in the mean plasma levels of all the systemic inflammatory markers between the subjects with normal and low albumin status levels as well as between the clinically insignificant and clinically significant low plasma albumin status subgroups ($p<0.05$). Furthermore, no statistically significant relationship existed between the plasma albumin status levels and all the markers of hepato-biliary dysfunctions ($p>0.05$). However, significant inverse relationships existed between plasma albumin status levels and all the systemic inflammatory markers/indices ($p<0.05$). *Conclusion*: The present study indicates that low plasma albumin level status is common among COVID-19 patients and correlates significantly with systemic inflammation. Since COVID-19 is invariably associated with systemic inflammation, albumin may have therapeutic value in COVID-19 management. However, further studies are highly recommended.

Keywords: COVID-19, Low Albumin Status, Hepato-biliary Dysfunction, Inflammation

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathologic viral agent of the current coronavirus disease 2019 (COVID-19) pandemic, has continued to spread all over the world despite all the measures meted against it by both developed and developing societies [1]. Its definitive biology of SARS-CoV-2 has also remained a source of controversy even among the most medical experts to date [1-3]. Additionally, its precise pathophysiologic basis has not also been clearly defined since its evolution in China by the end of 2019 [2-4].

However, the SARS-CoV-2 infection is heralded by varying disturbances in various biochemical and hematologic indices; a feature of the disease that has not been disputed to date [3, 4]. As widely documented in the literature, one of the deranged biochemical hallmarks of the SARS-CoV-2 infection is altered plasma albumin status [5, 6]. The altered plasma albumin status has been linked with various adverse consequences and poor outcomes of the COVID-19 disease in recent times [6].

Several mechanisms have been adduced as the basis for the altered plasma albumin status frequently documented among the SARS-CoV-2 infected patients in the literature [5-9]. Some investigators have suggested the amplified systemic inflammatory events frequently inherent among those infected [6]. The hepato-biliary system also expresses the ACE2 (Angiotensin Converting Enzyme 2) receptors for the SARS-CoV-2 leading some investigators to suggest the hepato-biliary effects of the virus as the culprit for the altered plasma albumin status in COVID-19 disease [10].

Previous studies have evaluated plasma albumin status among COVID-19 patients. However, most of these studies have been documented among the western populations and had included mostly patients with various comorbid conditions, gastrointestinal (GIT) features, and those on medications known to influence plasma albumin status [5-9].

Besides the hepato-biliary dysfunctions and amplified systemic inflammation events as suggested [6, 9], the exact basis of altered plasma albumin remains ill-defined in COVID-19 disease and requires further investigations. Consequently, the current study aimed to determine the plasma albumin status and to determine the relationship between the plasma albumin status and markers of hepato-biliary dysfunction and systemic inflammation among COVID-19 patients of Nigerian origin.

2. Materials and Methods

2.1. Study Design and Population Criteria

The present study was an observational retrospective cross-sectional study including data of patients with confirmed COVID-19 disease who were managed at the Eleme COVID-19 treatment center in Port Harcourt, Southern Nigeria from 2020 to 2022. The Eleme treatment center is one of the three treatment centers set up by the Nigerian Rivers State Government for patients diagnosed with COVID-19 disease. The center has an attached laboratory laden with fully-automated laboratory analyzers.

The eligibility status for inclusion into the study are as follows:

(1). Aged ≥18 years of age.
(2). Positive real time reverse transcription-polymerase chain reaction (RT PCR) test from properly collected nasopharyngeal swab specimens.
(3). Complete relevant demographic, clinical, and laboratory data at presentation.
(4). Nil history of being on drugs known to influence plasma albumin status levels and hepatic functions at least a month before COVID-19 diagnosis.
(5). Nil history of any pre-existing comorbid conditions including liver/renal diseases before diagnosis.
(6). Nil history of anorexia, vomiting, and diarrhea to warrant a significant loss of GIT fluids.
(7). Nil history of current acute/chronic liver and renal disorders at presentation.
(8). Nil history or evidence of abnormal urinalysis findings including microalbuminuria and proteinuria before and at presentation.
(9). Nil history of any form of assisted respiratory at the time of specimen collection for all the laboratory tests.

The study was approved by the Research Ethics Committee of the Rivers State Government Hospital Management Board and was conducted in compliance with the Declaration of Helsinki.

2.2. Data Collection

All data were obtained at the point of diagnosis before any medical/surgical intervention was commenced. Demographic, clinical, and laboratory data were abstracted by well-trained research assistants using validated data collection templates. These data were collected from each patients' case notes, medical review charts, nurses' vital signs/medication charts, laboratory records, and archived data from the electronic medical records in the treatment center.

The demographic data included age, sex, occupation, education levels, marital status, residential area, religion, and smoking/alcohol consumption status. The clinical data included respiratory rate, pulse rate, blood pressure, body mass index, oxygen saturation, comorbid conditions, disease severity, and outcome (discharged home, intensive care admission or treatment, and mortality). The laboratory parameters included biochemical parameters [plasma sodium, chloride, potassium, bicarbonate, urea, creatinine, albumin, and total protein (TP)], hematologic parameters [hemoglobin, total white blood cell count and, differentials including neutrophils, lymphocytes, monocytes, eosinophils, and basophils counts], inflammatory markers [pro-calcitonin, C-reactive protein (CRP), ferritin, Glasgow prognostic score (GPS), fibrinogen, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR)], and liver function test parameters [total bilirubin (TB), conjugated bilirubin (CB), alanine aminotransferase (ALT),

aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) enzyme activities].

2.3. Laboratory Protocols

All blood specimens were obtained immediately on presentation and at admission and analyzed by standard methods in the side laboratory by well-experienced analysts.

At least two levels of commercial control materials were used during each analytical run to evaluate intra-assay and inter-assay coefficient of variations.

2.4. Data Definitions and Stratifications

COVID-19 severity was defined as per the guidelines of the Nigerian Centre for Disease Control National (NCDC) case management as non-severe and severe [11]. The disease severity was defined as the presence of fever >38˚C or suspected respiratory infection, plus one of respiratory rate > 30 breaths/min; severe respiratory distress; oxygen saturation (SpO_2) of ≤ 93% on room air and the presence of co-morbid conditions such as diabetes, asthma, hypertension in adults and cough or difficulty in breathing and at least one of the following central cyanosis or SpO_2 < 92%; severe respiratory distress e.g. grunting breathing, very severe chest in-drawing and signs of pneumonia in children. Confirmed COVID-19 case was defined as positive real-time RT-PCR from a nasal and/or throat swab together with signs, symptoms, and/or radiological findings suggestive of COVID-19 infection. Hematologic-based inflammatory indices such as the composite NLR and the PLR were also derived by calculation using the relevant laboratory indices. While the GPS was determined as previously described [12]. The COVID-19 disease outcome was categorized as discharged home, intensive care unit transfer/treatment care, and mortality. Serum albumin status was defined as normal albumin status (35-52 g/L) and hypoalbuminemia (<35 g/L) [13]. Hypoalbuminemia was further categorized as clinically significant (<25 g/L) or clinically insignificant (25-34 g/L) as previously documented [13].

2.5. Data Management/Statistical Analysis

Data were managed/analyzed using the Statistical Package for Social Sciences software version 25.0 (IBM Co., Armonk, NY, USA). The continuous variables were evaluated for Gaussian distribution using both visual (histogram/probability plots) and statistical (Kolmogorov-Smirnov/Shapiro-Wilk tests) statistical tools.

Those continuous data found not be of Gaussian distribution were log-transformed before analysis and summarized using means ± standard deviations; the comparison was made with the independent student t-test or analysis of variance (ANOVA), where necessary. The categorical data were summarized using proportions with counts/percentages; the comparison was made with the chi-square test or Fisher's exact test and the Yate's continuity correction was applied, where necessary. Simple linear regression models were used to determine the relationships between dependent and independent variables at 95% Confidence Intervals (CI). A p-value difference of less than 0.05 was considered statistically significant.

3. Results

Between 2020 and 2021, 678 RT-PCR positive COVID-19 patients presented at the Eleme COVID-19 treatment center. However, only 473 met the eligibility criteria to be included in the current study. Among the 473 eligible cases, 112 (23.7%) had normal plasma albumin status levels while 361 (76.3%) has low plasma albumin status levels at the initial laboratory evaluation before any form of medical intervention on presentation to the treatment center (Table 1). Among those with low plasma albumin status levels, 208 (57.6%) had clinically insignificant low plasma albumin status levels while 149 (42.4%) had clinically significant low plasma albumin status levels (Table 3).

As shown in Table 1, males predominated among those studied including those with low plasma albumin status levels. Those with low plasma albumin status levels had higher systolic blood pressure, more severe disease, and poor clinical outcomes but had lower oxygen saturation at diagnosis compared with those with normal plasma albumin status levels (<0.05) (Table 1).

As depicted in Table 2, no difference was observed in the mean levels/activities of all the markers of hepato-biliary dysfunctions between the normal and low albumin status subgroups (p>0.05) (Table 2; Panel B). However, those with low plasma albumin status levels had higher mean levels of biochemical parameters including plasma sodium, bicarbonate, urea, and creatinine but lower potassium and total proteins concentrations compared to those with normal plasma albumin status levels (p<0.05) (Table 3; Panel A). Those with low plasma albumin status levels had higher means levels of total white cell count and differential neutrophil counts but lower hemoglobin concentration, differential lymphocyte counts, platelet count, and red cell counts compared with those with normal plasma albumin status levels (Table 2; Panel C).

Also depicted in Table 2, those with low plasma albumin status levels had higher mean values of all the inflammatory markers and indices including pro-calcitonin, C-reactive protein, ferritin, Glasgow prognostic score, fibrinogen, D-dimer, and the composite neutrophil to lymphocyte and the platelet to lymphocyte ratios compared to those with normal plasma albumin status levels (p<0.05) (Table 3; Panel D).

Shown in Table 3, no difference was also observed in the mean levels/activities of all the markers of hepato-biliary dysfunctions between those with clinically insignificant and clinically significant low albumin status levels (p>0.05) (Table 3; Panel B). However, those with clinically significant low plasma albumin status levels also had higher mean levels of various biochemical parameters including plasma sodium, bicarbonate, urea, and creatinine but lower potassium and total proteins concentrations compared to those with clinically significant low plasma albumin status levels (p<0.05) (Table 3; Panel A).

Differences in all the hematologic parameters were also observed between the studied subjects with clinically insignificant and clinically significant low plasma albumin status levels (Table 3; Panel C). Those with clinically significant low plasma albumin status levels had higher means levels of total white cell count and the differential neutrophil counts but lower hemoglobin concentration, differential lymphocyte counts, platelet count, and red cell counts compared with those with clinically insignificant low plasma albumin status levels (Table 3; Panel C).

Also depicted in Table 3, those with clinically significant low plasma albumin status levels had higher mean values of all the inflammatory markers/indices including pro-calcitonin, C-reactive protein, ferritin, Glasgow prognostic score, fibrinogen, D-dimer, and the composite neutrophil to lymphocyte and the platelet to lymphocyte ratios compared to those with clinically insignificant low plasma albumin status levels ($p<0.05$) (Table 3; Panel D).

Table 4 shows the relationship between serum albumin status levels and markers of hepato-biliary dysfunctions as well as the markers of systemic inflammation. As shown, no statistically significant relationship existed between plasma albumin status levels and markers of hepato-biliary dysfunctions ($p>0.05$) (Table 4; Panel A). However, varying degrees of inverse relationships existed between plasma albumin status levels and all the systemic inflammatory markers/indices ($p<0.05$) (Table 4; Panel B).

Table 1. *Basic characteristics of the demographic and clinical variables by plasma albumin status level of study cohorts at diagnosis.*

Variables	All Cohorts n=473 (100%)	PLASMA ALBMUMIN STATUS LEVEL, n=473		
		Normal Albumin Level (35 – 50 g/L) n=112 (23.7%)	Low Albumin level (<35 g/L) n=361 (76.3%)	Normal versus Low p-value
	Mean ± SD/n	Mean ± SD/n	Mean ± SD/n	
Mean Age, years	43.41±7.04	41.7-61±6.53	42.73±6.16	0.073
Sex: Male/female	288/185	69/43	219/142	<0.001*
Occupation: Health worker (Yes/No)	330/143	75/37	255/106	<0.001
Past/current cigarette smoker: Yes/No	51/422	20/92	31/330	0.061
Alcohol consumption status: Yes/No	98/375	28/84	70/291	0.131
Mean BMI, kg/m^2	27.86±4.67	28.03±4.70	28.17±4.13	0.240
Body temperature, °C	37.9±1.33	37.83±1.06	37.96±1.11	0.069
SBP, mmHg	136.41±6.98	135.80±7.02	140.01±7.10	<0.001*
DBP, mmHg	88.71±5.34	86.63±5.21	87.03±5.06	0.096
HR/minute	77.64±4.83	78.12±4.74	79.01±4.83	0.096
RR/minute	24.45±3.41	23.67±3.33	24.06±3.17	0.114
Oxygen saturation (SpO_2), %	93.36±6.23	92.51±5.94	90.34±5.07	<0.001*
Comorbid conditions:** Yes/No	0/473	0/112	0/361	NA
Disease severity: Yes/No	51/422	2/110	49/312	0.013*
Clinical Outcome				
Discharged/ICU transfer/mortality	394/76/3	108/4/0	286/69/3	<0.001*

*Statistically significant; M±SD: mean ± standard deviation; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; ICU: Intensive Care Unit.

Table 2. *Distribution of laboratory parameters among all studied subjects and by albumin status.*

Parameters (Reporting Units)	All Cohorts n=473	PLASMA ALBUMIN STATUS LEVEL, n=473		
		Normal Albumin Level (35 – 50 g) n=112	Low Albumin Level (<35 g/L) n=361	Normal versus Low P-value
		Mean ± SD/n	Mean ± SD/n	
A. Basic Biochemical Parameters				
Plasma sodium, mmol/L	142.44±8.11	139.71±8.14	144.43±8.06	<0.001*
Plasma potassium, mmol/L	3.27±1.11	3.32±1.07	3.08±1.06	0.017*
Plasma chloride, mmol/L	96.63±41	94.62±7.54	95.80±7.65	0.067
Bicarbonate, mmol/L	28.78±6.66	26.67±5.88	30.73±6.91	<0.001*
Plasma urea, mmo/L	7.13±1.74	5.90±1.76	7.30±1.82	0.003*
Plasma creatinine, µmol/L	137.67±7.34	118.57±9.06	129.17±10.23	0.041*
Plasma total protein, g/L	64.24±5.18	66.31±5.44	56.32±5.86	<0.001*
B. Hepato-biliary Injury Markers				
Total serum bilirubin, µmol/L	16.39±4.16	15.97±4.22	16.24±4.51	0.277
Conjugated serum bilirubin, µmol/L	6.14±2.70	5.56±2.34	5.93±2.70	0.414
ALT, U/L	58.78±7.13	57.78±6.09	58.14±6.33	0.344
AST, U/L	36.77±6.71	35.44±6.22	36.02±6.54	0.466
ALP, U/L	154.14±11.13	149.36±10.55	151.71±11.01	0.104
GGT, U/L	59.63±7.88	57.55±6.89	58.15±7.07	0.306
C. Hematologic Parameters				
Hemoglobin concentration, g/L	111.63±9.64	109.71±9.71	99.17±8.79	<0.001*
Total WBC x 10^9/L	17.87±3.41	15.51±3.07	18.14±3.32	<0.001*
WBC differentials, n				

Parameters (Reporting Units)	All Cohorts n=473	PLASMA ALBUMIN STATUS LEVEL, n=473		Normal versus Low P-value
		Normal Albumin Level (35 – 50 g) n=112	Low Albumin Level (<35 g/L) n=361	
		Mean ± SD/n	Mean ± SD/n	
Neutrophil count x 10^9/L	13.52±2.77	11.13±2.06	14.08±3.12	<0.001*
Lymphocyte count x 10^9/L	1.20±0.23	1.40±0.27	1.05±0.20	0.011*
Platelet count x 10^9/L	135.61	140.44±8.71	122.3±6.93	<0.001*
Red cell count x 10^{12}/L	3.31±0.93	3.91±0.84	3.22±0.77	0.012*
D. Inflammatory Markers/Indices				
1. Biochemical				
Serum pro-calcitonin, µg/L	2.21±0.79	1.9±0.95	2.96±1.21	<0.001*
Serum C-reactive protein, nmol/L	236.45±9.97	155.61±10.71	269.65±11.34	<0.001*
Serum ferritin, pmol/L	790.67±19.54	648.83±18.43	973±21.37	<0.001*
GPS (as continuous data) x 10^2	127.83±9.78	86.35±6.90	139.46±7.93	<0.001*
2. Coagulation				
Fibrinogen, g/L	6.89±1.55	5.06±1.12	8.71±1.79	<0.001*
D-dimer, µg/L FEU	1,484±91.31	980.57±78.91	1,869±94.83	<0.001*
3. Hematologic				
Neutrophil to lymphocyte ratio	7.45±2.07	6.02±1.24	10.94±2.44	<0.001*
Platelet to lymphocyte ratio	91.21±7.92	78.78±7.41	98.43±8.05	<0.001*

*Statistically significant; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; WBC: white cell count.

Table 3. *Distribution of laboratory parameters based on clinical categories of low plasma albumin.*

Parameters (Reporting Units)	CLINICAL CATEGORIES OF LOW PLASMA ALBUMIN STATUS, n=361		
	Clinically Insignificant (25 – 34 g/L) n=208 (57.6%)	Clinically Significant (<25 g/L) n=149 (42.4%)	P-value
	Mean ± SD/n	Mean ± SD/n	
A. Basic Biochemical Parameters			
Plasma sodium, mmol/L	137.74±8.04	147.71±8.53	<0.001*
Plasma potassium, mmol/L	3.37±1.13	3.02±1.03	<0.001*
Plasma chloride, mmol/L	96.44±7.51	97.03±7.30	0.133
Bicarbonate, mmol/L	27.81±5.56	31.77±6.33	<0.001*
Plasma urea, mmo/L	7.01±1.53	8.81±1.82	<0.001*
Plasma creatinine, µmol/L	121.64±9.76	187.34±11.56	<0.001*
Plasma total protein, g/L	67.76±6.05	52.41±5.31	<0.001*
B. Hepato-biliary Injury Markers			
Total serum bilirubin, µmol/L	16.83±4.13	17.02±4.31	0.168
Conjugated serum bilirubin, µmol/L	6.44±2.08	6.51±2.11	0.604
ALT, U/L	56.53±5.87	56.76±6.03	0.274
AST, U/L	37.65±6.13	36.99±6.20	0.353
ALP, U/L	148.73±9.88	149.01±9.22	0.239
GGT, U/L	59.71±6.43	58.97±6.84	0.133
C. Hematologic Parameters			
Hemoglobin concentration, g/L	117.64±9.43	99.65±8.69	<0.001*
Total WBC x 10^9/L	14.67±3.18	17.31±3.66	<0.001*
WBC differentials, n			
Neutrophil count x 10^9/L	10.08±2.11	15.23±3.51	<0.001*
Lymphocyte count x 10^9/L	1.43±0.33	1.01±0.17	0.001*
Platelet count x 10^9/L	143.03±7.89	117.24±7.20	<0.001*
Red cell count x 10^{12}/L	4.02±1.01	3.02±0.42	0.007*
D. Inflammatory Markers/Indices			
1. Biochemical			
Serum pro-calcitonin, µg/L	1.5±0.72	3.03±1.33	<0.001*
Serum C-reactive protein, nmol/L	147.98±9.67	278.44±10.66	<0.001*
Serum ferritin, pmol/L	617.43±17.51	994±18.56	<0.001*
GPS (as continuous data) x 10^2	79.46±6.43	144.31±8.06	<0.001*
2. Coagulation			
Fibrinogen, g/L	4.95±1.07	9.11±1.84	<0.001*
D-Dimer, µg/L FEU	967.84±67.17	1,905±96.67	<0.001*
3. Hematologic			
Neutrophil to lymphocyte ratio	5.77±1.16	12.53±2.73	<0.001*
Platelet to lymphocyte ratio	72.44±7.05	100.86±8.73	<0.001*

*Statistically significant; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; WBC: white cell count.

Table 4. *Adjusted linear logistic regression analysis between plasma albumin status level and markers of hepato-biliary injuries and systemic inflammation.*

Parameters (Reporting Units)	β**	SE	95% Confidence Interval		p-value
			Lower Border	Upper Border	
A. Hepato-biliary Injury Markers					
Total serum bilirubin, µmol/L	-0.212	1.132	-0.316	-0.145	0.251
Conjugated serum bilirubin, µmol/L	-0.136	1.117	-0.297	-0.108	0.523
ALT, U/L	-0.201	1.138	-0.312	-0.131	0.234
AST, U/L	-0.236	1.122	-0.335	-0.156	0.109
ALP, U/L	-0.122	1.143	-0.278	-0.090	0.331
GGT, U/L	-0.241	1.101	-0.327	-0.165	0.113
B. Inflammatory Markers/Indices					
1. Biochemical					
Serum pro-calcitonin, µg/L	-0.411	0.332	-0.588	-0.276	<0.001*
Serum C-reactive protein, nmol/L	-0.644	0.213	-0.760	-0.477	<0.001*
Serum ferritin, pmol/L	-0.346	0.361	-0.487	-0.307	0.004*
GPS (as continuous data) x 10^2	-0.267	0.241	-0.123	0.386	0.016*
2. Coagulation					
Fibrinogen, g/L	-0.119	0.310	-0.187	-0.063	<0.001*
D-Dimer, µg/L FEU	-0.693	0.198	-0.807	-0.489	<0.001*
3. Hematologic					
Neutrophil to lymphocyte ratio	-0.674	0.214	-0.782	-0.455	<0.001*
Platelet to lymphocyte ratio	-0.224	0.471	-0.352	-0.116	0.027*

*Statistically significant; β: linear correlation coefficient; SE: standard error; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; GGT: gamma-glutamyl transferase; WBC: white cell count; **Adjusted for sex, systolic blood pressure, oxygen saturation, disease severity, plasma sodium, potassium, bicarbonate, total protein, hemoglobin concentration, total WBC, platelet count, and red blood cell.

4. Discussion

4.1. Principal Findings

The current study evaluated the plasma albumin status level and also the relationship between plasma albumin status level and markers of hepato-biliary dysfunctions and systemic inflammation among COVID-19 patients of Nigerian origin. Unlike similar previous studies [5, 6], the present study excluded COVID-19 patients with varied pre-existing comorbid conditions and those on medications known to influence plasma albumin status levels.

Among those studied in the present series, 76.3% had low plasma albumin status levels of which 57.6% and 42.4% had clinically insignificant and clinically significant low plasma albumin status levels, respectively. There was no significant difference in the mean plasma levels/activities of all the markers of hepato-biliary dysfunctions between the subjects with normal and low albumin status levels as well as between the clinically insignificant and clinically significant low plasma albumin status subgroups. However, a statistically significant difference was observed in the mean plasma levels of all the systemic inflammatory markers between the subjects with normal and low albumin status levels as well as between the clinically insignificant and clinically significant low plasma albumin status subgroups. Furthermore, no statistically significant relationship existed between plasma albumin status levels and all the markers of hepato-cellular dysfunctions. However, varying degrees of inverse relationships were observed between plasma albumin status levels and all the systemic inflammatory markers/indices ($p<0.05$).

4.2. Relationship with Existing Literature

In a similar study documented among the Chinese by Chen and colleagues which concurs with the current findings, the authors had reported a 53.7% rate of hypoalbuminemia among their COVID-19 study populations [5].

Chen and colleagues also observed that patients with hypoalbuminemia had higher levels of CRP, D-dimer, and lower levels of lymphocyte and concluded that elevated CRP and decreased lymphocytes were the independent predictors for decreased albumin in COVID-19 patients [5]. Recently, Huang and colleagues had explored the impact of hypoalbuminemia on COVID-19 among Chinese patients and concluded that hypoalbuminemia was associated with poor COVID-19 outcome [6]. Huang and colleagues also surmised that the pronounced hypoalbuminemia reported in their study was may not be explained by hepatocellular dysfunction alone but due to the overwhelming systemic inflammation inherent in COVID-19 disease, which was further corroborated by the significant `negative correlation established between plasma albumin and inflammation markers in that study. Although Huang and colleagues had reported a 35.5% rate of hypoalbuminemia in that study which is lower than the 76.3% rate documented in the present series, their entire study findings seem to concur with the present study findings. The difference in the reported hypoalbuminemia rates between that of Huang and colleagues and the present study may be related to differences in sample size (299 versus 473) and study population characteristics [6]. Similar findings have been reported in two other previous studies documented in Spain among COVID-19 patients [8, 9]. These findings strengthen the existing literature on the inverse relationship between low

plasma albumin status and systemic inflammation in COVID-19 disease [5-9].

4.3. Mechanistic Considerations

Normal plasma albumin status has important physiological functions including maintenance of plasma oncotic pressure, binding different compounds, platelet function inhibitor, vascular permeability effects, and plasma antioxidant activities [14, 15].

In COVID-19 disease, plasma albumin has been reported to down-regulate the biologic receptor [(Angiotensin Converting Enzyme 2 (ACE2)] for SARS-CoV-2 [14].

Plasma albumin decreases in several acute and chronic diseases related to the degree of inflammatory responses generated by these diseases including COVID-19 [14, 15]. Several mechanisms have been described to explain the induction of low plasma albumin status by systemic inflammation in COVID-19 disease. Firstly, the capillary leakage is induced by the release of various inflammatory cytokines and chemokines, which distributes great amounts of albumin to the interstitial space, where it acts as an anti-oxidative agent and a source of amino-acids for cell and matrix synthesis [8, 14]. Secondly, there is also an increased degradation and a decreased albumin synthesis during inflammatory response due to a cytokine-mediated reduced gene transcription, mainly mediated by interleukin-6 and tumor necrosis factor [8, 14-16]. Huang and colleagues had shown that COVID-19-induced cytokine storm causes hepatotoxicity and subsequently critical hypoalbuminemia, which are associated with exacerbation of disease-associated inflammatory responses and progression of the disease and ultimately leads to death for some critically ill patients [16].

4.4. Relevance to Clinical Practice and Future Research

Since the pathophysiology of the SARS-CoV-2 infection is hinged on exuberant systemic inflammation, findings from the current study do indicate that exogenous albumin may be of therapeutic value in the ongoing COVID-19 pandemic. However, a large-scale clinical trial should be undertaken in this regard.

4.5. Strength and Limitations

The study was strengthened by the use of patients' data with no pre-existing comorbidities, GIT clinical features, and on medications known to adversely affect plasma albumin. However, it was limited by a few factors which are areas of improvement in future studies. As with other observational studies, its findings do not indicate a causal inference but are merely association-related.

Secondly, it was a single-centered study with predominantly black populations, so, its findings may not be representative of other regions. Hence, its interpretation and clinical application should be applied with caution. Finally, since the study data were acquired retrospectively, the under-reporting of the actual number of eligible cases cannot also be ruled with certainty.

5. Conclusion

The present study indicates that low plasma albumin level status is common among COVID-19 patients and correlates significantly with systemic inflammation rather than hepatic dysfunction among the studied patients. Based on the reported COVID-19 association with systemic inflammation, plasma albumin may have some therapeutic value in the management of COVID-19 disease. However, further studies, especially large-scale clinical trials, are highly recommended to validate the findings from the current study.

Statement of Ethics

The ethical approval of the study was obtained from the Research Ethics Committee of RSHMB following the review of the study protocols and the study was subsequently executed in compliance with the principles embodied in the Helsinki Declaration.

Disclosure Statement

The authors declared that there is no conflict of interest.

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Author Contributions

All the authors were involved substantially in the concept and design of the study, data acquisition, analysis and interpretation of the data, drafting the article, revising the article critically for its intellectual content, and in the final approval of the version to be published.

Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (CA) upon reasonable request.

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