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Cellular Inflammatory Indices in Hospitalized Nigerian COVID-19 Patients

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Abstract

The pandemicity of coronavirus disease 2019 (COVID-19) necessitated its novel biomarkers in prognosis and monitoring in low resource settings. Changes in total white blood cell counts have been associated with the progression of diseases. This study determined the prognostic value of some cellular inflammatory cells and their indices in relation to duration of hospital admission, gender, and age of COVID-19 patients. This longitudinal and case–control study determined blood cell components (total white blood cells (TWBC), neutrophil, lymphocyte, monocyte, and platelet) and inflammatory indices (neutrophil lymphocyte ratio [NLR], lymphocyte monocyte ratio [LMR], platelet lymphocyte ratio [PLR], derived NLR [DNLR], and systemic immune inflammatory index [SII]) in 95 symptomatic hospitalized COVID-19 patients and 45 COVID-19 free controls. These parameters were related to age, sex, and days of admission of the patients. Blood samples obtained were analyzed using hematological autoanalyzer (Sysmex XN-450) and indices calculated. Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., USA) version 20.0. The mean platelet count ($P = 0.016$) and PLR ($P = 0.000$) were significantly lower while TWBC counts ($P = 0.013$) were significantly increased in COVID-19 patients compared with control. The mean TWBC count ($P = 0.030$) and SII ($P = 0.029$) were significantly increased while lymphocyte count ($P = 0.015$) and LMR ($P = 0.026$) were significantly decreased in COVID-19 patients at discharge compared with COVID-19 patients at admission. The mean neutrophil count ($P = 0.048$), PLR ($P = 0.015$), and SII ($P = 0.022$) were significantly lower while mean lymphocyte count ($P = 0.026$) was significantly higher in COVID-19 patients aged <40 years compared with patients aged ≥40 years. This study concluded that inflammatory response is a phenomenon in COVID-19 patients especially in patients ≥40 years of age and that this inflammation persist till discharge, though gender has no influence on cellular inflammatory indices of COVID-19 patients.

Keywords: Hematological parameters, Inflammation, Prognosis, Severe acute respiratory syndrome coronavirus 2 infection

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease called coronavirus disease 2019 (COVID-19) is characterized by cytokine storm, acute respiratory distress syndrome, and systemic inflammation–related pathology[1]. Coronaviruses (CoVs) are positive sense, single-stranded RNA, and spherical shaped virus having non-segmented club-like projecting spikes on their surface. SARS-CoV-2 binds to the cell surface Angiotensin Converting Enzyme 2 (ACE2) to infect humans[2] and spike glycoprotein promotes its entry into the host target cells. Active replication and release of the virus in the lung cells lead to non-specific symptoms such as fever, myalgia, headache, and respiratory symptoms[3]. The binding of the virus with host cell receptors is a significant determinant for the pathogenesis of infection. Following viremia, SARS-CoV-2 primarily affects the tissues expressing high levels of ACE2 including the lungs, heart, and gastrointestinal tract[4]. Approximately

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7–14 days from the onset of the initial symptoms, there is a surge in the clinical manifestations of the disease with a pronounced systemic increase of inflammatory mediators and cytokines[5].

Changes in blood cell counts and functions have important roles in early diagnosis of diseases, considering the information it provides during various disease conditions[6]. Inflammatory response plays a critical role in the progression of COVID-19 disease and hematological parameters had been reported to be altered by the coronavirus in infected patients[7]. Blood cells such as neutrophils, lymphocytes, and thrombocytes are essential in the pathophysiology of inflammation, immune responses, homeostasis, and oncogenesis[8-10]. Systemic inflammation changes the features of circulating blood cells and this has been suggested to be biomarkers for assessment of inflammatory activity[11]. Total white blood cells (TWBC) count, neutrophil, lymphocyte, monocyte, basophil, eosinophil, platelet count (PLT), and their ratios have been used as inflammatory markers in health conditions[10,12,13]. Some inflammatory factors such as cytokines (interleukin [IL]-6 and IL-10) and C- reactive protein have been found to be raised in COVID-19 patients[14]. Furthermore, COVID-19 infection affects the hematopoietic system with hematological abnormalities such as anemia, leucopenia, leukocytosis, thrombocytopenia, lymphocytopenia, and neutrophilia[15-17].Since the number and activities of these blood cells have been reported to change in COVID-19 patients[7], this present study conjectured that hematological parameters (total- and differential- white blood cell counts), calculated inflammation parameters (neutrophil: lymphocyte ratio [NLR], lymphocyte: monocyte ratio [LMR], platelet: lymphocyte ratio [PLR], and Derived NLR [DNLR]) and systemic immune-inflammatory index (SII) might be useful prognostic predictors of COVID-19 disease.

2. Materials and Methods

2.1. Participants

This study involved a total of 95 hospitalized COVID-19 patients aged between 15 and 80 years (28 females and 67 males) was carried out between April 27, 2020, and June 20, 2020. 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 the WHO guideline[18]. Patients with co-morbidities/blood cells disorders and those who did not consent for follow-up study were excluded among COVID-19 patients. The control subjects consisted of 45 uninfected healthy adults (25 males and 20 females) aged between 18 and 65 years.

2.2. Sample collection

3 ml venous blood sample was collected using pyrogen-free needle and syringes from each participant and dispensed into K_3-EDTA (Potassium Ethylene Diamine Tetra Acetic Acid) bottle and immediately analyzed using hematological auto analyzer of specification Sysmex XN-450. Patients' blood sample was collected on the day of admission and at the point of discharge when patients had been tested negative after 5–15 days for SARS-CoV-2 virus using nucleic acid RT-PCR.

2.3. Autoanalyzer principle

This was done using the Sysmex auto-analyzer. 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[19].

2.4. Inflammatory indices

NLR, LMR, PLR, DNLR, and SII were determined using the following equations[20]:

$$\text{NLR} = \frac{\text{Absolute Number of Neutrophil}}{\text{Absolute Number of Lymphocyte}}$$

$$\text{DNLR} = \frac{\text{Absolute Number of Neutrophil}}{\text{White Blood Cells Concentration} - \text{Absolute Neutrophil Count}}$$

$$\text{PLR} = \frac{\text{Absolute Numberof Platelet}}{\text{Absolute Number of Lymphocyte}}$$

$$\text{LMR} = \frac{\text{Absolute Numberof Lymphocyte}}{\text{Absolute Number of monocyte}}$$

$$\text{SII} = \frac{\text{Platelets Count} \times \text{Neutrophil Count}}{\text{Lymphocytes Count}}$$

2.5. Statistical analysis

Data obtained were analyzed using Statistical Package for the Social Science (SPSS) (version 20). Gender, age, and days of admission were presented as frequencies and percentages in each category. Blood cell counts and inflammatory indices were presented as Mean ± SD. 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 $P < 0.05$.

2.6. Ethical consideration

The study was conducted after obtaining approval 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.

3. Results

Demography and length of hospital admission of the 95 COVID-19 patients are shown in Table 1. Most of the COVID-19 patients aged <40 years (72.6%) and were employees of private establishments (45.3%). Most of the patients spent ≤10 days (60%) and were males (71%) (Table 1). Blood cell components and cellular inflammatory indices of COVID-19 patients were compared with un-infected controls as shown in Table 2. The mean levels of PLT and PLR were significantly lower in COVID-19 patients ($P = 0.016$ and $P = 0.000$, respectively) compared with control. Mean TWBC count was significantly higher in COVID-19 patients compared with control ($P = 0.013$) (Table 2). The mean TWBC count ($P = 0.030$) and SII ($P = 0.029$)

Table 1. Demography and length of hospital admission of COVID-19 patients

Variable	Categories	Frequency	Percentage
Gender	Male	67	71
	Female	28	29
Age (years)	<40 years	69	72.6
	≥ 40 years	26	27.4
Occupation	Self employed	28	29.5
	Private	43	45.3
	Civil servant	14	14.7
	Unemployed	10	10.5
DOA	≤10 days	57	60
	>10 days	38	40

DOA: Days of admission

Table 2. Comparison of age, blood cell components and cellular inflammatory indices 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
TWBC count ($\times10^9$/L)	5.58±1.78	4.45±1.97	2.530	0.013*
Lymphocyte count (%)	48.21±12.78	45.34±11.92	1.291	0.200
Monocyte count (%)	7.68±3.86	9.24±3.76	−1.680	0.097
Neutrophil (%)	40.07 ±13.22	46.14±13.65	−1.454	0.118
Platelet count ($\times10^9$/L)	229.89 ± 88.73	305.35 ± 197.50	−2.459	0.016*
NLR	0.98±0.66	0.77±0.49	1.417	0.160
DNLR	0.77±0.49	0.61±0.39	1.416	0.161
PLR	94.98±44.24	162.96±109.72	−4.137	0.000*
LMR	7.85 ± 7.36	6.30±2.58	0.983	0.328
SII ($\times10^9$/L)	239 ± 200	229 ± 187	0.204	0.839

TWBC: Total white blood cell count, NLR: Neutrophil lymphocytes ratio, DNLR: Derived neutrophil lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LMR: Lymphocyte monocyte ratio, SII: Systemic immune inflammatory index. *Significant at P<0.05

Table 3. Comparison of blood cell components and cellular inflammatory indices in COVID-19 patients at admission and at discharge

Variables	At admission (*n*=25)	At discharge (*n*=25)	t – values	*P* – values
TWBC count ($\times10^9$/L)	5.25±0.67	6.34±1.25	−2.519	0.030*
Lymphocyte count (%)	53.42±12.80	47.16±8.60	2.939	0.015*
Monocyte count (%)	7.46±2.42	7.30±1.31	0.210	0.838
Neutrophil (%)	34.94±13.16	41.10±7.68	−1.932	0.082
Platelet count ($\times10^9$/L)	236.55±88.73	241.64±63.89	−0.223	0.828
NLR	0.73±0.38	0.92±0.32	−2.113	0.061
DNLR	0.59±0.30	0.72±0.23	−1.685	0.123
PLR	89.31±34.31	100.78±29.95	−1.550	0.152
LMR	7.97±3.76	5.76±2.21	2.612	0.026*
SII ($\times10^9$/L)	173±105	283±163	−2.557	0.029*

TWBC: Total white blood cell count, NLR: Neutrophil lymphocyte ratio, DNLR: Derived neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LMR: Lymphocyte monocyte ratio, SII: Systemic immune inflammatory index. *Significant at P<0.05

were significantly increased in COVID-19 patients at discharge compared with those at admission. There were significant decreases in lymphocyte count and LMR of COVID-19 patients at discharge compared with COVID-19 patients at admission (P = 0.015 and P = 0.026), respectively (Table 3). There were no significant differences in the mean ages, blood cell components, and cellular inflammatory indices of males COVID-19 patients compared with females COVID-19 patients (Table 4). The mean neutrophil count (P = 0.048), PLR (P = 0.015), and SII (P = 0.022) was significantly lower in COVID-19 patients aged <40 years compared with patients aged ≥40 years. However, the mean lymphocyte

Table 4. Comparison of age, blood cell components and cellular inflammatory indices in males with females COVID-19 patients

Variables	Males (*n*=49)	Females (*n*=21)	t – values	*P* – values
Age(years)	34.03±10.66	33.25±14.59	0.219	0.827
TWBC count ($\times10^9$/L)	5.23±1.73	6.20±1.80	−1.854	0.069
Lymphocyte count (%)	50.30±12.22	45.95±15.18	1.112	0.271
Monocyte count (%)	8.38±4.65	6.66±1.79	1.428	0.159
Neutrophil (%)	36.68±12.03	44.14±14.92	−1.936	0.058
Platelet count($\times10^9$/L)	226.16±100.23	221.19±63.95	0.183	0.856
NLR	0.86±0.62	1.15±0.66	−1.589	0.118
DNLR	0.66±0.46	0.91±0.48	−1.778	0.081
PLR	95.00±50.84	88.50±35.71	0.464	0.645
LMR	8.17±9.25	7.48±3.52	0.289	0.774
SII ($\times10^9$/L)	206±197	268±193	−1.073	0.288

TWBC: Total white blood cell count, NLR: Neutrophil lymphocyte ratio, DNLR: Derived neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LMR: Lymphocyte monocyte ratio, SII: Systemic immune inflammatory index. *Significant at P<0.05

count (P = 0.026) was significantly higher in COVID-19 patients aged <40 years compared with those aged ≥40 years (Table 5).

Blood cell components and inflammatory indices were not significantly different in COVID-19 patients with ≤10 days of admission compared with those who spent >10 days on admission (Table 6). Pearson's correlation showed significant negative correlation between days of admission with LMR (r = −0.290, P = 0.035) or positive correlation between days of admission with monocyte (r = 0.039, P = 0.003) (Table 7).

Table 5. Comparison of age, blood cell components and cellular inflammatory indices of COVID-19 patients with age<40 with those ≥ 40 years

Variables	Age <40years (n = 51)	Age ≥40 years (n = 19)	t – values	P – values
Age (years)	27.88±6.57	49.60±7.02	−10.721	0.000
TWBC count ($\times 10^9$/L)	5.47±1.88	5.66±1.58	−0.344	0.732
Lymphocyte count (%)	51.47±13.33	42.63±10.71	2.297	0.026*
Monocyte count (%)	7.60±4.27	8.56±3.57	−0.766	0.447
Neutrophil count (%)	36.68±13.40	44.61±11.41	−2.024	0.048*
Platelet count ($\times 10^9$/L)	214.82±74.40	250.33±122.28	−1.301	0.199
NLR	0.85±0.58	1.20±0.72	−1.856	0.069
DNLR	0.67±0.44	0.90±0.54	−1.659	0.103
PLR	83.65±31.57	117.57±68.09	−2.511	0.015*
LMR	8.85±6.13	5.70±2.43	1.313	0.195
SII ($\times 10^9$/L)	187±157	322±254	−2.364	0.022*

TWBC: Total white blood cell count, NLR: Neutrophil lymphocyte ratio, DNLR: Derived neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, LMR: Lymphocyte monocytes ratio, SII: Systemic immune inflammatory index. *Significant at P<0.05

Table 6. Comparison of age, blood cell components and cellular inflammatory indices of COVID-19 patients based on their days of admission

Variables	DOA ≤10 days (n=42)	DOA >10 days (n=28)	t – values	P – values
Age (years)	34.22±11.24	33.22±12.78	0.308	0.759
TWBC count ($\times 10^9$/L)	5.58±2.01	5.44±1.48	0.264	0.793
Lymphocyte count (%)	51.78±13.41	45.28±12.14	1.833	0.073
Monocyte count (%)	7.19±2.53	8.78±5.46	−1.430	0.159
Neutrophil count (%)	37.17±13.12	41.21±13.40	−1.109	0.272
Platelet count ($\times 10^9$/L)	233.81±85.88	212.39±96.77	0.858	0.395
NLR	0.85±0.58	1.07±0.70	−1.206	0.233
DNLR	0.68±0.43	0.81±0.53	−1.021	0.312
PLR	90.59±41.27	96.42±53.80	−0.451	0.654
LMR	9.37±6.19	6.13±2.36	1.491	0.142
SII ($\times 10^9$/L)	208±181	246±216	−0.709	0.481

TWBC: Total white blood cell count, TC: Total cholesterol, NLR: Neutrophil lymphocyte ratio, DNLR: Derived neutrophil lymphocyte ratio, PLR: Platelet-lymphocyte ratio, LMR: Lymphocyte monocyte ratio, SII: Systemic immune inflammatory index, DOA: Days of admission. *Significant at P<0.05

4. Discussion

The emergence of a new zoonotic pathogen (SARS-CoV-2), which causes a variety of clinical symptoms collectively termed COVID-19 is of major public health concerns as it is a global pandemic[21]. However, most infected people are asymptomatic or develop only mild symptoms[22]. This observation might have been related to non-fatal nature of SARS-CoV-2 strain as previously suggested in hospitalized COVID-19 patients in Ibadan, Nigeria[23]. In the present study, most (70%) of COVID-19 patients were males and this is consistent with the previous reports[23,24]. The reduced susceptibility of females to some viral infections could be attributed to the protection from X chromosome and sex hormones, which play an important role in innate and adaptive immunity[25].

Our study showed a significant increase in TWBC counts in COVID-19 patients compared with control although this is in contrasts to the reported leucopenia by Guan *et al.*[26]. Increased mean TWBCs count was reported to be caused by inflammation[27,28] and inflammation is a confirmed phenomenon in COVID-19 patients[29], thus increased TWBCs counts is expected

Table 7. Pearson's correlation coefficients between age, days of admission with blood cell components, and cellular inflammatory indices of COVID-19 patients

Cellular Inflammatory Indices	r	*P* – values
Age		
TWBCs	0.068	0.625
LYMPH	−0.252	0.066
MONO	0.085	0.540
NEUT	0.245	0.075
PLAT	0.116	0.404
NLR	0.195	0.158
DNLR	0.196	0.155
PLR	0.221	0.108
LMR	−0.037	0.794
SII	0.220	0.101
DOA		
TWBCs	−0.041	0.796
LYMPH	−0.210	0.128
MONO	0.396	0.003*
NEUT	0.093	0.505
PLAT	0.076	0.584
NLR	0.120	0.386
DNLR	0.095	0.496
PLR	0.191	0.166
LMR	−0.290	0.035*
SII	0.135	0.313

DOA: Days of admission, TWBC: Total white blood cells counts, LYPH: Lymphocyte count, NEUT: Neutrophil count, MONO: Monocyte count, PLT: Platelet count, NLR: Neutrophils-lymphocytes ratio, DNLR: Derived neutrophils-lymphocytes ratio, PLR: Platelet-lymphocytes ratio, LMR: Lymphocytes-monocytes ratio, SII: Systemic immune inflammatory index. *Significant at P<0.05

in COVID-19 patients. Significant decreases in platelet and PLR were observed in COVID-19 patients compared with controls. This might be due to the stimulation of anti-platelet auto antibodies by SARS-CoV-2[30], which triggers immune-mediated platelet destruction. Thus, immune complexes formed on the surfaces of platelets predispose platelets to destruction by the reticuloendothelial system. This may suggest that COVID-19 is an immune complex disease which requires further investigations[30].

Mean TWBC count and SII in COVID-19 patients at discharge were significantly increased compared with COVID-19 patients at admission. This might be linked with persistence inflammatory responses in COVID-19 patients at discharge. Significant decreases in lymphocytes and LMR were also noted at discharge compared with values at admission. This suggests continuous destruction of lymphocytes in COVID-19 patients at discharge leading to reduced LMR. A significant decrease in lymphocyte was observed in COVID-19 patients older than or equal to 40 years compared with those younger than 40 years of age. Lymphopenia in this age group might have been caused by the invasion and destruction of lymphocytes by SARS-CoV-2 in patient's ≥40 years old as a result of cytokine storm. Cytokine storm characterized by markedly increased levels of interleukins (mostly IL-6, IL-2, IL-7, granulocyte colony stimulating factor, and interferon-γ inducible protein 10) and tumor necrosis factor-alpha promotes lymphocyte apoptosis[31,32]. Increases in the levels of certain cytokines with ages have been previously reported[33]. Moreover, cytokine storm and platelet activation had been directly linked[34,35], thus, supporting increased PLR in COVID-19 patients ≥40 years.

A significant increase in neutrophil was also observed in COVID-19 patients aged ≥40 years and this corroborate neutrophilia found in COVID-19 disease[24,36]. Henry *et al*.[37] attributed neutrophilia to a compensatory mechanism due to reduced lymphocytes, monocytes, and eosinophils in COVID-19 patients. It was previously reported that neutrophilia is an expression of the cytokine storm and hyper inflammatory state which has an important pathogenetic role in SARS CoV-2 infection[35,38]. The SII has been proposed as a prognostic indicator in the follow-up of sepsis[39]. In this study, SII was found to be significantly higher in COVID-19 patients aged ≥40 years compared to those <40 years. This signifies higher systemic inflammatory reaction in older age groups of COVID-19 patients. Putting together,

reduced mean lymphocyte count, increased PLR, high SII and mean neutrophil count in COVID-19 patient's ≥40 years of age indicated raised inflammation, therefore supporting susceptibility of this age group to severe form of COVID-19 and other inflammatory conditions.

Significant negative correlation between days of admission with LMR showed that inflammation decreases with treatment or hospital stay. In addition, days of admission was positively correlated with monocyte counts. Monocytes and macrophages play key role in tissue repair, phagocytosis and protective immunity[40]. Thus, the positive correlation of days in admission with monocytes suggests the involvement of monocytes and macrophages in the resolution of COVID-19.

5. Conclusion

This study concluded that inflammatory response is a phenomenon in COVID-19 patients especially in patients ≥40 years of age and that this inflammation persist till discharge, though gender or duration of admission based on 10 days stratification (>10 days or ≤ 10 days) has no influence on cellular inflammatory indices of COVID-19 patients.

6. Conflicts of Interest

No conflict of interest is declared.

7. References

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