

# Assessment of Surrogate Markers/Indices of Systemic Inflammation Among COVID-19 Patients with and Without Comorbid Conditions

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**Abstract:** Background: As widely reported, comorbid conditions are a significant risk for severe COVID-19 infection which is characterized by heightened adverse consequences. Since cytokine-induced inflammatory processes define COVID-19 severity, this study was aimed to evaluate the burden of COVID-19-induced inflammatory episodes, assessed using surrogate markers/indices of inflammation, among COVID-19 patients with and without comorbid conditions in Nigeria. Methods: This was a retrospective analysis of data obtained from treatment-naïve real-time polymerase chain reaction (RT-PCR) confirmed COVID-19 patients at the Eleme COVID-19 treatment center in Port Harcourt within the southern region of Nigeria. All relevant data was acquired from case notes, medical review charts, nurses' charts, and laboratory records by trained research assistants using data acquisition templates. All the data acquired were analyzed and compared between the COVID-19 patients with and without comorbid conditions using standard descriptive and comparative statistical tools. Results: Among those studied (n=604), 31.8% (n=192) had at least one pre-existing comorbid condition while 68.2% (n=412) had no comorbid conditions before COVID-19 diagnosis/subsequent presentation. The comorbid positive subgroup were mostly males and had higher mean age, BMI, body temperature, SBP, DBP, and higher proportions of elderly patients, high-risk occupational status (health workers) and social behavior (cigarette smoking), obesity, severe disease, and worse disease outcome, but lower oxygen saturation compared to the comorbid negative subjects at presentation. Additionally, the comorbid positive subjects also had higher mean levels of blood urea, creatinine, pro-calcitonin, CRP, ferritin, Glasgow prognostic scores, fibrinogen, D-Dimer, and the fibrinogen-albumin ratio, total white cell counts, isolated neutrophil counts, neutrophil-lymphocyte count ratio, and the platelet-lymphocyte count ratio but lower levels of potassium, albumin, isolated lymphocyte count and isolated platelet count compared to the comorbid negative subjects ( $p < 0.05$ ). The inflammatory markers/indices were significantly associated with obesity, age  $\geq 65$  years, hypertension, past/current cigarette smoking, diabetes, and cardiovascular disease. Conclusion: Comorbidities are significantly associated with amplified systemic inflammatory markers and indices among COVID-19 subjects. This may indicate the pathophysiologic link between various comorbidities and the COVID-19 severity among Nigerians. However, further studies are recommended to substantiate the findings of the current study.

**Keywords:** COVID-19, Inflammatory Markers, Comorbid Conditions

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## 1. Introduction

The ongoing coronavirus disease of 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has put an enormous strain on the global health system and economic activities since it evolved in the late part of 2019 [1, 2]. The disease has continued to spread in virtually every country on earth resulting in the deaths of millions and leaving millions more in shattered health due to post-recovery consequences [2].

Since its evolution, the pathophysiologic background of the disease has been a focus of intense research by several medical experts [3]. This has led several experts to conclude that the pathophysiologic background of the COVID-19-induced morbidity/mortality is hinged on the induction and initiation of overwhelming cytokine storm in the host [4]. This is subsequently followed by massive inflammatory processes that tend to account for the severity of the COVID-19 infection which heightens its morbidity/mortality potentials [4, 5].

The global trend of COVID-19 severity and the COVID-19-induced morbidity and mortality is disproportionately tilted towards those with pre-existing comorbid conditions such as being of age greater than 65 years; having any cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, HIV/AIDS, diabetes, cancer, obesity, or chronic kidney disease, chronic liver diseases; being a cigarette smoker; being a transplant recipient, and receiving immunosuppressive therapy which are all associated with worse COVID-19 outcomes [6-10].

Since the cytokine-induced inflammatory processes define COVID-19 severity, this may be the link between the COVID-19-induced inflammatory processes and the high mortality and mortality potentials of the disease among those with some of these comorbid conditions [4, 5, 10].

Hence, the present study assessed and compared varied systemic inflammatory markers among the treatment-naïve COVID-19 patients with and without comorbid conditions in Nigeria.

## 2. Materials and Methods

### 2.1. Study Design and Site

This was a retrospective analysis of data of all eligible patients managed for COVID-19 at the COVID-19 treatment center in Eleme Local Government Area of Rivers State, South-south Nigeria. The treatment center was set up and is under the management of the Rivers State Government. The center receives and admits hundreds of COVID-19 cases per year and has a side laboratory that is well-equipped with standardized automated chemistry/hematology analyzers dedicated for the laboratory investigations following COVID-19 diagnosis and during the management of each patient. The results from these investigations are properly archived at the treatment center. The COVID-19 patients are usually referred to the treatment center following a positive real-time reverse-transcriptase polymerase chain reaction

(RT-PCR) test result from a nasal and/or throat swab at the Rivers State University Teaching Hospital (RSUTH) molecular testing center dedicated for COVID-19 molecular diagnosis.

### 2.2. Ethical Considerations

Research approval was granted by the Research Ethics Committee of Rivers State Hospital Management Board (RSHMB) before commencement. The study was conducted by the RSHMB Research Ethics guidelines and the principles embodied in the Helsinki Declarations of 1964, and was subsequently revised in 2013.

### 2.3. Determination of Sample Size

The sample size was calculated using the sample size formula for studying attributes 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% [11]. Though the calculated minimum sample size obtained was approximately 480 including an anticipated 10% attrition rate, we had recruited 604 due to data accessibility and availability to amplify the power of the study.

### 2.4. Study Tools and Population

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

### 2.5. Eligibility Criteria

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

### 2.6. Data Collection

Data was acquired from the case notes, medical review charts, nurses' charts, and laboratory result sheets by well-trained research assistants (nurses, laboratory scientists, and doctors) mandated to work at each treatment center.

Data extraction was carried out using a well-designed data extraction pro forma. The basic variables of which data was acquired included the socio-demographic, clinical, and anthropometric data and the associated comorbidities. The identified comorbidities included being aged  $\geq 65$  years; having cardiovascular disease, hypertension, chronic lung disease, asthma, sickle cell disease, HIV/AIDS, diabetes, cancer, obesity, or chronic kidney /liver diseases; being a cigarette smoker; being a transplant recipient, and receiving immunosuppressive therapy.

The biochemical inflammatory variables of which data were determined included the pro-calcitonin, C-reactive protein (CRP), and ferritin. The coagulation inflammatory parameters included plasma fibrinogen and D-Dimer levels. The hematological parameters from which the inflammatory indices were derived included the full blood counts (FBC), WBC differentials, and platelet counts (PLC).

The other laboratory parameters determined were hemoglobin concentration, plasma sodium, potassium, chloride, bicarbonate, urea, creatinine, albumin, and total plasma protein levels.

### 2.7. Specimen Acquisition, Processing, and Laboratory Analysis

Specimens were obtained following standard protocols in the treatment center including all laboratory analyses. Heparinized plasma was analyzed for plasma sodium, potassium, bicarbonate, chloride on an ion-selective electrode chemistry analyzer (SFRI 6000, SFRI Diagnostics, Berganton, France). 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). Plain tube-derived serum was analyzed for CRP using a CRP automated analyzer (HEALES, Shenzhen, China). Citrated plasma was analyzed for fibrinogen using a coagulation autoanalyzer (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 recommendations as non-severe and severe [12]. The disease severity was defined as the presence of fever  $>38^{\circ}\text{C}$  or suspected respiratory infection, plus one of respiratory rate  $>30$  breaths/minute; severe respiratory distress; oxygen saturation ( $\text{SpO}_2$ ) of  $\leq 93\%$  on room air and the presence of comorbid conditions such as diabetes, asthma, hypertension in adults and cough or difficulty in breathing and at least one of the following central cyanosis or  $\text{SpO}_2 < 92\%$ ; severe respiratory distress e.g. grunting breathing, very severe chest in-drawing and signs of pneumonia in children.

Confirmed COVID-19 infection 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.

Hematologic-based inflammatory indices such as the neutrophil to lymphocyte ratio (NLR) and platelet to 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 from 0, 1 to 2 as previously published [13]. The COVID-19 disease outcome was classified into discharged, ICU transfer/treatment care, and mortality. The BMI ( $\text{kg/m}^2$ ) was defined based on the recommendations of the World Health Organization as underweight ( $<18.5$ ), ideal weight ( $18.5\text{--}24.9$ ), overweight ( $25.0\text{--}29.9$ ), and obese ( $\geq 30.0$ ) [14].

### 2.9. Data Management/Statistical Analysis

Data management and analyses were conducted using the Statistical Package for Social Sciences software version 23.0 (IBM Co., Armonk, NY, USA). The continuous variables were first tested for departure from a normal distribution using both visual (histogram) and statistical protocols (Kolmogorov-Smirnov test). The continuous data found to have deviated from normal distribution were subsequently log-transformed before analysis and summarized using means  $\pm$  standard deviations following analyses; comparison made with the independent student t-test. Categorical data were summarized and presented as proportions in counts and percentages; comparison made with the chi-square test or Fisher's exact test as appropriate. Logistic regression analysis was conducted to evaluate the magnitude of associations between the dependent and the independent variables with the respective odd ratios reported at 95% confidence intervals. Any p-value difference of less than 0.05 (5%) was deemed statistically significant.

## 3. Results

During the 2020-2021 period, 678 inpatients/outpatients were referred to the treatment center with RT-PCR confirmed SARS-CoV-2 infection. However, data of 604 patients met the inclusion criteria and were recruited for the study.

Table 1 depicts the different comorbid conditions assessed and documented among the 604 COVID-19 infected subjects at presentation. The six most pronounced comorbid conditions observed in descending order were: obesity ( $n=84$ ; 44.2%), age  $\geq 65$  years ( $n=76$ ; 40.1%), hypertension ( $n=67$ ; 35.3%), being a past/current smoker ( $n=30$ ; 15.8%), being a diabetic ( $n=17$ ; 8.9%) and having a cardiovascular disease ( $n=15$ ; 7.9%).

Table 2 depicts the basic characteristics of the studied COVID-19 patients based on the presence or absence of comorbid conditions. As shown, a total of 604 eligible cases were studied. Among these eligible cases, 192 (31.8%) had comorbid conditions, while 412 (68.2%) had no comorbid conditions before diagnosis.

The comorbid positive subgroup had higher proportions of elderly patients (comorbid positive:  $n=76$ ; 40.0% vs. comorbid negative:  $n=5$ ; 1.2%), mostly males, and had higher proportions of those in high-risk occupation (health workers) and social behavior (cigarette smoking status), obesity, severe disease, and worse disease outcome compared to the comorbid negative subjects ( $p<0.05$ ) (Table 2). Furthermore, the comorbid positive subgroup also had higher

mean age, BMI, body temperature, SBP, DBP but lower oxygen saturation at presentation compared to the comorbid negative subjects ( $p < 0.05$ ) (Table 2).

In Table 3, the comorbid subjects had higher mean levels of potassium, urea, creatinine but lower levels of albumin and total protein (Panel A). The comorbid positive subjects also had higher mean levels of blood levels of urea, creatinine, pro-calcitonin, CRP, ferritin, GPS parameters, fibrinogen, D-Dimer, and the fibrinogen-albumin ratio, total white cell count, isolated neutrophil counts, neutrophil-lymphocyte count ratio, and the platelet-lymphocyte count

ratio but lower potassium concentration, hemoglobin levels, and isolated lymphocyte and platelet counts compared to the comorbid negative subjects ( $p < 0.05$ ) (Table 3; Panels B, C, & D).

In Table 4, the inflammatory markers/indices were significantly associated with obesity, age  $\geq 65$  years, hypertension, past/current cigarette smoking, diabetes, and cardiovascular disease among the comorbid positive subjects on both crude logistic regression analysis and following adjustment for potential cofounders.

**Table 1.** Distributions of comorbid conditions among the COVID-19 subjects.

Comorbid conditions	Total COVID-19 Cases with Comorbid Conditions, n = 192	
	Number/Counts, n	Percentage, %
Aged $\geq 65$ years (elderly)	76	40.10
Having Cardiovascular Disease	15	7.90
Hypertension	67	35.3
Chronic lung disease	2	1.04
Asthma	3	1.58
HIV/AIDS	4	2.10
Diabetes Mellitus	17	8.90
Obesity	84	44.20
Chronic kidney disease	1	0.53
Chronic liver disease	1	0.53
Being a cigarette smoker**	30	15.80
Being a transplant recipient	1	0.53
Receiving immune-suppressant	4	2.10

\*\*Past/current.

**Table 2.** Basic characteristics of comorbid/non-comorbid COVID-19 subjects at presentation.

Variables	All Cases, n = 604 (100%)	Comorbid +ve, n = 192 (31.8%)	Comorbid -ve, n = 412 (68.2%)	p-value, comorbid +ve vs. comorbid -ve
	Mean $\pm$ SD/n	Mean $\pm$ SD/n	Mean $\pm$ SD/n	
Mean Age, years	42.20 $\pm$ 6.71	46.44 $\pm$ 6.15	42.44 $\pm$ 5.23	<0.003*
Age groups: 18-44/45-64/ $\geq 65$	360/163/81	50/66/76	310/97/5	0.004*
Gender: Male/female	376/227	118/74	258/153	<0.001*
Occupation: Health worker (Yes/No)	348/256	109/83	239/173	0.003*
ES: None/primary/secondary/tertiary	13/55/139/397	3/22/61/106	10/33/78/291	0.054
Marital status: Married/single/bereaved	429/169/6	145/46/2	284/123/4	0.089
Residential area: Urban/Rural	574/30	190/2	384/28	0.087
Religion: Christian/Moslem	567/37	182/10	392/27	0.068
Past/current cigarette smoker: Yes/No	83/521	30/162	53/359	<0.001*
Mean BMI, kg/m <sup>2</sup>	28.15 $\pm$ 4.33	29.94 $\pm$ 5.33	27.71 $\pm$ 5.62	<0.001*
BMI grades: Ideal weight/overweight/obese	207/167/226	59/47/84	148/120/142	<0.001*
Body temperature, °C	36.9 $\pm$ 1.33	37.75 $\pm$ 1.13	36.66 $\pm$ 1.21	0.069
SBP, mmHg	135.66 $\pm$ 7.55	141.33 $\pm$ 7.71	138.83 $\pm$ 7.91	<0.001*
DBP, mmHg	88.74 $\pm$ 5.74	90.75 $\pm$ 5.62	87.92 $\pm$ 5.64	0.003*
Oxygen saturation (SpO <sub>2</sub> ), %	95.88 $\pm$ 6.19	87.92 $\pm$ 5.79	93.65 $\pm$ 5.13	0.003*
Disease severity: severe/not severe	59/545	48/144	11/401	<0.001*
Outcome: Discharged/ICU transfer/mortality	494/106/4	175/13/4	479/96/0	<0.001*
Contact with known case: Yes/No	205/300	51/141	154/159	0.083

\*Statistically significant; M  $\pm$  SD: mean  $\pm$  standard deviation; body mass index; ED: Educational status; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; ICU: Intensive Care Unit.

**Table 3.** Comparative distribution of laboratory parameters among the COVID-19 subjects.

Parameters (Reporting Units)	Comorbid +ve, n = 190 (31.8%)	Non-comorbid -ve, n = 410 (68.2%)	p-value	All cases, n = 604 (100%)
	Mean $\pm$ SD/n	Mean $\pm$ SD/n		Mean $\pm$ SD
A. General biochemical parameters				
Plasma sodium, mmol/L	134.5 $\pm$ 7.47	134.54 $\pm$ 7.23	0.351	134.03 $\pm$ 0.72
Plasma potassium, mmol/L	3.34 $\pm$ 1.10	3.80 $\pm$ 1.09	0.004*	4.55 $\pm$ 1.13
Plasma Chloride, mmol/L	94.62 $\pm$ 6.10	95.41 $\pm$ 6.36	0.206	96.77 $\pm$ 6.03

Parameters (Reporting Units)	Comorbid +ve, n = 190 (31.8%)	Non-comorbid -ve, n = 410 (68.2%)	p-value	All cases, n = 604 (100%)
	Mean $\pm$ SD/n	Mean $\pm$ SD/n		Mean $\pm$ SD
Bicarbonate, mmol/L	20.39 $\pm$ 4.62	23.18 $\pm$ 4.17	0.013*	22.4 $\pm$ 4.33
Plasma urea, mmol/L	7.47 $\pm$ 1.68	5.31 $\pm$ 1.08	<0.001*	6.21 $\pm$ 1.18
Plasma creatinine, $\mu$ mol/L	194.43 $\pm$ 11.63	123.47 $\pm$ 10.41	<0.001*	138.66 $\pm$ 9.33
Plasma albumin, g/L	29.91 $\pm$ 4.38	34.84 $\pm$ 4.71	<0.001*	33.71 $\pm$ 4.07
Plasma total protein, g/L	56.32 $\pm$ 5.80	62.05 $\pm$ 5.31	<0.001*	59.13 $\pm$ 4.76
Hemoglobin levels, g/L	100.34 $\pm$ 9.54	110.24 $\pm$ 9.67	0.013*	112.71 $\pm$ 10.26
<b>B. Biochemical inflammatory markers/indices</b>				
Serum pro-calcitonin, $\mu$ g/L	3.8 $\pm$ 1.65	1.5 $\pm$ 0.82	<0.001*	2.87 $\pm$ 1.76
Serum C-reactive protein, nmol/L	287.19 $\pm$ 11.94	129.43 $\pm$ 9.65	<0.001*	176 $\pm$ 9.43
Serum ferritin, pmol/L	2,411.17 $\pm$ 26.31	594 $\pm$ 33.87	<0.001*	1,103 $\pm$ 31.71
GPS (as continuous data) $\times 10^2$	171.73 $\pm$ 8.38	54.17 $\pm$ 7.61	<0.001*	68.22 $\pm$ 7.14
GPS (as categorical data), score 0/score 1/score 2	0/80/302	90/10/12	<0.001*	90/90/300
<b>C. Coagulation inflammatory markers/indices</b>				
Fibrinogen, g/L	8.14 $\pm$ 1.12	5.11 $\pm$ 1.09	<0.001*	6.41 $\pm$ 1.20
D-Dimer, (normal $\leq 500 \mu$ g/L FEU)	2,855.17 $\pm$ 100.04	691 $\pm$ 34.84	<0.001*	876.13 $\pm$ 61.40
Fibrinogen (g/L)/albumin (g/L) ratio, $\times 10^3$	367.62 $\pm$ 28.83	114.62 $\pm$ 11.66	<0.001*	188.11 $\pm$ 12.13
<b>D. Hematologic inflammatory markers/indices</b>				
Total WBC $\times 10^9$ /L	18.7 $\pm$ 4.78	14.5 $\pm$ 3.80	<0.001*	13.42 $\pm$ 3.21
<b>WBC differentials</b>				
Neutrophil count $\times 10^9$ /L	13.64 $\pm$ 2.84	8.51 $\pm$ 2.08	<0.001*	7.94 $\pm$ 2.16
Lymphocyte count $\times 10^9$ /L	1.00 $\pm$ 0.13	1.30 $\pm$ 0.14	0.034*	1.10 $\pm$ 0.11
Platelet count $\times 10^9$ /L	118.31 $\pm$ 7.92	130.7 $\pm$ 5.87	<0.001*	137.8 $\pm$ 6.31
Neutrophil to lymphocyte ratio	14.16 $\pm$ 3.61	5.31 $\pm$ 1.08	<0.001*	6.81 $\pm$ 2.61
Platelet to lymphocyte ratio	119.8 $\pm$ 8.10	65.34 $\pm$ 8.92	<0.001*	79.34 $\pm$ 7.81

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

**Table 4.** Association between comorbidities and inflammatory markers/indices among comorbid +ve COVID-19 subjects.

Comorbid conditions	n (%)	Crude Logistic Regression	Adjusted Logistic Regression**
		OR; (95% CI); p-value	OR; (95% CI); p-value
Aged $\geq 65$ years (elderly)***	76 (40.10)	5.61 (4.56-6.73); <0.001*	4.95 (3.93-5.67); <0.001*
Having Cardiovascular Disease	15 (7.90)	2.3 (1.23-2.41); 0.006*	1.94 (1.22-2.34); 0.013*
Hypertension	67 (35.30)	6.96 (5.58-7.67); <0.001*	6.17 (5.29-7.08); <0.001*
Chronic lung disease	2 (1.04)	1.31 (1.10-1.67); 0.041*	-----
Asthma	3 (1.58)	1.49 (1.12-1.83); 0.180	-----
HIV/AIDS	4 (2.10)	0.94 (0.76-1.06); 0.120	-----
Diabetes Mellitus	17 (8.9)	3.74 (2.56-4.67); <0.001*	2.66 (1.87-3.87); <0.001*
Obesity	84 (44.20)	8.32 (7.35-9.78); <0.001*	7.71 (6.68-8.67); <0.001*
Chronic kidney disease	1 (0.53)	1.06 (0.71-1.60); 0.191	-----
Chronic liver disease	1 (0.53)	0.87 (0.67-0.98); 0.340	-----
Being a cigarette smoker	30 (15.6)	2.84 (2.15-3.45); <0.001*	2.62 (1.83-3.29); <0.001*
Being a transplant recipient	1 (0.53)	0.89 (0.65-1.23); 0.084	-----
Receiving immune-suppressant	4 (2.10)	0.67 (0.43-0.96); 0.122	-----

\*Statistically significant; OR: Odds ratio; CI: confidence interval; \*\*adjusted for age (continuous/categorical), gender, occupational status, smoking status, BMI (continuous/categorical), systolic/diastolic blood pressure, oxygen saturation, disease severity/outcome, and plasma potassium, urea, creatinine, albumin, total protein levels, hemoglobin concentrations, total white cell, neutrophil, and lymphocyte counts; \*\*\*age was specifically exempted from adjustment during the regression analysis for this comorbid condition.

## 4. Discussion

### 4.1. Essential Findings

The current study had evaluated the burden of inflammation, assessed using inflammatory markers/indices, among COVID-19 infected patients with and without comorbid conditions. Following analysis, the comorbid positive subgroup were mostly males and had higher mean age, BMI, body temperature, SBP, and DBP, and higher proportions of elderly patients, high-risk occupation (health workers)/social behavior (cigarette smoking), obesity, severe disease, and worse disease

outcome but lower oxygen saturation compared to the comorbid negative subjects at presentation. In addition, the comorbid positive subjects also had higher mean levels of blood potassium, urea, creatinine, pro-calcitonin, CRP, ferritin, GPS parameters, fibrinogen, D-Dimer, and the fibrinogen-albumin ratio, total white cell count, isolated neutrophil counts, neutrophil-lymphocyte count ratio, and the platelet-lymphocyte count ratio but lower isolated lymphocyte/platelet counts and albumin compared to the comorbid negative subjects. The inflammatory markers and indices were observed to be significantly associated with obesity, age  $\geq 65$  years, hypertension, past/current cigarette smoking, diabetes, and cardiovascular disease.

#### **4.2. Relationship with Existing Literature**

Following a detailed literature search, very few previous studies were found to have examined and compared the burden of inflammatory markers between comorbid positive and comorbid negative COVID-19 patients. Moreover, none have been documented in Nigeria to date. This is unsurprising as the scientific knowledge on the COVID-19 infection is still evolving. In one of the very few similar studies documented in Turkey by Afsin and colleagues, the authors had investigated the effects of comorbidities on the clinical course and mortality of COVID-19 infection among 155 RT-PCR positive COVID patients and found no difference in the inflammatory markers between the comorbid positive and comorbid negative COVID-19 patients [15]. This very report from Afsin and colleagues contrasts with the findings in the present study and may be related to some factors. First, the study by Afsin and colleagues evaluated only the severe COVID-19 patients, and secondly, that study was limited by its small sample size [16]. Furthermore, racial differences in the COVID-19 epidemiology may have also played a role in the discordant findings between this current study and that of Afsin and colleagues. However, Rahman and colleagues in their recent study documented in Bangladesh among COVID-19 patients had noted that the elevated hematologic inflammatory markers and indices observed among their studied cohorts significantly correlated with underlying comorbidities, and the identified comorbidities were concurrently associated with severe COVID-19 infection [16]. That report by Rahman and colleagues concurs with the finding of the current study.

#### **4.3. Mechanistic Links**

Several reports have been published on the relationship between pre-existing comorbidities among patients with COVID-19 infection and exaggerated inflammatory episodes characteristic of severe COVID-19 [17-22]. These pre-existing comorbidities including age  $\geq 65$  years, having cardiovascular disease, hypertension, diabetes mellitus, obesity, and being a cigarette smoker seem to share one common cardinal feature with the COVID-19 infection, which is the exaggerated pro-inflammatory state with concurrent dysfunction of the innate and adaptive immunity as observed in the current study and in previous reports [18-22].

The presence of these comorbidities has been proposed to amplify the pro-inflammatory episodes in COVID-19 infection and has also been reported to be the key driver of the worse clinical outcomes in COVID-19 infection in association with these comorbidities [19-22].

#### **4.4. Relevance to Clinical Practice/Future Research**

The contributory influence of these comorbidities on the exaggerated inflammatory episode in COVID-19 makes them

reliable therapeutic targets which could halt the progression of COVID-19 infection. As potential therapeutic targets, further clinically-oriented studies are recommended to fully explore the relationship between these comorbidities and the exaggerated inflammatory storm in COVID-19 infected subjects.

#### **4.5. Study Limitations**

The study was limited by some factors which need to be acknowledged. First, as a single-institution-based study, its findings may not be representative of the entire population within the studied region. Secondly, since the data in the current were retrospectively acquired, the likelihood of under-reporting of the number of cases cannot also be ruled out with certainty.

### **5. Conclusion**

The current study highlights the role of comorbidity and exaggerated inflammation among cases of COVID-19 infection. The associated comorbidities were significantly associated with heightened inflammatory markers/indices among the COVID-19 subjects. These amplified inflammatory markers/indices may be indicative of the pathophysiologic link between various comorbidities and the disease severity among Nigerians. This could serve as therapeutic targets. However, further studies are recommended to substantiate the findings of 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 executed in compliance with the principles embodied in the Helsinki Declaration.

### **Disclosure Statement**

The authors have no conflict of interest to declare.

### **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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