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Immunometabolic Profile of Nigerian COVID-19 Patients

Ganiyu Olatunbosun Arinola, B.Sc., M.Sc., Ph.D.[1],
Abdulfatah Adekunle Onifade, MBBS, M.Sc., Ph.D.[1],
Victory Fabian Edem, B.Sc., M.Sc., Ph.D.[1], Sheu Kadiri Rahamon, B.Sc., M.Sc., Ph.D.[1],
Oluwagbenga Temitope Alonge, MBBS, M.D., FRSC, FWACS[2,3]

[1]Department of Immunology, College of Medicine, University of Ibadan, Ibadan 200212, Nigeria.
[2]Department of Surgery, College of Medicine, University of Ibadan, Ibadan 200212, Nigeria.
[3]Infectious Disease Centre, Olodo, Ibadan, Oyo State 200103, Nigeria.

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Abstract:

Objective: Existence of crosstalk between metabolic and immune response against severe, acute respiratory syndrome coronavirus 2 (SARS-CoV-2) indicates that its full understanding could facilitate therapeutic insights for Coronavirus disease 2019 (COVID-19) management. Therefore, selected immunometabolic indices were determined in COVID-19 patients at a Nigerian Isolation Centre.

Material and Methods: Haematological parameters (Total White Blood Cell [TWBC] and Differential White Blood Cell Counts), inflammation indices (C-Reactive Protein [CRP], Albumin, Pre-albumin and Neutrophil/Lymphocyte ratio [NLR]), anti-SARS-CoV-2 specific immunoglobulin (Ig) M and IgG, respiratory burst factors, lipid profile as well as renal and liver functions were determined in COVID-19 patients and controls.

Results: Seventy percent of the COVID-19 patients were less than 40 years of age and largely had mild COVID-19. The mean TWBC, neutrophil, NLR and CRP levels were significantly higher, while the lymphocyte count was significantly lower in COVID-19 patients compared with the controls. Also, the mean plasma levels of anti-SARS-CoV-2 specific IgG and IgM in addition to superoxide dismutase (SOD) activity were significantly higher, while the mean plasma levels of nitric oxide, hydrogen peroxide and myeloperoxidase activity were significantly lower in COVID-19 patients compared with the controls. High proportions of COVID-19 patients had values of the liver (59%-96%) and renal (43%-97%) function

Contact: Ganiyu Olatunbosun Arinola, B.Sc., M.Sc., Ph.D.
Department of Immunology, College of Medicine,
University of Ibadan, Ibadan 200212, Nigeria.
E-mail: drarinolaog64@yahoo.com

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test parameters within the normal reference intervals. Similarly, high proportions of COVID-19 patients had values of lipid profile (71%-86%) within the normal reference intervals.

Conclusion: The infrequent alteration in lipid metabolism as well as liver and renal functions suggest mild COVID-19. However, hyper-inflammation remains a significant observation in COVID-19 patients, irrespective of the form of the disease.

Keywords: hyperinflammation, metabolic changes, SARS-CoV-2

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory infectious disease, with widespread associated morbidity and mortality. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), whose common modes of transmission are droplet and contact transmission[1,2].

A highly organized cellular and molecular network is essential during the activation, perpetuation and resolution of anti-SARS-CoV-2 immune response. This network is necessary to ensure tight control between the elimination of the virus and immune response-associated tissue damage[2]. However, reports have shown that infection with SARS-CoV-2 is largely associated with immune system dysregulation and impairment[3]. Similarly, it has been shown that perturbation in cell metabolism is a common feature in COVID-19, as it is with several other viral infections[4]. Available reports have shown that several viruses, including SARS-CoV-2, cause disturbances in the glycolytic pathway, tricarboxylic acid cycle, amino acids metabolism, lipid metabolism and cell metabolic reprogramming in immune cells[4,5]. These disturbances have been associated with viral escape from immune response and induction of severe tissue inflammation[6].

Generally, host response against infectious diseases involves both metabolic adaptations and immune responses. Immune responses are regulated by metabolic pathways and dysmetabolism leads to immune dysfunction[7]. Although, the role of immunometabolism in COVID-19 pathogenesis is poorly understood, an avalanche of reports continues to show that there is crosstalk between metabolic and immune response against SARS-CoV-2[8,9]. SARS-CoV-2 infection affects intracellular metabolism, such as, glycolysis and oxidative phosphorylation in immune cells that participate in innate immunity[10]. Siska et al.[7] reported an increased mitochondrial mass in T cells, monocytes, and granulocytes. They also reported accumulation of intracellular reactive oxygen species (ROS), metabolic quiescence and disrupted mitochondrial architecture within T cells. It is apparent therefore, that an adequate understanding of immunometabolism and its reprogramming in patients with SARS-CoV-2 infection could facilitate potential immunotherapeutic targets for the management of COVID-19, and even future viral zoonotic diseases. Therefore, this study was designed to assess the immunometabolic profile of selected COVID-19 patients seen at a Nigerian Isolation Centre, with the aim of providing information that could facilitate some therapeutic insights for COVID-19 management.

Material and Methods

Study participants

A total of 310 adults (12-83 years), with COVID-19, were enrolled into the study from an Infectious Diseases Centre in Ibadan, Nigeria, from April 2020 until July 2021. Nucleic acid Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) on nasal and pharyngeal swab specimens was used to confirm SARS-CoV-2 infection, according to the guidelines of the World Health Organization (WHO)[11]. Forty-two (42), apparently healthy, adults who tested negative for RT-PCR testing served as controls.

Ethical consideration

Before the commencement of the study, ethical approval was obtained from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Review Committee (UI/EC/20/0233). Furthermore, informed consent was obtained from each study participant.

Blood sample collection and laboratory analyses

Ten millilitres (10 ml) of a venous blood sample was obtained from each participant; 3 ml was dispensed into K_3-EDTA (Potassium Ethylene Diamine Tetra Acetic Acid) containing sample bottles (for haematology analysis), while 7 ml was dispensed into lithium heparin containing sample bottles (for clinical chemistry analysis). Total White Blood Cell, lymphocyte, monocyte, neutrophil, eosinophil, basophil, red blood cells, platelets counts as well as haematocrit and haemoglobin levels were determined using a haematology autoanalyzer (Sysmex XN-450). Plasma levels of total-bilirubin (Bil-T) and conjugated- bilirubin (Bil-D), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma Glutamyl Transferase (GGT), albumin, urea, creatinine (Cr), total cholesterol (TC), Sodium (Na), Potassium (K), Chloride (Cl) and Bicarbonate (HCO_3) were determined using an auto-analyzer (Erba Mannheim XL-200, Germany).

The plasma activity of superoxide dismutase, catalase and myeloperoxidase were determined as previously reported[12]. Similarly, the plasma levels of hydrogen peroxide (H_2O_2) and nitric oxide (NO) were also determined as previously reported[12]. The plasma levels of selected, acute phase proteins (albumin, prealbumin and CRP) and the SARS-CoV-2 Spike proteins IgM and IgG (in the patients) were determined using ELISA; following the manufacturer's instruction (Elabscience Biotechnology Inc, USA). Reference intervals, obtained from the Clinical Biochemistry laboratory of the University College Hospital, Ibadan, Nigeria, were used to categorise patients' laboratory values into those within normal reference ranges or otherwise.

Statistical analysis

Data obtained were presented as mean±S.D. The Statistical Package for the Social Science (SPSS) statistical software, version 21 for windows was used for statistical analysis. Differences in the means of variables were determined using either the independent or paired Student's t-test, as appropriate: a p-value less than 0.05 was considered as statistically significant.

Results

As shown in Table 1, most COVID-19 patients were male, less than 40 years of age, spent less than ten days in the Isolation Centre and presented with a mild form of COVID-19.

Table 1 Characteristics of the COVID-19 patients

Variables	COVID-19 Percentage
Gender	
Male	75.0
Female	25.0
Age (years)	
<40	70.0
≥40	30.0
DOA (days)	
≤10	70.0
>10	30.0
Severity	
Mild	65.0
Moderate	35.0
Severe	0.0
Co-morbidity types	
Hypertension	60.0
Peptic Ulcer Disease	15.0
Diabetes mellitus	15.0
Others	10.0

DOA=days on admission

The mean TWBC count, neutrophil count, NLR and CRP levels were significantly higher, while the lymphocyte count was significantly lower in COVID-19 patients compared with the controls (Table 2). The mean concentrations of anti-SARS-CoV-2-IgG, and IgM as well as superoxide dismutase (SOD) activity were significantly higher, while the mean concentrations of NO, H_2O_2 and myeloperoxidase (MPO) activity were significantly lower in COVID-19 patients compared with the controls (Table 3).

Table 2 Haemocytometric parameters and plasma levels of selected, acute phase proteins in COVID-19 patients and controls

Variables	COVID-19	Controls
Total WBC (x10^9/L)	6.00±1.80	5.40±1.72*
Lymphocyte (%)	44.80±11.63	52.45±11.00*
Monocyte (%)	8.16±3.26	9.42±3.60
Neutrophil (%)	42.59±12.00	34.99±12.69*
Eosinophil (%)	3.50±2.83	3.19±3.55
NLR	1.14±0.91	0.77±0.49*
CRP (mg/L)	5.00±0.50	3.50±0.80*
Albumin (g/dL)	5.00±0.01	5.21±0.10
Prealbumin(mg/dL)	22.00±1.30	23.90±1.60

*Significant at p-value<0.05, WBC=white blood cell, NLR=neutrophil-lymphocyte ratio, CRP=C-reactive protein

High proportions (96.0%, 93.0%, 86.0%, 84.0% and 57.0%) of COVID-19 patients had values of liver function test parameters (direct bilirubin, total bilirubin, albumin, ALP and total protein, respectively) within normal reference ranges (Figure 1). Similarly, high proportions (86.0%, 80.0% and 72.0%) of COVID-19 patients had values of lipid profile (TG, HDL and TC respectively) within normal reference ranges (Figure 2). Furthermore, high proportions (97.0%, 82.0%, 81.0%, 72.0% and 62.0%) of COVID-19 patients had values of renal function test parameters (urea, HCO_3, K, Na and creatinine, respectively) within normal reference ranges (Table 4).

Table 3 Plasma levels of anti-SARS-CoV-2 IgG and IgM, and respiratory burst factors in COVID-19 patients and controls

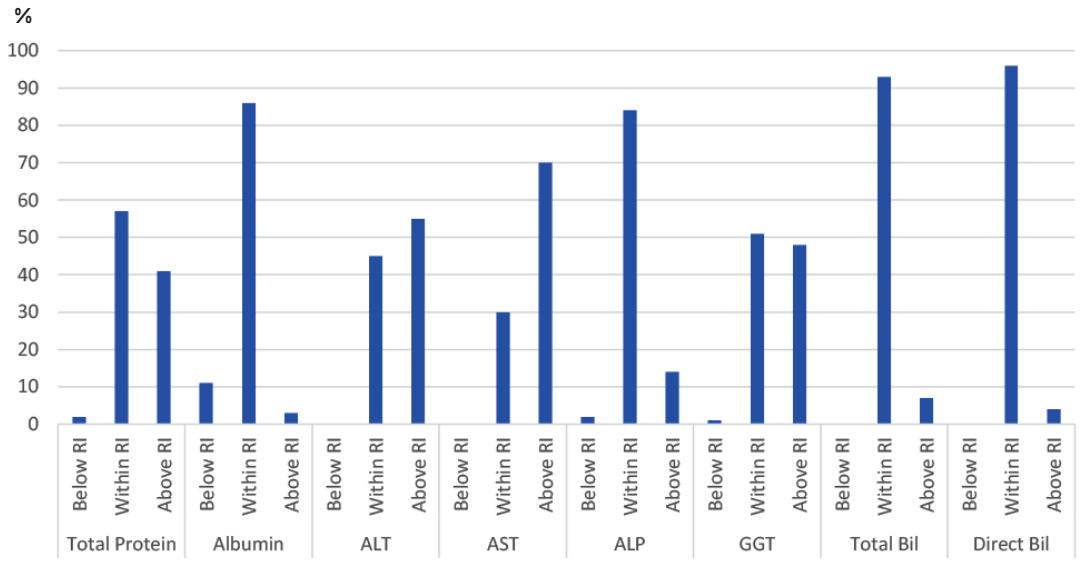
Variables	Controls	COVID-19 patients
Anti-SARS-CoV-2 IgG	0.002±0.001	0.092±0.03*
Anti-SARS-CoV-2 IgM	0.100±0.01	0.400±0.48*
NO (µg/dL)	110.02±19.53	60.11±5.11*
H_2O_2 (µmol/L)	10.27±1.49	6.03±0.70*
SOD (U/mL)	1.98±0.004	2.00±0.001*
CAT (U/mg protein)	1.99±0.17	1.97±0.10
MPO (U/mL)	0.83±0.10	0.63±0.07*

*Significant at p-value<0.05, Ig=immunoglobulin, NO=nitric oxide, H_2O_2=hydrogen peroxide, SOD=superoxide dismutase, CAT=catalase, MPO=myeloperoxidase

Table 4 Proportion of COVID-19 patients with renal function parameters within and outside normal reference intervals at admission

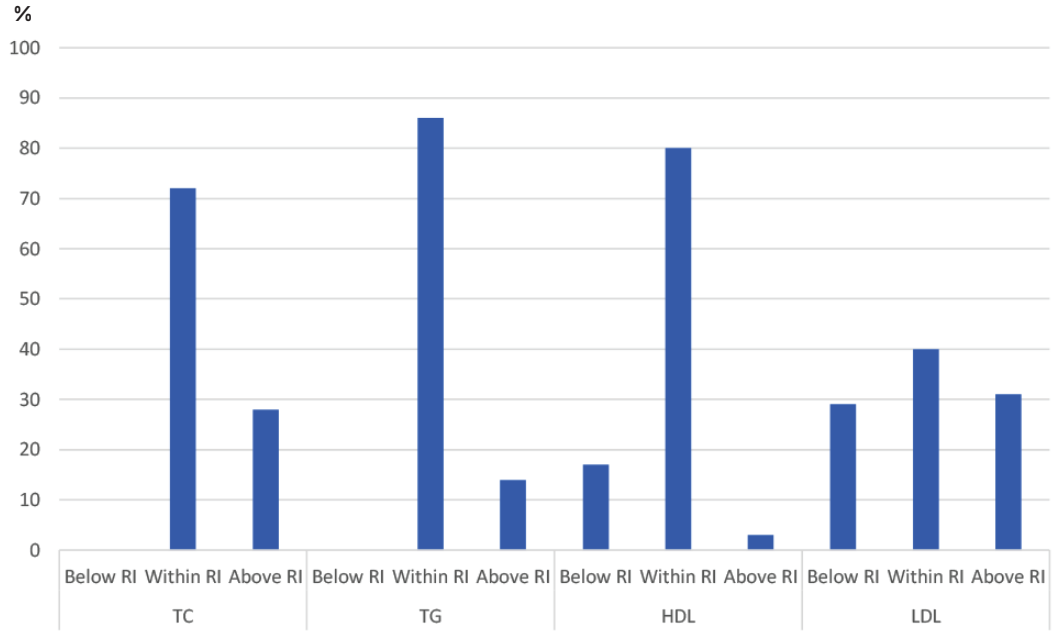
Variables	Within Reference Ranges	Abnormal Reference Ranges
Urea	169 (97.0)	6 (3.0)
Creatinine	107 (62.0)	65 (38.0)
Na	146 (72.0)	57 (28.0)
K	165 (81.0)	38 (19.0)
Cl	87 (43.0)	116 (57.0)
HCO_3	166 (82.0)	36 (18.0)

Results are presented as number (percentage), Na=sodium, K=potassium, Cl=chloride, HCO_3=bicarbonate



RI=reference intervals, ALT=Alanine Aminotransferase, AST=spartate Aminotransferase, ALP=Alkaline Phosphatase, GGT=Gamma Glutamyl Transferase, Bil=bilirubin

Figure 1 Proportion of COVID-19 patients having liver function parameters within and outside normal reference intervals (RI) on admission



RI=reference intervals, TC=total cholesterol, TG=Triglycerides, HDL=high density lipoprotein, LDL=low density lipoprotein

Figure 2 Proportion of COVID-19 patients with lipid profiles within and outside normal reference intervals (RI) on admission

Discussion

Immunometabolic disturbances are key features of several infections; including SARS-CoV-2. In this study, the renal and liver functions were assessed, and the plasma levels of lipid profile, innate humoral immune factors (respiratory burst factors) and adaptive humoral immune factors (anti-SARS-CoV-2 specific IgG and IgM) were determined.

Generally, recent infection to SARS-CoV-2 antigens is reflected by positive SARS-CoV-2 specific IgM antibodies, or concurrence of IgM and IgG; whereas, an infection of more than a few weeks previously, or a response to COVID-19 vaccination is reflected by positive SARS-CoV-2 specific IgG only. In this study, anti-SARS-CoV-2 specific -IgG and -IgM were detected in both the controls and COVID-19 patients; however, they were at significantly higher levels in COVID-19 patients. The detection of anti-SARS-CoV-2 specific IgG and IgM in the control could indicate large-scale, undetected community transmission. Therefore, this underscores the vital role of seroprevalence studies in determining the magnitude of SARS-CoV-2 infection, and in assessing the possibility of achieving herd immunity. IgG, IgA and IgM have neutralising functions though, with different affinities. Iwasaki and Yang[13] reported that, during antibody-mediated viral neutralization, the neutralizing antibodies bind to the receptor-binding domain (RBD) of the viral spike protein and other domains, preventing the virus from binding to ACE2, its entry receptor. However, when these antibodies are of low quality and quantity, or as a result of pre-existing SARS-CoV-specific antibodies, antibody-dependent enhancement (ADE) of infection, independent of ACE2 expression, can result. Fc receptors (FcRs), which are well expressed on monocytes, macrophages and B cells bind to antibodies via the Fc domains and facilitate entry of the virus, and consequently infection results. After binding to the Fc domain of the antibodies, FcRs are activated, thereby, initiating signaling to up-regulate pro-inflammatory cytokines and down-regulate anti-inflammatory cytokines. Immune pathology results when immune complexes and viral RNA in the endosomes activate host cells via Toll-like receptor 3 (TLR3), TLR7 and/or TLR8.[14]

The observed elevation in the TWBC count in COVID-19 patients could be due to COVID-19 associated inflammation[15,16]. This observation is further buttressed by the observed elevation of NLR, a cellular marker of inflammation in patients with COVID-19. In contrast, there was a significant reduction of the lymphocyte percentage in patients with COVID-19 compared with the controls. The observed low percentage of lymphocyte in COVID-19 patients could be attributed to increased lymphocyte death through membrane destruction, reduced lymphocyte formation or redistribution of lymphocytes from circulation to infected lungs. Histopathological studies have reported dominant lymphocytes infiltration in the interstitial lung of COVID-19 patients[17-19].

Neutrophils are among the first phagocytic responders to viral infection, they play active roles in innate immune responses[20,21]. The observed elevation in the neutrophils count in COVID-19 patients supports earlier reports[22,23]. This observation might suggest increased formation from stem cells in response to the viral infection.

During intracellular killing, there is a consumption of oxygen to generate H_2O_2 through a reaction catalysed by SOD[24,25]. The produced H_2O_2 combines with halide ions to form hypochlorous acid via the activity of myeloperoxidase, and consequently the hypochlorous acid produced reacts with $O_2\cdot^-$ or Fe^{2+} to produce stronger oxidants. The observed reduction in plasma levels of H_2O_2 and MPO activity in COVID-19 patients, compared with the controls, could be due to increased consumption of H_2O_2, with its attendant reduction in MPO activity from the viewpoint of eliminating SARS-CoV-2. Similarly, nitric oxide (NO) is produced during intracellular killing by phagocytes and inflammation[26].

The observed reduction in NO levels in COVID-19 patients compared with the controls might suggest increased utilisation as the host immune system responds to SARS-CoV-2 infection.

COVID-19 is associated with multiple organ dysfunction through direct virus-induced cytopathic effects, induction of inflammatory mediators, reactive oxygen species production, apoptosis or profibrotic factor releases[27]. In this study, a high proportion of patients with COVID-19 had liver and renal function parameters within the reference interval. This observation might not be surprising, as 65.0% of the patients had mild COVID-19. Liver and renal dysfunctions are more associated with severe COVID-19 and these have been attributed to SARS-CoV-2 infection-associated cytopathic effects, cytokine storm/hyper inflammation, dysregulation in immune responses, hypoxia and abnormal coagulation among others[28-31].

Aside from alteration in glycolytic and gluconeogenic pathways in COVID-19 patients, lipid and mitochondrial metabolisms are also affected[32,33]. However, lipid alteration was uncommon in our study participants, due to the majority of them having mild COVID-19. This observation is in tandem with the observed, uncommon liver and renal dysfunctions in the participants.

Prealbumin is a nutritional marker used in the evaluation of recent nutritional status, due to its rapid synthesis rate and short half-life[34,35]. It has an inverse association with inflammation; and thus, is considered a negative acute phase protein[36]. Lower levels of prealbumin, indicating decreased hepatic synthesis, have been reported in patients with severe forms of COVID-19[37]. Similarly, several reports have shown that hypoalbuminaemia, which is a common feature in patients with acute kidney injury (AKI), is associated with severe COVID-19[38,39]. The observed, non-significant differences in the plasma levels of pre-albumin and albumin in COVID-19 patients compared with the controls further supports these observed, relatively normal renal and liver functions as well as lipid metabolism in those patients with mild COVID-19.

C-reactive protein (C-RP), an acute-phase protein, is synthesized by the liver following cytokine stimulation, infection or inflammation[39]. It performs a myriad of functions, including, complement activation and phagocytosis enhancement. Its relatively short half-life, approximately 19 hours, makes it an important index for the diagnosis and assessment of infections, including severe pulmonary infectious diseases[39,40]. The observed, elevated level of CRP in COVID-19 patients might be a result of inflammation and increased phagocytic processes against invading SARS-CoV-2. It is well-established that hyperinflammation is a significant feature in COVID-19 patients.

Conclusion

It could be concluded from this study that renal and liver dysfunctions as well as lipid dysmetabolism are uncommon in patients with mild COVID-19. However, hyperinflammation remains a significant observation in COVID-19 patients; irrespective of the form of the disease.

Conflict of interest

The authors have no competing interest to declare.

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