



## Association between laboratory parameters and CT severity in patients infected with Covid-19: A retrospective, observational study

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### ABSTRACT

**Introduction:** Patients diagnosed with COVID-19 have presented to emergency departments (EDs) worldwide with a wide range of symptoms. In this study we reported the clinical, laboratory and radiological features of the cases diagnosed with COVID-19.

**Methods:** This is a single-center, retrospective, descriptive, and observational study. The patients who have admitted to ED between March 11 and May 31, 2020 and diagnosed COVID-19 infection.

**Results:** 130 (73 male and 57 female) patients with COVID-19 polymerase chain reaction (PCR) positive test were included in the study. The average age of the study group was calculated as  $52.63 \pm 17.95$  year. While 15.4% of the patients were asymptomatic, the most common symptom was identified as cough (46.2%), followed by dyspnea (23.1%), fever (17.7%). The computed tomography (CT) severity scores proved significantly higher in the patients with hypertension and coronary artery disease (CAD) than in those without these diseases ( $p = 0.010$  and  $p = 0.042$ , respectively). The moderate positive correlation between serum ferritin level and CT severity score is another finding worth noting ( $\rho = 0.530$  and  $p = 0.0001$ ). In a similar vein, the high level of D-dimer in the CT-positive group and its positive moderate correlation with CT severity ( $\rho = 0.375$  and  $p = 0.0001$ ).

**Conclusion:** In our study, serum ferritin and D-dimer levels were observed to be high in the CT-positive group and have moderate positive correlation with CT severity. We thus argue that D-dimer and ferritin levels measured at the time of admission to the ED can be taken into consideration to predict radiological severity.

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## 1. Introduction

Having appeared in Wuhan, China in the last month of 2019 and subsequently spread to the whole world, COVID-19 infected approximately 5.9 million people as of May 31 and developed into a pandemic leading to 367,166 deaths worldwide. By the same date, about 1.7 million cases were detected in the United States (USA), while the number of the identified cases amounted to around 163,000 in Turkey [1]. Patients diagnosed with COVID-19 have presented to emergency

departments (EDs) worldwide with a wide range of symptoms, such as cough, shortness of breath, difficulty breathing, fever, chills, repeated shaking with chills, muscle pain, headache, sore throat, and new loss of taste or smell [2]. Clinical manifestations appearing in patients admitted to hospitals have a broad spectrum, ranging from asymptomatic forms to severe pneumonia progressing into respiratory failure, sepsis, septic shock, and multiple organ failure [3].

In addition, conditions, including acute respiratory distress syndrome (ARDS), septic shock, acute kidney injury, cardiac injury, and multi-organ failure are reported as complications of COVID-19 infection [1]. On the other hand, conditions, such as advanced age, immunodeficiency, diabetes, cardiovascular diseases, hypertension, and chronic lung disease, are identified as risk factors in COVID-19 disease [4,5].

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The first confirmed case was detected on March 10, 2020 in Turkey and on March 15, 2020 in our hospital [6]. Within this framework, our study set out to report the clinical, laboratory and radiological features of the cases admitted to the adult ED of our tertiary care hospital and diagnosed with COVID-19.

## 2. Methods

### 2.1. Study type

This is a single-center, retrospective, descriptive, and observational study. The clinical procedures were inaugurated once the approval numbered 60116787-020/26607 was granted by the Non-Interventional Research Ethics Committee of Pamukkale University.

### 2.2. Study population

Carried out in Pamukkale University Emergency Department, the present study included the patients admitted to the COVID-19 outpatient clinic of our hospital and diagnosed with COVID-19 infection [confirmed by polymerase chain reaction (PCR)].

### 2.3. Subject selection

The subjects, which admitted to the ED between March 11 and May 31, 2020, confirmed by PCR and performed thorax CT, were included for the study.

### 2.4. Research protocol

The dataset was composed of vital parameters [fever, blood pressure (BP), peripheral oxygen saturation (sPO<sub>2</sub>)] at the time of admittance to the ED extracted from the hospital information system; complete blood count; C-reactive protein (CRP), urea, creatinine, D-dimer, Ferritin and high-sensitive troponin T (hsTnT) parameters; status of hospitalization; type of department referred for hospitalization; status of being dead or alive; patient complaints at the time of admittance; and presence of comorbid diseases.

### 2.5. Clinical scoring

The diagnosis of COVID-19 pneumonia was performed in accordance with the current criteria, and after the pneumonia severity index (PSI) and CURB-65 scores were calculated as suggested in the literature, they were recorded in the dataset [7–10].

### 2.6. Radiological examination

The thoracic CT severity scores were calculated, as cited in the literature, by a radiologist blinded to the study [11].

### 2.7. Statistical analysis

Data management was performed using SPSS package program. While the continuous variables were provided as mean ± standard deviation, median [interquartile range (IQR)] and the categorical variables were presented as numbers and percentages. In the absence of parametric test assumptions, a Mann-Whitney *U* test was carried out to compare the differences of independent groups, whereas the association between the continuous variables was tested by Spearman correlation analysis. In all the analyses, the significance level was defined as  $p < 0.05$ .

## 3. Results

A total of 130 patients with COVID-19 PCR-positive test for whom CT imaging was performed were eventually included in the study between March 11, 2020 and May 31, 2020. Out of 80 hospitalized patients diagnosed with COVID-19 infection, 11 received treatment in the ICU, while 50 patients were outpatients.

The average age of the study group, which consisted of 73 (56.2%) male and 57 (43.8%) female individuals, was calculated as 52.63 ± 17.95 years.

While 15.4% of the patients were asymptomatic, only one symptom developed in 21.5%, and 63.1% suffered two or more symptoms. The most common symptom was identified as cough (46.2%), followed by dyspnea (23.1%), fever (17.7%), weakness (16.9%), myalgia (11.5%), and sore throat (10%) (Table 1). Fever > 37.8 °C was measured only in 17.7% of our subjects on admission. No significant relation was noted between the underlying comorbidities (hypertension, coronary artery disease (CAD), diabetes mellitus, chronic obstructive pulmonary disease (COPD) or asthma) and the measured fever degrees (all *p* values are > 0.05).

Considering the imaging data of the patients, CT imaging was performed in 130 patients (88.04%). Though 62 (42.5%) patients with CT imaging did not manifest any clinical findings, 68 patients (46.5%) showed signs of pneumonia in their CT.

As for the patients with and without normal tomography findings, the sPO<sub>2</sub>, White Blood Cell (WBC), lymphocyte, neutrophil-to-lymphocyte ratio (NLR), platelet and monocyte values were significantly lower in the CT positive group than in the negative group ( $p = 0.002$ ;  $p = 0.003$ ;  $p = 0.0001$   $p = 0.034$ ;  $p = 0.027$  and  $p = 0.033$ , respectively). On the other hand, the systolic BP, urea, creatinine, D-Dimer and ferritin levels were established to be high ( $p = 0.001$ ;  $p = 0.016$ ,  $p = 0.033$ ,  $p = 0.002$ ,  $p = 0.018$ , respectively) (Table 2).

As regards the comorbid diseases and the CT severity scores of the patients with pneumonia, the CT severity score tended to be higher in those with two or more comorbidities ( $p = 0.042$ ). The CT severity scores proved significantly higher in the patients with hypertension and coronary artery disease (CAD) than in those without these diseases ( $p = 0.010$  and  $p = 0.042$ , respectively). These scores were also higher in the patients undergoing endotracheal intubation than in their non-intubated counterparts ( $p = 0.0001$ ) (Table 3).

Given the vital and laboratory parameters as well as the association between CT severity scores, a moderately low negative correlation was

**Table 1**  
Symptoms of the patients.

Symptoms	Asymptomatic	One symptom	Two or more symptoms	N (%)
	20 (15.4%)	28 (21.5%)	82 (63.1%)	
Cough			60 (46.2%)	
Dyspnea			30 (23.1%)	
Fever > 37.8 °C			23 (17.7%)	
Weakness			22 (16.9%)	
Myalgia			15 (11.5%)	
Sore throat			13 (10%)	
Diarrhea			8 (6.2%)	
Headache			8 (6.2%)	
Chest pain			5 (3.8%)	
Nausea			5 (3.8%)	
Abdominal pain			5 (3.8%)	
Postnasal drip			3 (2.3%)	
Vomiting			3 (2.3%)	
Back pain			2 (1.5%)	
Unconsciousness			2 (1.5%)	
Nasal congestion			1 (0.7)	
Anosmia			1 (0.7)	

**Table 2**  
Vital and laboratory parameters of the CT-positive and negative groups.

	CT negative group (N = 62)		CT positive group (N = 68)		p Value
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	
Fever (°C)	36.8 ± 0.58	36.7 (36.4–37.1)	37 ± 0.72	36.7 (36.52–37.4)	0.159
sPO <sub>2</sub>	96.77 ± 1.91	97 (95–98)	95.2 ± 4.11	95 (94–97)	<b>0.002</b>
Systolic BP (mmHg)	119.88 ± 13.23	120 (110–120)	129.52 ± 17.96	130 (117.25–140)	<b>0.001</b>
Diastolic BP (mmHg)	74.87 ± 9.33	78 (70–80)	76.79 ± 11.77	80 (70–84)	0.494
WBC (K/μl)	8.07 ± 3.45	7.88 (6.02–9.55)	7.04 ± 3.96	5.76 (4.51–8.53)	<b>0.003</b>
Hb (g/dl)	13.16 ± 3.72	14 (12–15.6)	13.44 ± 2.38	13.8 (12.75–14.9)	0.654
Neu (K/μl)	5.2 ± 3.11	4.55 (3.39–6.45)	4.82 ± 3.56	3.8 (2.71–5.08)	0.078
%Neu	58.74 ± 17.95	59.2 (52.62–66.15)	63.93 ± 16.07	65.65 (54.8–74.65)	0.044
NLR	3.08 ± 3.87	1.9 (1.4–2.59)	4.2 ± 5.52	2.45 (1.57–4.04)	<b>0.034</b>
Lymph (K/μl)	2.2 ± 0.97	2.25 (1.67–2.95)	1.62 ± 0.92	1.52 (0.96–1.98)	<b>0.0001</b>
%Lymph	27.25 ± 12.49	30.7 (20.62–34.77)	25.82 ± 12.62	26.2 (17.17–34)	0.233
Plt (K/μl)	240.4 ± 84.07	245 (209–239.25)	219.79 ± 75.7	220.5 (158.25–270)	<b>0.027</b>
Monocyte	0.53 ± 0.26	0.51 (0.39–0.66)	0.47 ± 0.29	0.39 (0.27–0.63)	<b>0.033</b>
CRP (mg/l)	21.22 ± 52.92	1.21 (0.39–5.43)	40.44 ± 51.11	18.93 (4.33–66.54)	<b>0.0001</b>
Urea (mg/dl)	26.87 ± 26.06	22 (18.75–28)	33.29 ± 23.05	26.5 (20–35.25)	<b>0.016</b>
Creatinine (mg/dl)	0.76 ± 0.28	0.73 (0.62–0.93)	0.92 ± 0.43	0.85 (0.65–1.02)	<b>0.033</b>
D-Dimer (ng/mL)	373.57 ± 833.63	75 (41–256.5)	379.24 ± 551	197 (100–385.5)	<b>0.002</b>
Ferritin (ug/L)	149.87 ± 250.39	84 (31.65–133)	221.43 ± 329.43	113 (19.18–259)	<b>0.018</b>
hsTnT (μg/l)	9.26 ± 17.04	3 (3–7.87)	25.35 ± 98.17	3.98 (3–9.87)	0.204

p Values were derived from Mann-Whitney U test.  
sPO<sub>2</sub>, peripheral oxygen saturation; BP, blood pressure; WBC, White Blood Cell; Hb, hemoglobin; Neu, neutrophil; NLR, neutrophil-to-lymphocyte ratio; Lymph, lymphocyte; Plt, platelete; CRP, C-reactive protein; hsTnT, high-sensitive troponin T.  
CT, computed tomography; IQR, interquartile range; SD, standart deviation.  
Bold values are statistically significant p values.

**Table 3**  
CT Severity score, gender, and comorbidities of the subjects diagnosed with pneumonia.

		Median (IQR)	p Value
Gender	Male (N = 43)	6 (3–9)	*0.035
	Female (N = 25)	2 (1.5–8)	
Comorbidity	No comorbidity (N = 36)	4 (1.25–8)	**0.042
	One comorbidity (N = 13)	4 (2–6.5)	
	More comorbidities (N = 19)	8 (4–11)	
Hypertension diagnosis	Yes (N = 14)	8.5 (3.75–11)	*0.010
	No (N = 54)	4 (2–8)	
CAD diagnosis	Yes (N = 13)	9 (5–10.5)	*0.021
	No (N = 55)	4 (2–8)	
DM Diagnosis	Yes (N = 13)	8 (3.5–9.5)	*0.105
	No (N = 55)	5 (2–8)	
COPD, Astma Diagnosis	Yes (N = 9)	3 (2–7.5)	*0.489
	No (N = 59)	5 (2–8)	
Endotracheal Intubation	Yes (N = 10)	10.5 (8–13.5)	*0.0001
	No (N = 58)	4 (2–8)	
Hospitalization	Yes (N = 57)	6 (2.5–9)	*0.002
	No (N = 11)	2 (1–5)	
ICU Unit Admission	Yes (N = 11)	10 (8–13)	*0.001
	No (N = 57)	4 (2–11)	

CAD, coronary artery disease; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.  
CT, computed tomography.  
IQR, interquartile range.  
\* p values were derived from Mann-Whitney U test.  
\*\* p value is derived from Kruskal-Wallis test.

established between CT severity scores, sPO<sub>2</sub>, and lymphocyte count (rho = -0.360 and p = 0.0001; rho = -0.434 and p = 0.0001, respectively). A low positive correlation was noted between CT severity score and systolic BP, CRP value, PSI score as well as hospitalization time (rho = 0.397 and p = 0.0001; rho = 0.390 and p = 0.0001; rho = 0.346 and p = 0.008; rho = 0.338 and p = 0.009, respectively). The moderate positive correlation between serum ferritin level and CT severity score is another finding worth noting (rho = 0.530 and p = 0.0001). In a similar vein, the high level of D-dimer in the CT-positive group and its positive moderate correlation with CT severity (rho = 0.375 and p = 0.0001) (Table 4).

#### 4. Discussion

The present study reports information on the symptomatic manifestations and underlying comorbid disorders as well as laboratory, clinical, and radiological results of the patients admitted to the ED of our tertiary hospital. Accordingly, 15.4% of the subjects were asymptomatic, and 80 subjects (61.5%) received treatment during hospitalization, while 8 subjects (6.15%) diagnosed with COVID-19 died. On the other hand, the most recurrent symptoms in our study population were established as cough (46.2%) and dyspnea (23.1%). CT severity scores were observed to be high in those with comorbid diseases, particularly in the subjects with hypertension and CAD than those who did not suffer from such diseases. Besides, the level of ferritin, one of the laboratory parameters, seemed to moderately correlate with CT severity.

Fever, one of the fundamental signs of COVID-19 disease, is recognized as a symptom found in 42.8–87.9% of the infected cases [12–14]. In a study by Thakaran et al., body temperature is reported to correlate with mortality [15]. In contrast to earlier findings, however, fever > 37.8 °C was measured only in 17.7% of our subjects at the time of admittance, though fever stood out as a highly common arrival complaint among them. In this regard, this finding can lead us to conclude that COVID-19 infected patients might not necessarily be afflicted with fever. There was no discrepancy between CT-positive and negative cohorts in terms of fever values, but we are of the opinion that this situation may be attributed in part to the small number of subjects developing fever. No discrepancy was observed between CT-positive and negative cohorts in terms of fever values. Likewise no significant discrepancy was found between the comorbidities and fever. However, we are of the opinion that this situation may be attributed in part to the small number of subjects developing fever. Tahakaran et al. argue that body temperature correlates with mortality, yet no correlation coefficient was reported in their study [15]. The significant, though weak, correlation between the CT severity and the measured fever values during the admittance in our study can be considered as the data that can corroborate the association between clinical severity and body temperature.

Angiotensin converting enzyme 2 (ACE-2) receptors, which interact with COVID-19 virus for penetration into the cell, are involved

**Table 4**  
Correlations between CT Severity score and vital, laboratory, and clinical parameters in patients with pneumonia.

Fever	rho	<b>0,214</b>
	p Value	<b>0,015</b>
SpO <sub>2</sub>	rho	<b>-0,360</b>
	p Value	<b>0,0001</b>
Systolic blood pressure	rho	<b>0,397</b>
	p Value	<b>0,0001</b>
Diastolic blood pressure	rho	0,062
	p Value	0,482
WBC	rho	-0,108
	p Value	0,220
Hemoglobin	rho	0,014
	p Value	0,873
Neutrophil count	rho	0,037
	p Value	0,674
% Neutrophil	rho	<b>0,294</b>
	p Value	<b>0,001</b>
Lymphocyte count	rho	<b>-0,434</b>
	p Value	<b>0,0001</b>
%Lymphocyte	rho	<b>-0,236</b>
	p Value	<b>0,007</b>
NLR	rho	<b>0,398</b>
	p Value	<b>0,001</b>
Platelet	rho	-0,164
	p Value	0,063
Monocyte count	rho	<b>-0,214</b>
	p Value	<b>0,014</b>
CRP	rho	<b>0,390</b>
	p Value	<b>0,0001</b>
Urea	rho	0,149
	p Value	0,090
Creatinine	rho	<b>0,244</b>
	p Value	<b>0,005</b>
D-Dimer	rho	<b>0,375</b>
	p Value	<b>0,0001</b>
Ferritin	rho	<b>0,530</b>
	p Value	<b>0,0001</b>
hsTnT	rho	-0,037
	p Value	0,754
CURB-65 score	rho	0,246
	p Value	0,066
Pneumonia severity index score	rho	<b>0,346</b>
	p Value	<b>0,008</b>
Hospitalization time	rho	<b>0,338</b>
	p Value	<b>0,009</b>

p and rho values were derived from Spearman Correlation test.

sPO<sub>2</sub>, peripheral oxygen saturation; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; hsTnT, high-sensitive troponin T; CT, computed tomography.

Bold values are statistically significant p values.

in hypertension pathogenesis [16–18]. The association between the presence of hypertension and disease severity has been established in some earlier research [18,19]. These previous works highlight the presence of hypertension and the increase in the mortality risk, rather than high BP measured at the ED admittance. In another study, the patients with poor prognosis was reported to have higher systolic and diastolic pressure on admission [20]. Similar to this study, our results indicated that the systolic BP recorded at the ED admittance was found to be higher in the CT-positive group than in the negative one. In other words, the subjects diagnosed with hypertension tended to have higher CT severity scores in our study. Further to this, the systolic BP recorded at the ED admittance was found to be higher in the CT-positive group than in the negative group. The significant correlation between systolic BP and CT severity makes us conclude that the BP regulation of the subjects is likely to be disrupted due to the interaction between COVID-19 virus and ACE-2 receptors.

The current data on the role of comorbidity in COVID-19 reveal that the clinical stage of the disease progresses more severely in patients with hypertension, CAD, diabetes, COPD or male gender, but we did not come across any report that associates the disease with CT severity

[18,19,21]. In line with prior research, our study shows that CT severity also tended to be higher in male individuals, patients with hypertension, and those with CAD than in those without these diseases, yet it was not higher in diabetes and COPD-asthma patients than in those without these diseases. Although earlier studies have based their evaluation on the data related to the clinical condition and mortality, taking CT severity into consideration, as in our study, may provide some insight into severity of COVID-19 disease.

A large body of clinical work investigating the abnormalities in laboratory parameters of COVID-19 disease documents high D-dimer, Ferritin, CRP values and low lymphocyte count [13,22,23]. A recent meta-analysis addresses this issue by emphasizing that lymphopenia and higher CRP levels are common laboratory findings of COVID-19 [24]. Another study reporting that CRP levels and CT findings are positively correlated concludes that CRP level might be a key factor in the early diagnosis of this disease [25]. As a matter of fact, extensive research has been undertaken to analyze the relationship between CRP level and CT severity [26,27]. For instance, a study probing the relationship between early CT score and laboratory parameters suggests that neutrophil count, WBC and CRP level ( $r = 0.502$  and  $p < 0.001$ ;  $r = 0.414$  and  $p = 0.001$ ;  $r = 0.511$  and  $p < 0.001$ , respectively) have moderately positive correlation [28]. In another study where the relationship between CT lesion scores and laboratory parameters was analyzed, neutrophil percentage %neu and CRP levels were found to have moderate positive correlation with CT scores ( $r = 0.436$  and  $p < 0.001$ ;  $r = 0.489$  and  $p < 0.001$ , respectively), while lymphocyte count and lymphocyte percentage were found to have moderate negative correlation ( $r = -0.331$  and  $p < 0.001$ ;  $r = -0.457$  and  $p < 0.001$ , respectively) [27]. A meta-analysis on the relationship between thrombocytopenia and COVID-19 reveals that thrombocytopenia condition is associated with severe clinic findings of COVID-19 disease [29]. In a study on monocyte count, pulmonary inflammation index and monocyte level were observed to have moderate–weak negative correlation [26]. When it comes to our study, the CRP level was considerably higher in the CT-positive cohort, and the CT severity and CRP levels were established to have correlation close to the levels documented in previous studies, and we thus argue that CRP level may act as a potential predictor of CT severity. In addition, %neu, CRP, and creatinine levels were higher in the subjects with CT findings than in those with normal CT, and CT severity positively correlated with these levels. This suggests that the elevation of these laboratory parameters might prove helpful in predicting the presence of abnormal CT findings and CT severity. Our findings differ markedly from those reported in the literature in that the neutrophil count was not higher in CT-positive subjects and did not correlate with CT severity. We also observe that the %neu levels were not higher but correlated with CT severity in the CT-positive cohort, which corroborates the literature data revealing the association between %neu and CT severity.

It is also note worthy that the subjects with CT-positive were likely to have lower WBC, lymphocyte count, platelet count, and monocyte count than CT-negative patients. Among these laboratory parameters, we did not find a correlation between WBC and platelet count and CT severity. In this respect, our study came up with a different conclusion from the literature data, and we hold the view that these two parameters are not suggestive of CT severity but of CT findings. Further analysis indicates that the lymphocyte and monocyte counts were lower in the CT-positive group in line with the literature data, and a significant negative correlation existed between these laboratory parameters and CT severity. Based on these findings, we can conclude that the low scores in these parameters can help to predict the severity of CT.

In numerous reports, serum ferritin and D-dimer levels are established to be higher in patients with severe COVID-19 than those with a mild clinical picture [30–32]. However, there seems to be a lack of research analyzing the relationship between CT severity and serum ferritin and D-dimer levels in the light of our literature review. In our study, serum ferritin levels were observed to be high in the

CT-positive group and have moderate positive correlation with CT severity. This situation indicates that serum ferritin level is closely related to the radiological severity as well as the clinical severity of the subjects. In a similar vein, the high level of D-dimer in the CT-positive group and its positive correlation with CT severity, though not as high as ferritin, indicate that the serum D-dimer level is associated with clinical and radiological severity. We thus argue that D-dimer and ferritin levels measured at the time of admission to the ED can be taken into consideration to predict radiological severity.

## 5. Limitations

The generability of our results are subject to some limitations. For one thing, it is primarily retrospective in nature. Although ours is the only tertiary-level hospital in the region, the results may not be generalized for all the patients in the region, as it is not the only hospital admitting COVID-19 patients. In addition, we are not knowledgeable about the patients who are asymptomatic and do not present to the hospital. Within this scope, our findings are confined to the patients we were able to detect.

## 6. Conclusion

In contrast to earlier findings, however, fever  $> 37.8^{\circ}\text{C}$  was measured only in 17.7% of our subjects at the time of admittance. In this regard, this finding can lead us to conclude that COVID-19 infected patients might not necessarily be afflicted with fever. The subjects diagnosed with hypertension tended to have higher CT severity scores in our study. Further to this, the systolic BP recorded at the ED admittance was found to be higher in the CT-positive group than in the negative group. We think that NLR elevation, high CRP levels, high D-dimer and ferritin levels may act as a potential predictor of CT severity. The severity of COVID-19 can be suggested to have some association with serum ferritin and d-dimer levels. Especially, D-dimer and ferritin levels measured at the time of admission to the ED can be taken into consideration to predict radiological severity.

## Author contribution statement

1-Study concept and design: A.Y. and R.S. 2-Acquisition of data: A.Y., A.O., M.S., M.O., and T.G. 3-Analysis and interpretation of data: A.Y., V.C. and R.S. 4-Drafting of the manuscript: A.Y. and R.S. 5-Critical revision of the manuscript for important intellectual content: A.Y. and R.S. 6-Statistical analysis: R.S. and A.Y. 7-Administrative, technical and material support: I.T., M.S., M.O., and T.G. 8-Study supervision: A.Y.

## Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

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