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The Impact of Systemic Inflammation on Sex-based Bias Following SARS-CoV-2 Infection

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Abstract: Background: The unfavorable clinical outcome (higher rates of severity/morbidity/mortality) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has a disproportionate bias towards the male sex despite no sex-based difference noted in the risk for the infection. These outcomes have widely been hinged on dysregulated systemic inflammation. Hence, this study was aimed to evaluate the influence of systemic inflammation on sex-based bias in SARS-CoV-2 infection among indigenes of Nigerian Methods: Patients' data with positive real-time polymerase chain reaction (RT-PCR) test for coronavirus disease 2019 (COVID-19), who were admitted/managed at the Eleme treatment center in Port Harcourt, southern Nigeria, were enrolled for this study. All relevant data was acquired from archived case notes, medical review charts, nurses' charts, and laboratory records by trained research assistants using validated data collection templates. All the collated/abstracted data were analyzed/compared between the male and female patients using both descriptive and comparative statistical tools. Results A total of eligible 598 patients were included in the analysis among them 373 (62.4%) and 225 (37.6%) males and females, respectively. The males were much older (43.63±5.93 vs. 41.15±6.09; $p<0.036$) with higher mean body mass index and body temperature at presentation. Significant differences were observed in terms of the age distribution, occupational, educational, marital, residential status, cigarette smoking, alcohol consumption, body mass index, comorbid, severity, and clinical outcomes between the males and females (<0.05). In addition, the males had significantly higher mean levels of creatinine, C-reactive protein (CRP), Glasgow Prognostic Score (GPS), D-dimer, total WBC, neutrophil counts, composite neutrophil/lymphocyte ratio (NLR) but lower levels of albumin, total protein, isolated platelet count, and isolated lymphocyte count ($p<0.05$). The males maintained a significant linear relationship with the CRP (β: 0.61; SE: 0.13; $p<0.001$), composite GPS (β: 0.59; SE: 0.01; $p<0.001$), D-dimer (β: 0.52; SE: 0.09; $p<0.001$), and the composite NLR (β: 0.38; SE: 0.10; $p<0.001$) compare to their female counterparts. Additionally, CRP (OR: 8.86; 95%CI: 7.34-9.78; $p<0.001$), the composite GPS (OR: 7.41; 95%CI: 6.36-8.79; $p<0.001$), D-dimer (OR: 5.4; 95%CI: 4.32-6.65), and the composite NLR (OR: 4.23; 95%CI: 3.44-5.69; $p<0.001$) all had significant and robust associations with unfavorable clinical outcomes among the males compared to the females. Conclusion: Exaggerated systemic inflammatory markers/indices were more pronounced among the males in association with unfavorable clinical outcomes. These sex-based characteristics should be factored in during the management of SARS-CoV-2 infection. However, further studies are recommended to evaluate conclusions from the current study.

Keywords: SARS-CoV-2, COVID-19, Sex-based Inflammatory Markers/Indices

1. Introduction

The ravaging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the etiologic agent for the coronavirus disease 2019 (COVID-19), has placed a huge burden on the entire global health system and worldwide socio-economic activities since it is reported in China barely two years ago [1-3]. During the initial stages of the disease in China, some distinctive epidemiologic/clinical characteristics of the disease have been observed, documented, and published from various countries [4, 5]. In most of these reports, the male sex have disproportionately been associated with a greater burden of SARS-CoV-2 infection in terms of its severity, morbidity, and mortality relative to the female sex despite similar rates/risk of the viral infection [6-9].

Moreover, recent epidemiologic data also support the role of dysregulated systemic inflammation in the pathophysiologic basis underlying the severity, morbidity, and mortality of the SARS-CoV-2 infection [6, 10, 11]. Consequently, the sex-based bias of the adverse influence of the SARS-CoV-2 infection has been hinged on this dysregulated inflammatory cascade of events characteristic of the infection as vastly reported [6, 10, 11]. To date, the evidence of these sex-based epidemiologic characteristics has not been documented among Nigerians. In this context, the present study evaluated the impact of systemic inflammation on sex-based bias in SARS-CoV-2 infection among infected Nigerians.

2. Materials and Methods

2.1. Study Design

This was a sub-study of a large retrospective, observational, and cross-sectional performed at the Eleme COVID-19 treatment center, a Rivers State Government-owned center dedicated to the treatment of patients with COVID-19 infection in Port Harcourt, Nigeria. The center was set up and is currently under the management of the Government of Rivers State through the Ministry of Health and the Rivers State Hospital Management Board (RSHMB).

The center receives and admits hundreds of COVID-19 cases per year and has a fully-functional side laboratory that is well-equipped with automated chemistry/hematology analyzers dedicated for varying laboratory investigations following COVID-19 diagnosis before 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) COVID-19 testing laboratory.

The study protocol was approved by the RSHMB Ethics Committee and complies with the principles underlying the Declaration of Helsinki. The sample size population was obtained with the sample size formula for studying attributes in a population of>10,000, at a 95% confidence interval and 5% margin of error, using a COVID-19 prevalence rate of 50% [12]. Though the obtained minimum sample size was approximately 480 including an anticipated 10% attrition rate, we had recruited 598 to amplify the power of the study. Archived data of all eligible 598 patients with RT-PCR-confirmed COVID-19 infection who were admitted/managed at the COVID-19 treatment center between 2020 and 2021 was used as study tools.

The criteria for inclusion were data of adults, with apparently normal and relatively stable health status before the COVID-19 diagnosis, who are age ≥ 18 years at the time of primary diagnosis/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.

2.2. Data Collection

All baseline/clinical data including those of the laboratory were obtained upon presentation and before treatment. These data were acquired from the case notes, medical review charts, nurses' charts, and laboratory result sheets by well-trained research assistants (nurses/laboratory scientists/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 associated comorbidities.

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 relevant hematological-based inflammatory indices were derived from the full blood count (FBC), FBC differentials, and the platelet count. The other laboratory parameters obtained were the hemoglobin concentration, plasma sodium, potassium, chloride, bicarbonate, urea, creatinine, albumin, and total plasma protein levels.

2.3. Laboratory Protocols

All specimens were acquired 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). The heparinized plasma was also analyzed for urea, creatinine, albumin, and total protein on an automated chemistry analyzer (BS200, Mindray, Shenzhen, China).

Whole blood obtained from the EDTA tube was analyzed for Hb concentration, FBC, RBC, and platelet counts on an automated hematology analyzer (BC10, Mindray, Shenzhen, China). The 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 also analyzed to obtain CRP levels using a CRP analyzer (HEALES, Shenzhen, China). The Citrated plasma fibrinogen level was determined using a standardized coagulation analyzer (COA04, Biobase, China).

2.4. Data Definitions

COVID-19 severity was classified based on the Nigerian Centre for Disease Control National (NCDC) case management recommendations as non-severe and severe [13]. The disease severity was defined as the presence of fever>38°C or suspected respiratory infection, plus one of respiratory rate>30 breaths/minute; severe respiratory distress; oxygen saturation (SpO_2) of ≤ 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 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 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 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 biochemical-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 [14]. The BMI (kg/m^2) was defined based on the recommendations of the World Health Organization as underweight (<18.5), ideal weight (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0) [15].

The clinical outcome was classified into favorable (discharged) and unfavorable (ICU transfer/treatment care and mortality) outcomes.

2.5. Data Management and Analysis

Management and analysis of data were carried out using the Statistical Package for Social Sciences software version 23.0 (IBM Co., Armonk, NY, USA). Before analysis, the continuous variables were first tested for departure from a normal distribution using both visual (histogram) and statistical protocols (Kolmogorov-Smirnov test). Those identified continuous data found to have deviated from normal distribution were subsequently log-transformed before analysis and summarized using means±standard deviations; the comparisons were made with the independent student t-test.

The categorical data were summarized/presented as proportions in counts/percentages; the comparisons were made with the chi-square test or Fisher's exact test. The evaluation of sex as a determinant of systemic inflammatory markers/indices was evaluated using multivariable linear regression models while adjusting for confounders. The associations between the inflammatory markers/indices with the clinical outcomes were evaluated using multivariable logistic regression models while also adjusting for potential confounders. A p-value less than 0.05 (5%) was deemed statistically significant.

3. Results

During the period under study, 678 RT-PCR positive COVID-19 patients had been managed both as inpatients/outpatients through the treatment center. However, 598 met the eligibility criteria for the current study and were subsequently included in the analysis among them 373 (62.4%) and 225 (37.6%) males and females, respectively.

Table 1 depicts the basic characteristics of the non-laboratory data among the entire studied cohorts and by gender. A shown, the males were much older (43.63±5.93 vs. 41.15±6.09; p<0.036) compared to their female counterparts. In addition, significant differences were observed in terms of age distribution, occupational, educational, marital, residential status, cigarette smoking, alcohol consumption, BMI, comorbid, severity, and clinical outcomes between the males and females (<0.05) (Table 1). Besides the higher mean age observed among the males, the males also had significantly higher mean values of BMI and body temperature on presentation.

Table 2 depicts the comparative gender-based distribution of the laboratory parameters among the studied cohorts. The males had significantly higher mean levels of plasma creatinine, CRP, GPS, D-dimer, total WBC, neutrophil counts, composite NLR but lower blood levels of albumin, total protein, isolated platelet count, and isolated lymphocyte count (p<0.05) (Table 2).

Table 3 shows the adjusted linear regression evaluation of gender as a potential determinant of inflammatory markers/indices. As depicted, the male gender maintained a significant higher blood levels of CRP, GPS, D-dimer, and composite NLR and also a significant linear relationship with the CRP (β: 0.61; SE: 0.13; p<0.001), composite GPS (β: 0.59; SE: 0.01; p<0.001), D-dimer (β: 0.52; SE: 0.09; p<0.001), and the composite NLR (β: 0.38; SE: 0.10; p<0.001) compared to the females on adjusted linear regression model (Table 2).

Table 4 shows the relationship between the inflammatory markers/indices and the unfavorable clinical outcomes on adjusted logistic regression analysis among the studied cohorts.

As depicted, CRP (OR: 8.86; 95%CI: 7.34-9.78; p<0.001), composite GPS (OR: 7.41; 95%CI: 6.36-8.79; p<0.001), D-dimer (OR: 5.4; 95%CI: 4.32-6.65), and the composite NLR (OR: 4.23; 95%CI: 3.44-5.69; p<0.001) had robust associations with unfavorable clinical outcomes compared to the females on adjusted logistic regression model (Table 4).

Table 1. *Baseline characteristics of non-laboratory parameters among studied cohorts on presentation.*

Variables	Both Sexes, n=598 (100%)	Female Subjects, n=225 (37.6%)	Male Subjects, n=373 (62.4%)	p-value, Females vs. Males
	Mean ± SD/n	Mean ± SD/n	Mean ± SD/n	
Mean Age, years	42.20±6.71	41.15±6.09	43.63±5.93	0.036*
Age groups, years				0.001*
18-44 (young adults)	358	181	171	
45-64 (middle-aged)	159	25	134	
≥65 (elderly)	81	16	65	
Occupation: Health worker (Yes/No)	346/254	131/95	215/159	<0.001*
Educational status				<0.001*
None/primary/secondary/tertiary	13/53/135/397	3/17/35/169	10/35/100/228	
Marital status				<0.001*
Married/single/bereaved	425/169/4	155/71/0	270/98/4	
Residential Area: Urban/Rural	568/30	210/15	358/15	<0.001*
Religion: Christian/Moslem	563/35	216/9	347/26	0.184
Cigarette smoker**: Yes/No	81/517	4/221	76/296	<0.001*
Alcohol consumption status: Yes/No	126/472	49/176	77/296	0.004*
Mean BMI, kg/m^2	28.15±4.33	29.18±4.62	30.84±4.91	<0.001*
BMI classes, kg/m^2				<0.001*
Ideal weight (18.5 – 24.9)	205	75	130	
Overweight (25.0 – 29.9)	167	88	79	
Obese (≥30.0)	226	62	164	
Body temperature, °C	37.9±1.33	37.15±1.62	37.98±1.73	0.025*
SBP, mmHg	135.66±7.55	138.65±7.33	138.40±7.03	0.109
DBP, mmHg	88.74±5.74	89.63±5.87	89.65±5.47	0.361
HR/minute	78.16±4.83	76.65±4.19	76.38±4.08	0.143
RR/minute	24.37±3.22	24.73±2.98	24.81±3.12	0.234
Oxygen saturation (SpO_2), %	93.93±6.19	91.84±5.64	91.45±5.56	0.114
Comorbid conditions:*** Yes/No	190/408	164/61	26/347	<0.001*
Severity: Severe/non-severe	57/541	8/217	49/324	<0.001*
Clinical outcomes				<0.001*
Favorable/unfavorable	488/110	208/17	280/93	0.021*
Contact with known case: Yes/No	201/397	99/126	102/271	0.094

*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; **past/current smoker; ***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.

Table 2. *Comparative depiction of sex-segregated laboratory parameters at presentation.*

Parameters (Reporting Units)	Females, n=225	Males, n=373	p-value
	Mean ± SD/n	Mean ± SD/n	
A. Non-inflammatory laboratory parameters			
Plasma sodium, mmol/L	136.41±7.41	134.26±7.39	0.140
Plasma potassium, mmol/L	3.67±1.10	3.53±1.17	0.627
Plasma Chloride, mmol/L	97.14±6.71	96.96±6.65	0.593
Bicarbonate, mmol/L	21.70±4.56	20.33±4.81	0.304
Plasma urea, mmo/L	6.10±1.04	6.53±1.13	0.150
Plasma creatinine, µmol/L	129.74±8.92	141.72±9.05	<0.001*
Plasma albumin, g/L	34.93±3.87	31.44±3.91	<0.001*
Plasma total protein, g/L	62.63±5.63	58.07±5.89	<0.001*
Hemoglobin concentration, g/L	108.87±8.80	109.96±8.58	0.224
B. Biochemical inflammatory markers/indices			
Serum pro-calcitonin, µg/L	2.96±1.37	3.07±1.26	0.290
Serum C-reactive protein, nmol/L	143.7±11.68	261.43±12.34	<0.001*
Serum ferritin, pmol/L	940.36±24.37	968±89.65	0.074
GPS (as continuous data) x 10^2	57.65±4.77	159.15±10.73	<0.001*
GPS (as categorical data), score 0/score 1/ score 2	3/42/180	48/143/182	<0.001*
C. Coagulation inflammatory markers/indices			
Fibrinogen, g/L	6.31±1.61	6.46±1.34	0.223
D-Dimer, (normal ≤ 500 µg/L FEU)	969.51±94.31	1,784±101.72	<0.001*
Fibrinogen/albumin (g/L) ratio, x 10^3	169.73±11.87	174.69±19.83	0.061
D. Hematologic inflammatory markers/indices			
Total WBC x 10^9/L	14.01±2.41	16.93±3.37	<0.001*
WBC differentials, n			

Parameters (Reporting Units)	Females, n=225	Males, n=373	p-value
	Mean ± SD/n	Mean ± SD/n	
Neutrophil count x 10^9/L	9.94±2.06	14.94±2.15	<0.001*
Lymphocyte count x 10^9/L	1.56±0.16	1.20±0.19	0.007*
Monocyte count x 10^9/L	0.87±0.20	1.04±0.23	0.059
Eosinophil count x 10^9/L	0.34±0.07	0.24±0.05	0.061
Basophil count x 10^9/L	0.08±0.03	0.07±0.02	0.071
Platelet count x 10^9/L	139.81±7.92	126.8±7.12	<0.001*
Red cell count x 10^{12}/L	4.54±1.03	4.65±1.02	0.408
Neutrophil to lymphocyte ratio	6.10±1.13	12.07±2.89	<0.001*
Platelet to lymphocyte ratio	98.45±7.32	100.11±7.96	0.096

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

Table 3. *Adjusted linear regression evaluation of male sex as potential determinant of inflammatory markers/indices.*

Parameters (Reporting Units)	Females, n=225	Males, n=373		
	β	β**	SE	p-value
A. Biochemical inflammatory markers/indices				
Serum pro-calcitonin, µg/L	(Ref).	0.14	0.08	0.124
Serum C-reactive protein, nmol/L	Ref.	0.61	0.13	<0.001*
Serum ferritin, pmol/L	Ref.	0.10	0.07	0.061
GPS (as continuous data) x 10^2	Ref.	0.59	0.09	<0.001*
B. Coagulation inflammatory markers/indices				
Fibrinogen, g/L	Ref.	0.11	0.08	0.080
D-dimer, µg/L FEU	Ref.	0.52	0.08	<0.001*
Fibrinogen/albumin ratio, x 10^3	Ref.	0.10	0.07	0.094
C. Hematologic inflammatory markers/indices				
Neutrophil to lymphocyte ratio	Ref.	0.38	0.10	<0.001*
Platelet to lymphocyte ratio	Ref.	0.12	0.07	0.117

*Statistically significant; Ref.: reference; SE=standard error; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; WBC: white cell count; β: linear regression coefficients representing the difference between males and females for inflammatory markers/indices (as a variable); **adjusted for age/body mass index (both as continuous/categorical data), occupation, educational status, residential areas, cigarette smoking, alcohol consumption, body temperature, comorbid conditions, disease clinical outcome/severity, plasma creatinine, albumin, total protein, and platelet counts.

Table 4. *Evaluations of associations between inflammatory markers/indices and unfavorable clinical outcomes.*

Parameters (Reporting Units)	Females, n=225	Males, n=373		
	OR;	OR**	95%CI	p-value
A. Biochemical inflammatory markers/indices				
Serum pro-calcitonin, µg/L	Ref.	1.44	1.10-2.16	0.104
Serum C-reactive protein, nmol/L	Ref.	8.86	7.34-9.78	<0.001*
Serum ferritin, pmol/L	Ref.	1.18	0.89-1.75	0.167
GPS (as continuous data) x 10^2	Ref.	7.41	6.36-8.79	<0.001*
B. Coagulation inflammatory markers/indices				
Fibrinogen, g/L	Ref.	1.61	1.12-2.20	0.085
D-Dimer, µg/L FEU	Ref.	5.40	4.32-6.65	<0.001*
Fibrinogen (g/L)/albumin (g/L) ratio, x 10^3	Ref.	0.67	0.45-0.976	0.078
C. Hematologic inflammatory markers/indices				
Neutrophil to lymphocyte ratio	Ref.	4.23	3.44-5.69	<0.001*
Platelet to lymphocyte ratio	Ref.	1.10	0.78-1.46	0.086

*Statistically significant; Ref: Reference; GPS: Glasgow prognostic score; FEU: fibrinogen-equivalent unit; WBC: white cell count; OR: odds ratio; CI: confidence interval; **adjusted for age/body mass index (both as continuous/categorical data), occupation, educational status, residential areas, cigarette smoking, alcohol consumption, body temperature, comorbid conditions, disease clinical outcome/severity, plasma creatinine, albumin, total protein, and platelet counts.

4. Discussion

4.1. Key Findings

The severity, morbidity, and mortality of SARS-CoV-2 infection have a disproportionate bias towards the males despite no sex-based differences documented regarding the potential risk for the infection. These unique findings have largely been hinged on the dysregulated systemic inflammation that characterizes the infection. The current study evaluated the impact of systemic inflammation on sex-based bias in SARS-CoV-2 infection among Nigerians. In the current study, the males had significantly higher mean levels of inflammatory markers/indices including CRP, GPS, D-dimer, and the composite NLR. Moreover, the males still maintained a significant linear relationship with the CRP, composite GPS, D-dimer, and the composite NLR on the adjusted linear regression model. Moreover, the CRP, D-dimer, and the composite GPS/NLR parameters all had

significant and robust associations with the unfavorable clinical outcomes among the males when compared to their female counterparts.

4.2. Relationship with Pre-existing Literature

It has become common global knowledge that males bear the brunt of most of the adverse consequences of the SARS-CovV-2 infection. Several epidemiologic evidence has been documented and reported in this regard from many countries and seem to be a norm. Increased rates of the SARS-CoV-2 infection severity, morbidity, and mortality have a disproportionate bias toward the male sex as widely reported. Though many factors have been linked to these sex-based differences (chromosomal predisposition, endocrine influences, gender-specific behaviors, socio-cultural factors, and increased rates of comorbidities), the role of exaggerated/exuberant systemic inflammation seems to be more accepted, since the severity, morbidity, and mortality hinges on the exaggerated/exuberant SARS-CoV-2-stimulated systemic inflammation in males [8-10, 16].

In a similar recent study conducted at the Massachusetts General Hospital in the United States of America, the authors had examined sex differences in inflammatory markers among 453 men and 328 women hospitalized with SARS-CoV-2 infection at the hospital and demonstrated that men exhibited more robust inflammatory activation as evidenced by higher initial and peak inflammatory markers, as well as worse clinical outcomes [6]. In an in-depth analysis of laboratory parameters conducted among 33,266 Brazilian SARS-CoV-2 positive patients, the investigators had observed interplay between sex and systemic inflammation and concluded that differences in SARS-CoV-2 infection could be explained by biologic sex [8]. These previous reports corroborate the conclusions in the present study and underscore the impact of biological sex on SARS-CoV-2 severity, morbidity, and mortality.

4.3. Mechanistic Considerations

The exact mechanism underlying the sex-based disparity of the exaggerated/exuberant inflammation induced by SARS-CoV-2 infection is an ongoing area of intense research and remains poorly understood. However, different genetic and endocrine consequences, including the roles of key sex hormone actions, might influence and explain the sex-based mechanisms of the exaggerated/exuberant inflammatory responses. [16-19] Genetically, females have a more robust inflammatory response against viral infections, including SARS-CoV-2, leading to enhanced viral clearance due to the presence of potent immune-regulating genes located on the X chromosomes; genes that are inactivated in males due to rhe presence of only one X chromosome [17].

The different roles played by the male and female sex hormones have also been attributed to the sex-based differences in exaggerated/exuberant inflammatory responses in SARS-CoV-2 infection among males. [10, 11, 17-19]

Testosterone has a suppressive effect on several innate and adaptive immune functions and responses, while estrogen has stimulatory effects and tend to up-regulate several pathways that modulate inflammatory responses during infection with SARS-CoV-2. [10, 11, 17] Androgens have immunosuppressive and pro-inflammatory effects in SARS-CoV-2 infection, leading to a less effective innate and adaptive immune response, while the estrogens tend to have the opposite effects [10, 11, 17]. Moreover, sex hormones tend to interact with glucocorticoids and cooperate in the modulation of the immune and inflammatory responses [16, 17]. The glucocorticoids have suppressive effects on the innate and adaptive immune responses and inflammatory reactions [16-19]. Though the glucocorticoids tend to block the secretion of testosterone from the testes and that of estradiol from the ovaries [17], in turn, estradiol has a direct stimulatory effect, whereas testosterone has a suppressive effect on the glucocorticoids [17-19].

4.4. Significance to Current Clinical Practice and Subsequent Research

Based on the current findings, sex-based therapeutic measures, especially anti-inflammatory measures, should be incorporated and considered during the management of the current SARS-CoV-2 pandemic. However, further studies are highly recommended to fully explore the sex-based exaggerated inflammatory storm among SARS-CoV-2 infected subjects, to better understand the pathophysiologic basis of SARS-CoV-2 infection, which may enhance the development of sex-based therapeutic interventions.

4.5. Strength and Limitations

Though the current study was strengthened by its relatively large sample size, it was also limited by some factors which are of importance to be acknowledged. First, as single-center-based research, its findings may not be entirely reflective of the overall population around the studied zone.

Secondly, since the study was based on the acquisition of secondary data which was acquired retrospectively, the under-reporting of the actual number of SARS-Cov-2 infected patients cannot also be ruled out with certainty. Lastly, as an observational study, its findings do not infer causality but merely associations.

5. Conclusion

Taking together, the study findings show that the males who are infected with SARS-CoV0-2 have more exaggerated/exuberant inflammatory episodes, evidenced by higher levels of various inflammatory markers/indices at presentation compared to their female counterparts. Moreover, these higher inflammatory markers/indices

observed among the males were significantly associated with unfavorable clinical outcomes. More studies are highly recommended to fully explore the sex-based exaggerated/exuberant inflammatory storm among SARS-CoV-2 infected subjects, to better understand the pathophysiologic basis of SARS-CoV-2 infection, which may enhance the development of sex-based therapeutic interventions.

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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