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Full length Research Article

Calculated Nutritional Indices in Symptomatic Hospitalized Nigerian Covid-19 Patients

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Summary: Multifaceted approaches are needed to control the ongoing COVID-19 pandemic, therefore assessing the patients' nutritional status is desirable to justify the suggestion of biochemical nutritional markers or nutritional indices in the prognosis of COVID-19. This longitudinal study determined biochemical nutritional markers (albumin, prealbumin and total cholesterol) and nutritional indices [Controlling Nutritional Status (CONUT) score and Prognostic Nutritional Index (PNI)] in symptomatic hospitalized COVID-19 patients compared with control. These parameters were related to age, sex and days of admission of the patients. Plasma obtained were analyzed for biochemical nutritional markers and indices calculated. Data were analyzed using the Statistical Package for Social Sciences (SPSS Inc., USA) version 20.0. The mean prealbumin (PAB) and total cholesterol (TC) levels were significantly lower in COVID-19 patients compared to control (P<0.05). PNI classified 90% of COVID-19 patients as well-nourished while CONUT score classified 75.6% of COVID-19 patients as mildly malnourished. In COVID-19 patients at discharge, the mean level of TC was significantly increased compared with COVID-19 patients at admission. The mean albumin level in patients with ≤10days of admission was significantly lower when compared to those with those having >10days of admission. There were no significant differences in the PNI and CONUT scores of the participants in relation to age, gender and days of admission. This study concluded that Severe Acute Respiratory Syndrome Coronavirus 2 (SAR-COV 2) infection affects certain biochemical nutritional biomarkers and that PNI and CONUT could be use as cheap, reliable and affordable nutritional prognostic tools in the management of COVID-19 patients.

Keywords: *SARS-CoV-2 infection; Nutritional indices; Gender; Length of admission*.

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INTRODUCTION

COVID-19 is an infectious viral disease caused by coronavirus SARS-CoV-2. The most common symptoms in hospitalized COVID-19 patients are fever (up to 90% of patients), dry cough (60%-86%), shortness of breath (53%-80%), fatigue (38%), nausea/vomiting or diarrhoea (15%-39%), and myalgia (15%-44%) (Docherty *et al*., 2020). The symptoms appear after an incubation period of approximately 5.2 days (Li *et al*., 2020) and about 97.5% of people develops symptoms within 11.5 days of infection (Lauer *et al*., 2019).The virus is transmitted through respiratory droplets, contact and fomites with high degree of infectivity(Perlman, 2020). SARS-CoV-2 has two principal strains: 'L type' (70%) and 'S' (30%), with the L type being more aggressive and contagious than the S type (Guo *et al*., 2020; Tang *etal*., 2020). Current SARS-CoV-2 pandemic has brought tremendous pressure on public health and medical systems worldwide which requires concerted effort (Timor-Lester, 2020). It has been observed that people that are immune-compromised are highly prone to SARS-CoV-2 infection and least likely to recover (Long *et al*., 2020). Also, older adults and people of any age with serious underlying medical conditions might be at higher risk for severe forms of COVID-19 disease (Long *et al*., 2020). Therefore, susceptibility to SARS-CoV-2 may be related to nutritional status among other factors.

Nutrition has attracted more attention in various clinical fields. Generally, malnutrition is considered an indicator related to increased morbidity and mortality (Vandewoude*et al*., 2019). Therefore, the assessments of early nutritional status of different diseases are important means of identifying malnutrition, nutritional risks, and possible benefit of nutritional interventions. Traditional nutritional measurements (height or Body Mass Index) or laboratory indicators (albumin, prealbumin and total cholesterol levels) were used to assess the nutritional status (Cook *et al*., 2005) and these assist in the prognosis of COVID-19 patients. An expert consensus on COVID-19 suggested that nutritional risk screening should be conducted among in-hospital COVID-19 patients (Barrazzoni *et al*., 2020).This is supported by evidence that nutritional status on admission is closely associated with the prolonged hospitalization or increased mortality (Arodiwe *et al*., 2015; Das, 2015; Anaszewicz and Budznski, 2017). Mearrs, (1996) reported that early recognition of protein malnutrition shortens length of hospital stay and improve patient outcomes.

It has been shown that malnutrition is linked with inflammatory responses and the development of autoimmune diseases (Fukuda *et al*., 2005; Harrison *et al*., 2012). A normal nutritional state is the prerequisite for regulating oxidative stress and inflammatory process which ultimately have impact on immune system (Wu, 2020). Nutrition deficiency leads to different complications and act as negative prognostic factor in COVID-19 patients. Host nutritional status can predict the susceptibility of individuals to be infected with SARS-CoV-2. Malnutrition may promote viral replication by altering both the innate and adaptive immune responses leading to increase susceptibility to infections (Najera et al., 2004).

Controlling Nutritional Status (CONUT) score and Prognostic Nutritional Index (PNI) are increasingly being used as markers of patients' nutritional status (Narumi *et al*., 2013; Zhou *et al*., 2019). CONUT was used to assess early detection of patient poor nutritional status (Ignacio *et al*., 2005). It is calculated from the combination of serum albumin concentration, total blood cholesterol levels, and total peripheral lymphocyte count. Moreover, Prognostic Nutritional Index (PNI) used as a nutritional and inflammation-based index was derived from the serum combination of serum albumin level and total lymphocyte count. Albumin or total lymphocyte count has been used as marker of nutritional status (Gonzalez *et al*., 2011; Bharadwaj *et al*., 2016). Since components of CONUT and PNI changes in COVID-19 patients, it is expected that the CONUT and PNI will be useful in the prognosis of COVID-19 disease.

MATERIALS AND METHODS

Study design and subject's population: This study involved a total of ninety-five hospitalized COVID-19 patients aged between 15-80years (28 females and 67 males). They were confirmed to be infected with SARS-CoV-2 using nucleic acid Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) on nasal and pharyngeal swab specimens according to WHO guideline (Li, 2020). Excluded among COVID-19 patients were those with co-morbidities and who didn't consent for follow-up study. The control subjects consist of 45 uninfected healthy adults (25 males and 20 females) aged between 18years and 65years.

Sample collection: A total of 5ml venous whole blood was collected. Three milliliters (3ml) venous blood sample was collected using pyrogen-free needle and syringes from each participant and dispensed into lithium heparin bottle for albumin, prealbumin and total cholesterol estimation. The remaining 2ml was dispensed into EDTA bottle for total lymphocyte counts (TLC). The blood samples of the patients were collected on the day of admission and another blood sample were collected at the point of discharge when patient had been tested negative for SARS-CoV-2 virus using nucleic acid Reverse-Transcriptase Polymerase Chain Reaction.

Laboratory Analysis

Biochemical nutritional parameters: Plasma albumin and prealbumin were determined using Enzyme Linked Immunosorbent assay kit (Immunology Consultant Laboratory Incorporated) and total cholesterol level was determined using oxidase-peroxidase method (Randox kit) as described by the manufacturer.

Principle of the Enzyme Linked Immunosorbents Assays (ELISA): Human albumin and prealbumin ELISA kits were obtained from Immunology Consultant Laboratory Incorporated, Portland, United State of America with batch number E-80AL and E-80PRE respectively. The procedures of the ELISA kits are based on the Sandwich-ELISA principle as described by the manufacturer. In this assay the prealbumin or albumin present in samples reacts with the anti-prealbumin or anti-albumin antibodies which have been adsorbed to the surface of polystyrene microtitre wells. After the removal of unbound proteins by washing, anti-prealbumin or albumin antibodies conjugated with horseradish peroxidase (HRP) were added. These enzyme-labeled antibodies form complexes with the previously bound prealbumin or albumin. Following another washing step, the enzyme bound to the immunosorbent is assayed by the addition of a chromogenic substrate, 3,3',5,5'-tetramethylbenzidine (TMB). The quantity of bound enzyme is directly proportional to the concentration of prealbumin or albumin in the sample tested. Thus, the absorbanceat 450 nm is a measure of the concentration of prealbumin or albumin in the test sample. The quantity of prealbumin or albumin in the test sample can be interpolated from the standard curve constructed from the standards.

Cholesterol estimation (Oxidase-peroxidase method): Kit was obtained from Randox Laboratories Limited, County Antrim, BT29 4QY, United Kingdom. Plasma Cholesterol was estimated using the enzymatic assay method (Allain *et al*., 1974)**.** Cholesterol is determined after enzymatic hydrolysis and oxidation. The indicator quinoneimine is formed from Hydrogen peroxide and 4-aminoantipyrine in the presence of phenol and peroxidase. A coloured complex that can be measured spectrophotometrically is formed. The intensity of the colour indicates the concentration of cholesterol in the sample (Allain *et al*., 1974).

Total Lymphocyte Counts: This was done using The Sysmex auto-analyser. The Sysmex XN-450 is a multi-parameter quantitative automated hematology analyzer whose function is based on the hydrodynamically focused impedance measurement, the flow cytometry method (using a semiconductor laser) and the SLS-hemoglobin method.

Nutritional Indices

Controlling Nutritional Status score (CONUT Score): The CONUT score was calculated using serum albumin concentration, total cholesterol concentration and total peripheral lymphocytes cell count (Ignacio *et al*., 2005).CONUT scores were used for classification as: Normal scores (0-1), Mild scores (2-4), Moderate scores (5-8) and Severe scores (≥9) (Ignacio *et al*., 2005)

Prognostic Nutritional Index (PNI): PNI was calculated as 10 x Serum Albumin value (g/dL) + 0.005 x Total peripheral blood lymphocyte count (unit/L) (Onodera *et al*., 2005). PNI scores were used for classification as follows: Severe score = PNI < 35, Moderate score = 35≤PNI<38 and Normal score = PNI≥38 (Onodera *et al*.,1985).

Statistical analysis: Data obtained were analysed using Statistical Package for Social Science (SPSS) (version 20). Genders, age, days of admission were presented as frequencies and percentages in each category. Mean between two groups were compared using Student's t-test. Pearson's correlation was used to test the relationship between variables. Difference was considered significant when the p - value was less than 0.05.

Ethical Consideration: The study was conducted after approval was obtained from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Review Committee (UI/EC/20/0233) and informed consent was obtained from each study participant.

RESULTS

Most COVID-19 patients (89.5%) were well-nourished based on Prognostic Nutritional Index and 75% were mildly-malnourished based on Controlling Nutritional Status Score. High percentage (60%) of the patients spent ≤ 10 days on admission (Table 1).

Table 1:
Days of admission and classification of COVID-19 patients into severity groups based on CONUT and PNI.

Variable	Categories	Frequency	Percentage (%)
DOA	≤10 days >10 days	57 38	60 40
CONUT	Normal Mild Moderate Severe	24 71 0 0	25 75 0 0
PNI	Normal Moderate Severe	85 10 0	89.5 10.5 0

Abbreviations: *DOA = Days of Admission, CONUT = Controlling Nutritional Status Score, PNI = Prognostic Nutritional Index*

Table 2:
Comparison of age and biochemical nutritional markers in COVID-19 patients with un-infected controls.

Variables	COVID-19 Positive (n=70)	COVID-19 Negative (n=45)	t-values	p-values
Age (years)	33.80 ±11.80	37.11 ±9.06	-1.111	0.270
Albumin (ng/ml)	4.99 ± 0.70	4.68 ±0.67	1.729	0.088
Prealbumin (ng/ml)	33.82 ±4.53	36.50 ±3.08	-2.412	0.018*
TC (mg/dL)	121.43 ±35.98	163.33 ±27.05	-7.389	0.000*

TC = Total cholesterol
**Significant at p<0.05*

Biochemical nutritional markers of COVID-19 patients were compared with un-infected control. The means levels of prealbumin (p = 0.018) and total cholesterol (p = 0.000) were significantly lower in COVID-19 patients compared with control (Table 2). The mean level of total cholesterol was significantly increased in COVID-19 patients at discharge compared with at admission (p = 0.018) (Table 3).

Table 3:
Comparison of biochemical nutritional markers in COVID-19 patients on admission with those at discharge.

Variables	On admission (n=25)	At discharge (n=25)	t – values	p– values
Albumin (ng/ml)	5.32 ± 0.11	5.27 ±0.0.17	1.357	0.205
Prealbumin (ng/ml)	24.33 ±9.48	26.32 ±10.52	-0.780	0.453
TC (mg/dL)	110.55 ±19.45	149.91 ±55.99	-2.818	0.018*

*TC = Total Cholesterol, *Significant at p<0.05*

Table 4:
Comparison of biochemical nutritional markers in male with female COVID-19 patients.

Variables	Males (n= 49)	Females (n= 21)	t – values	p – values
Albumin (ng/ml)	5.06 ±0.67	4.98 ±0.83	0.374	0.710
Prealbumin (ng/ml)	33.99 ±3.58	32.85 ±6.62	0.829	0.411
TC (mg/dL)	124.84 ±37.42	125.50 ±39.69	-0.058	0.954

*TC = Total Cholesterol, *Significant at p<0.05*

Table 5:
Comparison of biochemical nutritional markers of COVID-19 patients aged less than 40 with COVID-19 patients aged greater than or equal to 40 years.

Variables	Age <40years (n = 51)	Age ≥40 years (n = 19)	t – values	p – values
Albumin (ng/ml)	5.07 ±0.75	4.95 ±0.62	0.542	0.590
Prealbumin (ng/ml)	33.79 ±5.05	33.30 ±3.42	0.350	0.728
TC (mg/dL)	119.65 ±29.78	141.62 ±53.80	-1.866	0.068

*TC = Total Cholesterol; *Significant at p<0.05*

Table 4 shows biochemical nutritional markers of male COVID-19 patients compared with female COVID-19 patients. All the variables showed no significant differences between both genders. Table 5 shows biochemical nutritional markers of COVID-19 patients aged<40 and ≥40 years. All the variables show no significant differences between the two groups. Table 6 shows comparison of biochemical nutritional markers of COVID-19 patients based on their days of admission. The mean albumin level of COVID-19 patients with ≤10days of admission was significantly lower when compared withCOVID-19 patients having >10days of admission (p = 0.030). Using CONUT score, more (39.3%) female COVID-19 patients than male (35.8%) patients, more patients (38.5%) ≥40 years of age than < 40 years of age (27.5%) and more patients (30%) with ≤10days hospital stays than >10days (29%) hospital stay were classified as having normal nutritional status (Table 7).Using PNI, more (82.1%) female COVID-19 patients than male (80.6%) patients, more patients (80.8%) ≥40 years of age than < 40 years of age (76.8%) and more patients (84.2%) with >10days hospital stays than ≤10days (77.2%) hospital stay were classified as having normal nutritional status (Table 8). Pearson's correlation coefficients between age, days of admission with nutritional markers or indices in COVID-19 patients showed no significant correlations (Table 9).

Table 6:
Comparison of biochemical nutritional markers ofCOVID-19patients based on days of admission.

Variables	DOA ≤10 days (n = 42)	DOA >10 days (n = 28)	t – values	p – values
Albumin (ng/ml)	4.86±0.67	5.28±0.71	-2.236	0.030*
Prealbumin (ng/ml)	33.85±4.21	33.39±5.26	0.363	0.718
TC (mg/dL)	123.52±40.27	127.18±34.66	-0.345	0.731

*TC = Total Cholesterol; *Significant at p<0.05*

DISCUSSION

Nigeria is a third world developing country with Low Gross Domestic Product and larger percentage suffering from different forms of malnutrition due to abject poverty. Nutrition has attracted an extensive attention in various clinical fields. Generally, malnutrition is considered as an indicator related to increased morbidity and mortality (Vandewoude *et al*., 2019), therefore an assessment of nutritional state of Nigeria COVID-19 patients is necessary. The early cases of COVID-19 patients in Ibadan, Nigeria presented mostly with mild conditions, and this was related to non-fatal nature of SARS-CoV-2 strain in Nigeria at that time among other factors (Arinola *et al*., 2021).

A significant decrease was observed in prealbumin levels of COVID-19 patients when compared with un-infected healthy control. Inflammation due to cytokine storm and oxidative stress are present in COVID-19 patients (Cecchini and Cecchini, 2020). A study had reported inflammation as an effective inhibitor of protein synthesis, which may inhibit the synthesis of prealbumin (Keller, 2019). Thus, low levels of prealbumin are expected in COVID-19 patients as reported in this study. Also, prealbumin clears circulating toxic metabolites, toxic oxygen species and viral metabolites are known to be in high levels in COVID-19 patients (Wu *et al*., 2020). Thus, consumption of prealbumin in order to neutralize circulating soluble toxic matters might explain its low level in COVID-19 patients compared with controls.

Mean albumin level in COVID-19 patients compared with un-infected healthy control was non-significant compared with control. This is in tandem with previous findings that the level of albumin in COVID-19 patients was normal (Haiyan *et al*., 2020; Liu *et al*., 2020). It was reported that the Angiotensin Converting Enzymes 2 expression in human hepatocytes is not as high as in other organs (Hamming *et al*., 2004), which might explain the non-significant influence of SARS-CoV-2 infection on the synthesis of albumin by the liver.

Table 7:
CONUT distributions of COVID-19 patients according to age, gender and days of admission.

		CONUT distributions					
Variable	**Category**	**Normal**	**Moderate**	**Mild**	**Severe**	**χ^2-values**	**p – values**
Gender	Males	24 (35.8)	0 (0)	43 (64.2)	0 (0)	0.043	0.835
	Females	11 (39.3)	0 (0)	17 (60.7)	0 (0)		
Age	<40 years	19 (27.5)	0 (0)	50 (72.5)0 (0)		1.173	0.279
	≥40 years	10 (38.5)	0 (0)	16 (61.5)	0 (0)		
DOA	≤10 days	17 (30)	0 (0)	40 (70)	0 (0)	0.464	0.496
	>10 days	11 (29)	0 (0)	27 (71)	0 (0)		

DOA = Days of admission*Significant at p<0.05

Table 8:
PNI distributions of COVID-19Patients according to Age, gender and days of admission

		PNI distributions				
Variable	**Category**	**Normal**	**Moderate**	**Severe**	**χ^2-values**	**P – values**
Gender	Males	54 (80.6)	13 (19.4)	0 (0)	0.044	0.833
	Females	23 (82.1)	5 (17.9)	0 (0)		
Age	<40 years	53 (76.8)	16 (23.2)	0 (0)	0.415	0.519
	≥40 years	21 (80.8)	5 (19.2)	0 (0)		
DOA	≤10 days	44 (77.2)	13 (22.8)	0 (0)	1.856	0.173
	>10 days	32 (84.2)	6 (15.8)	0 (0)		

DOA: Days of Admission**;** *Significant at p<0.05

Table 9:
Pearson's correlation coefficients between age, days of admission with nutritional markers or indices in COVID-19 patients.

Correlating pairs		R	P – value
Age	ALB	-0.054	0.697
	PAB	0.016	0.906
	TC	0.228	0.101
	PNI	-0.046	0.740
	CONUT	-0.118	0.405
DOA	ALB	0.226	0.097
	PAB	0.108	0.430
	TC	0.026	0.854
	PNI	0.251	0.067
	CONUT	-0.006	0.967

Abbreviations: DOA = Days of Admission, ALB = Albumin, PAB = Prealbumin, TC = Total Cholesterol, CONUT: Controlling Nutritional Status Score, PNI: Prognostic Nutritional Index
*Significant at p<0.05

A significant decrease in total cholesterol levels of COVID-19 patients was observed when compared with healthy un-infected subjects. Previous authors reported abnormal lipid metabolism in COVID-19 patients (Cao *et al*., 2020; Fan *et al*., 2020). Our finding might be attributed to alteration of vascular permeability by SAR-CoV-2 leading to leakage of cholesterol molecules into tissues, such as alveolar spaces forming exudates. Also, low mean cholesterol level in COVID-19 patients might due to high degradation of lipids because of its vulnerability to free radicals generated by viral infected host cells. High concentrations of free radicals were reported in COVID-19 patients (Arinola, 2020). Reduced cholesterol level in COVID-19 patients considered for this study might also be due to its consumption since it was shown that cholesterol enhances viral entry, increases ACE 2 and furin availability (Wang *et al*, 2020). Therefore, cholesterol might have been used up during SARS-CoV-2 infectivity, therefore the use of cholesterol-lowering treatment may worsen the outcome of a COVID-19 infection as previously pointed out (Ravnskov, 2020; Guirgis *et al*., 2020).

Albumin shows a significant increase in COVID-19 patients who spent more than 10 days on admission compared to those that spent less than or equal to 10 days**.** This may be related to protein rich diet given to COVID-19 patients or evidence of reduced inflammation since albumin is a negative acute phase reactant. Increased total cholesterol or albumin reported at discharge of COVID-19 patients who spent >10days on admission might indicate patients' recovery because Fan *et al*., (2020) observed that the total cholesterol levels in COVID-19 patients showed significant decreases at the time of admission as compared to the levels prior to infection, remained relatively low during the course of treatment and returned to the levels prior to infection by the time of discharge.

In this study, Controlling Nutritional (CONUT) status and Prognostic Nutritional Index (PNI) were assessed as markers of nutritional status in COVID-19 patients. Based on CONUT and PNI score of COVID-19 patients, a larger percentage (75.6%) of COVID-19 patients at admission had a mild CONUT score, 24.4% had normal CONUT score while a larger percentage (90%) were classified to have a normal PNI score indicating a well-nourished state of COVID-19 patients. Normal to mild nutritional scores in our COVID-19 patients especially in female patients and those less than 40 years might predict reduced length of hospitalization because poor nutritional state was found to be linked with delay recovery and the protraction of the hospitalization (Van Tonder *et al*., 2017). This present finding confirmed earlier report that most cases of COVID-19 in an Infectious Disease Center, Olodo, Ibadan, Nigeria were mostly mild (Arinola *et al*., 2021).

This study concludes that PNI and CONUT could be use as cheap, reliable and affordable nutritional prognostic tools in the management of COVID-19 patients.

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