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Potentials of Varied Inflammatory Indices in the Prediction of COVID-19 Severity Among Nigerians

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Abstract: *Background:* The coronavirus disease of 2019 (COVID-19) is theorized to be associated with significant inflammatory episodes. This tends to define the severity and culminates in adverse consequences of the disease. Therefore, the current study evaluated the potentials of varied inflammatory markers/indices that define the COVID-19 severity. *Methods:* This was a retrospective analysis of pre-treatment data obtained from patients with positive real-time polymerase chain reaction (RT-PCR)-confirmed COVID-19 disease in one of the treatment centers in Port Harcourt, South-south Nigeria. Data were obtained from case notes, medical review charts, nurses' charts, and laboratory records by trained research assistants in the treatment center using pretested data acquisition templates. Abstracted data were compared between the severe positive and severe negative subgroups and the potentials of varied inflammatory indices were evaluated among the severe positive subgroup using standard protocols. *Results:* A total of 600 eligible cases were studied. Among the eligible cases, 543 (90.5%) had severe negative disease, while 57 (9.5%) had severe positive disease. The severe positive COVID-19 patients had higher mean blood levels of urea, creatinine, pro-calcitonin, C-reactive protein (CRP), ferritin, higher Glasgow prognostic scores (GPS), fibrinogen, D-dimer, fibrinogen-albumin ratio, total white cell count, neutrophil counts, composite neutrophil/lymphocyte ratio (NLR), composite platelet to lymphocyte ratio but lower potassium, albumin, hemoglobin levels, and isolated lymphocyte and platelet counts compared to the severe positive COVID-19 subjects ($p<0.05$). The C-reactive protein, GPS, D-dimer, and the composite NLR ratio indices significantly predicted COVID-19 severity on the crude regression model which was maintained in the adjusted model. However, serum CRP concentrations (AUC: 0.95; 95% CI: 0.82-1.00; $p<0.001$) maintained a more robust predictive potential compared to the GPS (AUC: 0.94; 95% CI: 0.84-1.00; $p<0.001$), D-dimer levels (AUC: 0.89; 95% CI: 0.79-0.94; $p=0.004$), and the composite NLR (AUC: 0.87; 95% CI: 0.77-0.92). *Conclusion:* The current study corroborates the role of inflammation in the COVID-19 disease severity. The clinical utility of these inflammation-induced markers/indices especially the CRP, GPS, D-dimer, and the NLR should be prioritized among Nigerians during the management of the disease.

Keywords: COVID-19, COVID-19 Severity, COVID-19 Inflammatory Markers/Indices

1. Introduction

Currently, the entire world is still grappling with the scourge of the novel coronavirus disease of 2019 (COVID-19) pandemic as the spread of the disease remains unabated in different regions of the world [1]. Many nations have gone through several waves of the pandemic since the evolution of the pandemic [2]. Nigeria is not left out in this regard as the country has already experienced three waves and seems to be entered the fourth wave at the end of 2021 [3].

Since the outbreak in late 2019, the exact origin and the disease pathophysiologic basis have remained elusive to medical experts [4, 5]. However, the most striking and well-understood pathophysiology feature of the COVID-19 disease episode is the induction of dysregulated inflammatory responses in the host, especially in the severe variants of the disease with attendant adverse consequences [4, 5]. As widely reported, these inflammatory responses have been associated with the severity of COVID-19 which culminates in high morbidity/mortality potentials [4].

Several inflammatory markers and indices including the biochemical, coagulation and hematologic parameters have been associated with dysregulated inflammatory cascade in COVID-19 [6-8]. These inflammatory markers/indices have been shown to aid clinical diagnosis and monitoring of COVID-19 patients in several reports [6-13]. However, most of these markers have been evaluated predominantly among the Caucasian populations and very few have evaluated the predictive potentials of these markers in severe COVID-19 infection [11].

Hence, the current study evaluated the potentials of varied, readily available, and inexpensive biochemical, coagulation, and hematologic inflammatory markers/indices in the prediction of severe COVID-19 among patients in Port Harcourt, Nigeria.

2. Materials and Methods

2.1. Study Design and Site

This was a retrospective analysis of data of all eligible inpatients/outpatients managed for COVID-19 at the Eleme treatment center in Rivers State. The treatment was set up by the Rivers State Government in response to the COVID-19 pandemic and receives hundreds of COVID-19 cases per year. The center has a side laboratory that is equipped with automated biochemistry and hematology analyzers for laboratory investigations before and during the management of COVID-19 infection. The laboratory results from these investigations are properly archived at the treatment center by trained medical personnel. The patient attendees in the center are usually referred following a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) positive test result, from a nasal and/or throat swab, at the Rivers State University Teaching Hospital (RSUTH) COVID-19 molecular testing center.

2.2. Ethical Considerations

Approval for the study was granted by the Research Ethics Committee of Rivers State Hospital Management Board (RSHMB) before commencement. The study was conducted with strict adherence to the RSHMB Research Ethics guidelines and in per the principles of the Helsinki Declarations of 1964 and as revised in 2013.

2.3. Sample Size Determination

The sample size was calculated using the sample size formula for evaluating characteristics in a population of >10,000, at a 95% confidence interval and 5% margin of error, using an assumed COVID-19 prevalence rate of 50% [14]. Though the calculated minimum sample size was approximately 480 including an anticipated 10% attrition rate, we had recruited 600 due to availability/accessibility of case records/data which enhanced the power of the present study.

2.4. Study Tools and Population

The study utilized properly archived data of 600 patients with RT-PCR-confirmed COVID-19 disease who were admitted/managed at Rivers State Government-owned Eleme COVID-19 treatment center between 2020 and 2021.

2.5. Eligibility Criteria

The criteria for inclusion were data of adults, with apparently normal/stable health status before COVID-19 diagnosis, and of age ≥18 years as at the time of primary diagnosis/admission in the treatment center. Those excluded were data of the pregnant patients, unconscious patients, COVID-19 re-infected patients, and those with pre-existing inflammatory conditions before COVID-19 diagnosis.

2.6. Data Collection

Data was acquired from the case notes, medical chart reviews, nurses' charts, and laboratory files by well-trained research assistants (nurses/laboratory scientists/doctors) authorized to work at the treatment center. Extraction of data was done using well-designed/pretested data extraction templates. The initial basic variables of which data was acquired included the socio-demographic, clinical and anthropometric data, and body mass index (BMI) calculated as the ratio of weight in kilograms divided by height in meters squared. The various biochemical inflammatory markers/indices of which data were acquired included the pro-calcitonin, C-reactive protein (CRP), and ferritin. The coagulation inflammatory parameters included plasma fibrinogen and D-dimer levels. The derived hematological inflammatory indices were obtained from the full blood count (FBC), WBC differentials, and the platelet count. The other laboratory parameters determined were plasma sodium, potassium, chloride, bicarbonate, urea, creatinine, albumin, total plasma proteins, and hemoglobin concentrations.

2.7. Specimen Acquisition, Processing, and Laboratory Analysis

All specimens were acquired following standard protocols in the treatment center including the laboratory analysis. The heparinized plasma was analyzed for plasma sodium, potassium, bicarbonate, chloride on an ion-selective electrode chemistry analyzer (SFRI 6000, SFRI Diagnostics, Berganton, France). The heparinized plasma was also analyzed for urea, creatinine, albumin, and total protein on an automated chemistry analyzer (BS200, Mindray, Shenzhen, China). EDTA whole blood was analyzed for Hb

concentration, FBC, RBC, and Platelet counts on an automated hematology analyzer (BC10, Mindray, Shenzhen, China).

Plain-tube processed serum was analyzed for pro-calcitonin, D-Dimer, ferritin on an automated immunoassay analyzer (Mini Vidas, Biomerieux, France). The plain tube-derived serum was analyzed for CRP using a CRP analyzer (HEALES, Shenzhen, China). Citrated plasma fibrinogen level was determined using a coagulation analyzer (COA04, Biobase, China).

2.8. Data Definitions/Stratifications

COVID-19 severity was classified based on the Nigerian Centre for Disease Control National (NCDC) case management guideline as non-severe and severe [15]. 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. A confirmed COVID-19 case was defined as a patient with a 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 makers/indices such as the composite neutrophil and lymphocyte ratio (NLR) and the platelet and lymphocyte ratio (PLR) were also derived by calculation using the relevant laboratory indices. While the novel inflammation-based prognostic scores such as the fibrinogen/albumin ratio (FAR) and the Glasgow Prognostic Score (GPS) were also determined. The GPS was further graded as 0, 1 to 2 as previously published [13]. The COVID-19 disease outcome was classified into discharged, ICU transfer/treatment care, and mortality.

2.9. Data Management/Statistical Analysis

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

The continuous data found not be of Gaussian pattern were logarithmically 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.

Crude/adjusted logistic regression models were used to determine the magnitude of the relationship between variables at 95% Confidence Intervals (CI).

Receiver operating characteristics curve (ROC) analysis was used to evaluate the predictive potentials of relevant inflammatory parameters. ROC cut-off points were determined by searching for the maximum Youden's index (sensitivity + specificity–1). A p-value difference of less than 0.05 was deemed statistically significant.

3. Results

During the studied period, 678 positive COVID-19 patient attendees presented in the treatment center, however, 600 met the eligibility criteria to be included in the analysis.

As depicted in Table 1, a total of 600 eligible cases were studied. Among these cases, 543 (90.5%) had severe negative disease, while 57 (90.5%) had severe positive disease. No age difference was observed among the severe negative and the severe positive subgroups (Table 1). However, there was significant gender difference with male predominance including differences in educational/marital status, area of residence, smoking history, BMI status, systolic blood pressure, oxygen saturation, and disease outcomes between the severe negative and the severe positive COVID-19 disease subgroups ($p<0.05$; Table 1).

Compared to the severe negative COVID-19 patients, the severe positive subjects had higher mean plasma levels of urea, creatinine but lower levels of potassium, albumin, total protein, hemoglobin concentrations (Table 1; Panel A). Additionally, the severe positive COVID-19 subjects also had higher mean levels of pro-calcitonin, CRP, ferritin, GPS parameters, fibrinogen, D-Dimer, and the FAR, total white cell count, isolated neutrophil counts, composite NLR, and composite PLR but lower isolated lymphocyte count and platelet count compared to the severe positive COVID-19 subjects ($p<0.05$) (Table 2; Panels B, C, & D).

On crude logistic regression analysis, serum CRP (OR: 9.44; 95% CI: 6.70 – 12.31; $P<0.001$), GPS (OR: 5.67; 95%CI: 3.66 – 8.31; $p<0.001$), D-dimer (OR: 8.44: 95%CI: 6.05 – 10.54; $p<0.001$), and composite NLR (OR: 7.74; 95%CI: 4.66 – 9.83; $p<0.001$) predicted COVID-19 severity (Table 3; Panels A, B, and C).

Furthermore, the significant associations between serum CRP (OR: 10.4; 95%CI: 7.51 – 13.89; $p<0.001$), composite GPS (OR: 6.78; 95%CI; 4.03 – 8.99; $p<0.001$), D-dimer (OR: 9.11; 95% CI: 7.04 – 12.77; $p<0.001$), composite NLR (OR: 8.55; 95%CI: 5.47 – 10.85; $p<0.001$) and severe COVID-19 was maintained on adjusting for covariates (Table 3; Panels A, B, and C).

In Table 4, serum CRP, GPS, D-dimer, and the composite NLR had significant predictive potentials for COVID-19 severity following ROC analysis. However, serum CRP (AUC: 0.95; 95%CI: 0.82-1.00; $p<0.001$) maintained more robust potentials compared to the composite GPS (AUC: 0.94; 95%CI: 0.84-1.00; $p<0.001$), D-dimer levels (AUC: 0.89; 95%CI: 0.79-0.94; $p=0.004$), and the composite NLR (AUC: 0.87; 95%CI: 0.77-0.92).

Table 1. *Descriptive characteristics of the non-laboratory variables among the studied COVID-19 subjects on presentation to the treatment center.*

Variables	All Cases n = 600 (100%)	Severe –ve cases n = 543 (90.5%)	Severe +ve Cases n = 57 (9.5%)	p-value severe
	Mean ± SD/n	Mean ± SD/n	Mean ± SD/n	–ve vs. +ve
Mean Age, years	42.20 ± 6.71	39.77 ± 5.87	40.89 ± 6.04	0.154
Age groups, years				0.063
18-44 (young adults)	360	351	9	
45-64 (middle-aged)	159	144	15	
≥65 (elderly)	81	48	33	
Gender: Male/female	374/226	339/204	35/22	0.018*
Occupation: Health worker (Yes/No)	346/254	313/230	33/24	0.090
Educational status				<0.001*
None/primary/secondary/tertiary	13/55/135/397	12/50/121/360	1/5/14/37	
Marital status				<0.001*
Married/single/bereaved	425/169/6	386/151/6	39/18/0	
Residential Area: Urban/Rural	570/30	517/26	53/4	<0.001*
Religion: Christian/Moslem	563/37	509/34	54/3	0.070
Cigarette smoker***: Yes/No	83/517	65/479	18/38	<0.001*
Alcohol consumption status: Yes/No	128/472	103/440	25/32	0.066
Mean BMI, kg/m^2	28.15 ± 4.33	28.44 ± 4.29	29.66 ± 5.07	0.011*
BMI classes, kg/m^2				0.094
Ideal weight (18.5 – 24.9)	207	203	4	
Overweight (25.0 – 29.9)	167	150	17	
Obese (≥30.0)	226	190	36	
Body temperature, ^oC	37.9 ± 1.33	37.83 ± 1.06	37.96 ± 1.11	0.069
SBP, mmHg	135.66 ± 7.55	134.43 ± 7.19	139.22 ± 7.03	0.037*
DBP, mmHg	88.74 ± 5.74	87.44 ± 6.02	89.22 ± 5.77	0.055
HR/minute	78.16 ± 4.83	77.32 ± 4.56	77.82 ± 4.91	0.122
RR/minute	24.37 ± 3.22	23.81 ± 3.04	24.13 ± 3.52	0.206
Oxygen saturation (SpO_2),%	93.93 ± 6.19	92.43 ± 6.11	90.88 ± 5.87	0.002*
Comorbid conditions:** Yes/No	190/410	149/394	41/16	<0.001*
Outcome				
Discharged/ICU transfer/mortality	490/106/4	444/99/0	46/7/4	<0.001*
Contact with known case: Yes/No	201/399	188/443	13/57	0.076

*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; **comorbidities include being aged ≥65 years; having cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, HIV/AIDS, diabetes, cancer, obesity, or chronic kidney disease, chronic liver disease; being a cigarette smoker; being a transplant recipient, and receiving immunosuppressive therapy; ***past/current smoker.

Table 2. *Comparative distribution of laboratory parameters at presentation among non-severe/severe COVID-19 subjects.*

Parameters (Reporting Units)	Severe –ve Cases n = 543 (90.5%)	Severe +ve Cases n = 57 (9.5%)	p-value
	Mean ± SD/n	Mean ± SD/n	
A. Non-inflammatory laboratory parameters			
Plasma sodium, mmol/L	134.6 ± 8.66	133.87 ± 8.14	0.278
Plasma potassium, mmol/L	3.71 ± 1.07	3.13 ± 1.12	0.020*
Plasma Chloride, mmol/L	95.55 ± 7.66	94.63 ± 7.14	0.193
Bicarbonate, mmol/L	22.11 ± 4.41	21.89 ± 4.66	0.451
Plasma urea, mmo/L	5.7 ± 1.83	6.8 ± 1.97	0.017*
Plasma creatinine, µmol/L	115.66 ± 10.74	174.89 ± 11.63	<0.001*
Plasma albumin, g/L	35.66 ± 4.51	33.96 ± 4.34	<0.001*
Plasma total protein, g/L	64.17 ± 6.74	59.91 ± 6.77	<0.001*
Hemoglobin concentration, g/L	110.23 ± 9.56	100.05 ± 8.17	0.024*
B. Biochemical inflammatory markers/indices			
Serum pro-calcitonin, µg/L	1.3 ± 0.47	3.4 ± 1.04	<0.001*
Serum C-reactive protein, nmol/L	139.4 ± 10.46	257.88 ± 12.11	<0.001*
Serum ferritin, pmol/L	690.44 ± 23.67	2,066 ± 94.11	<0.001*
GPS (as continuous data) x 10^2	59.14 ± 4.55	157.89 ± 11.54	<0.001*
GPS (as categorical data), score 0/score 1/ score 2	167/128/33	0/90/60	<0.001*
C. Coagulation inflammatory markers/indices			
Fibrinogen, g/L	4.88 ± 1.07	7.35 ± 1.41	<0.001*
D-Dimer, (normal ≤ 500 µg/L FEU)	756.34 ± 98.71	2,677 ± 110.66	<0.001*
Fibrinogen (g/L)/albumin (g/L) ratio, x 10^3	145.11 ± 12.39	307.84 ± 23.41	<0.001*
D. Hematologic inflammatory markers/indices			
Total WBC x 10^9/L	13.73 ± 2.33	17.78 ± 3.41	<0.001*
WBC differentials, n			
Neutrophil count x 10^9/L	10.70 ± 2.11	15.31 ± 2.73	<0.001*

Parameters (Reporting Units)	Severe –ve Cases n = 543 (90.5%)	Severe +ve Cases n = 57 (9.5%)	p-value
	Mean ± SD/n	Mean ± SD/n	
Lymphocyte count x 10^9/L	1.60 ± 0.34	1.10 ± 0.21	0.023*
Monocyte count x 10^9/L	0.90 ± 0.21	1.08 ± 0.26	0.076
Eosinophil count x 10^9/L	0.34 ± 0.07	0.23 ± 0.04	0.058
Basophil count x 10^9/L	0.09 ± 0.02	0.06 ± 0.01	0.059
Platelet count x 10^9/L	140.44 ± 8.71	122.3 ± 6.93	<0.001*
Red cell count x 10^{12}/L	4.30 ± 0.94	4.4 ± 0.83	0.236
Neutrophil to lymphocyte ratio	5.54 ± 1.10	11.22 ± 2.37	<0.001*
Platelet to lymphocyte ratio	87.6 ± 7.81	111.93 ± 8.22	<0.001*

*Statistically significant; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; WBC: white cell count.

Table 3. *The Magnitude of associations between varied inflammatory markers and severity of COVID-19.*

Parameters	COVID-19 Infection Severity			
	Crude logistic regression		Adjusted logistic regression**	
	OR; 95% CI	p-values	OR; 95% CI	p-values
A. Biochemical inflammatory indices				
Serum pro-calcitonin, µg/L	1.20 (0.66 - 1.61)	0.057	1.12 (0.63 – 1.74)	0.065
Serum C-reactive protein, nmol/L	9.44 (6.70 – 12.31)	<0.001*	10.4 (7.51 – 13.89)	<0.001*
Serum ferritin, pmol/L	1.34 (0.77 – 1.89)	0.083	1.27 (0.71 – 1.72)	0.091
GPS (as continuous data)	5.67 (3.66 – 8.31)	<0.001*	6.78 (4.03 – 8.99)	<0.001*
B. Coagulation inflammatory indices				
Fibrinogen, g/L	1.13 (0.64 – 1.37)	0.069	1.09 (0.59 – 1.29)	0.070
D-Dimer, µg/L FEU	8.44 (6.05 – 10.54)	<0.001*	9.11 (7.04 – 12.77)	<0.001*
Fibrinogen/albumin ratio	1.19 (0.73 – 1.73)	0.078	1.11 (0.69 – 1.74)	0.088
C. Hematologic inflammatory indices				
Neutrophil/lymphocyte ratio	7.74 (4.66 – 9.83)	<0.001*	8.55 (5.47 – 10.85)	<0.001*
Platelet/lymphocyte ratio	1.34 (0.98 – 1.92)	0.078	1.29 (0.91 – 1.96)	0.064

*Statistically significant; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; OR: odds ratio; CI: confidence interval; **Adjusted for gender, educational/marital status, residential area, smoking status, BMI, Systolic blood pressure, oxygen saturation, comorbid conditions, disease outcome, and plasma potassium, urea, creatinine, albumin, total protein levels, hemoglobin concentrations, and total white cell, neutrophil, and lymphocyte counts.

Table 4. *Predictive potentials of the significant inflammatory markers/indices for COVID-19 severity.*

Parameters/Reporting units	Cut-off value	Sensitivity,%	Specificity,%	AUC	95% CI	p-value
A. Biochemical inflammatory indices						
Serum C-reactive protein, nmol/L	17.30	95.30	86.50	0.95	0.82-1.00	<0.001*
GPS (as continuous data)	57.90	93.40	84.40	0.94	0.84 -1.00	<0.001*
B. Coagulation inflammatory indices						
D-Dimer, µg/L FEU	768.40	92.60	83.20	0.89	0.79 -0.94	0.004*
C. Hematologic inflammatory indices						
Neutrophil/lymphocyte ratio	7.65	91.70	82.20	0.87	0.77-0.92	0.011*

*Statistically significant; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; AUC: area under the curve; CI: confidence interval.

4. Discussion

4.1. Principal Findings

COVID-19 disease is characterized by significant inflammatory episodes that tend to define the disease severity and culminate in adverse consequences of the disease process. The present study evaluated the potentials of varied inflammatory indices that have been utilized to define the severity of the disease among indigenous blacks of Nigerian origin. In the current study, the severe COVID-19 patients had higher mean levels of plasma/serum pro-calcitonin, C-reactive protein, ferritin, higher Glasgow prognostic scores (both as continuous and categorical data), fibrinogen, D-Dimer, fibrinogen-albumin ratio, total white cell count, neutrophil counts, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio but lower lymphocyte and platelet counts compared to the non-severe COVID-19 subjects. On crude logistic regression model, C-reactive protein, Glasgow prognostic scores, D-dimer, and neutrophil to lymphocyte ratio predicted COVID-19 which remained statistically significant on the adjusted regression model. However, serum C-reactive protein levels maintained more robust potential compared to the Glasgow prognostic scores, D-dimer levels, and the neutrophil to lymphocyte ratio.

4.2. Relationship with Existing Literature

A large number of studies reported since the COVID-19 outbreak have previously shown the release of several markers/indices, pro-inflammatory in characteristics, such as CRP, D-Dimer, Glasgow prognostic scores, and the neutrophil to lymphocyte parameters due to altered physiological and biochemical processes initiated by the disease, resulting in the severity of the disease and resultant adverse consequences such

as heightened morbidity/mortality [16-19].

During the profiling of varying inflammatory biomarkers documented by Alam and colleagues among mild to critically ill severe acute respiratory syndrome corona virus-19 (SARS COVID-19) patients from Karachi, Pakistan, the authors concluded that the several pro-inflammatory markers such as CRP, D-Dimer, and others, which are released in abnormally high concentrations in COVID-19 patients of variable syndrome intensity, tend to be significant indicators of COVID-19 disease severity, progression, and success of treatments [6]. However, the study by Alam and colleagues was limited by sample size (n=48). In another study reported by Iqbal and colleagues among Indian COVID-19 patients with a relatively large sample size population (n=433) compared to that of Alam and colleagues, the authors found elevated pro-inflammatory markers including CRP among the severely ill patients and they concluded that the pro-inflammatory markers be used to differentiate severe from non-severe patients with COVID-19 infection [7]. Similar findings have been documented in two previous Nigerian studies [12, 16].

In another similar study documented in Bangladesh by Rahman and colleagues which agrees with the current study, the study found elevated inflammatory markers in severe COVID-19 infection which correlated with the worse disease outcomes [17]. Furthermore, alterations of novel inflammatory ratios have also been linked with COVID-19 severity. The NLR has been proved to be one of the most effective biochemical markers able to predict severe COVID-19 which have been reported to represent an immune-dysregulated response during the disease with lymphopenia and neutrophilia [20, 21]. As recently documented by Kuluöztürk, the Glasgow prognostic score also has been observed to correlate with COVID-19 infection severity and worse outcome among Turkish patients [22]. The current data presented in this study corroborates the widely observed pathophysiologic basis of COVID-19 severity and underscore the role played by hyper-inflammation in the disease evolution and progression [11-22].

4.3. Mechanistic Considerations

COVID-19 infection has been linked to accelerated exaggeration of cytokine storm (also known as hypercytokinemia) during the disease process, leading to the abnormally elevated production of pro-inflammatory cytokines and chemokines including interleukin-1, interleukin-6, interleukin-18, Tumor Necrosis Factor-alpha among others which have been adduced for the extensive tissue damages and multi-organ failures in COVID-19 infection [12, 18, 19]. These pro-inflammatory cytokines and chemokines-induced inflammatory storms generated by COVID-19 infection hyper-activates inflammatory responses in the host, resulting in the elevated release of varying inflammatory biomarkers/indices, such as the C-reactive protein, D-Dimer, procalcitonin, ferritin, and enzymes [11, 18, 19].

There is also an immune-dysregulated response resulting in distortions of the blood cell parameters notably the raised total WBC and neutrophils but lowered lymphocytes and platelets counts [19, 21]. This is the basis of the use of the hematological ratios because not all the blood cell parameters may be distorted at the same time during the disease process [19, 21].

4.4. Relevance to Clinical Practice and Future Research

Evidence from the current study suggests that these inflammatory markers could be employed as screening and adjunct diagnostic indices to delineate the non-severe from the severe cases of COVID-19 which could facilitate better treatment options. Their clinical utility could also aid in staging the disease since the few current global therapeutic options vary with the disease stage. As potential therapeutic targets, efforts should be geared towards elaborate clinical trials of effective anti-inflammatory agents in this regard. Moreover, the genetic basis of why some patients develop severe disease variants should also be another area of research.

4.5. Strength and Limitations

The study was strongly strengthened by the use of a relatively large sample size population and the recruitment/analysis of only those COVID-19 patients with confirmed positive RT-PCR tests. Yet, the study was limited by some factors which are potential areas for improvement in future research. As with most observational study, its findings does not indicate a cause-effect implication but merely associations.

Secondly, it was a single-center study with predominantly black populations, so, its findings may not be representative of the larger population within the studied region. Under-reporting of the number of cases cannot also be ruled with certainty since the data were retrospectively acquired.

5. Conclusion

The current study corroborates the role of inflammation and the inflammatory markers/indices in association with the COVID-19 disease severity. These inflammatory markers/indices were found in association with COVID-19 severity compared to the non-severe disease. The clinical utility of these studied inflammatory markers/indices especially the C-reactive protein, the Glasgow prognostic score, D-dimer levels, and the neutrophil to lymphocyte ratio should be prioritized among Nigerians. This will aid screening, diagnosis, staging, therapeutic monitoring, and as therapeutic targets, especially in severe COVID-19 infection.

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

All the authors do not have any possible conflicts of interest.

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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