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Original article

Predictors of deterioration of mild cases with COVID-19 during the third wave

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ABSTRACT

Background: The global pandemic of corona virus disease 2019 (COVID-19) still growing and its death toll has been progressing massively as well disregarding the human and financial resources. This necessitates early detection of severe cases and treats them promptly. Thus, in this study, we aimed at identification of predictors of deterioration of mild cases of COVID-19. **Methods**: In this case control study, we included 137 subjects with confirmed COVID-19 from Suez Canal University Hospital. Baseline characteristics, laboratory and radiological data were documented. These variables were compared between those who witnessed deterioration (cases) and those who did not (control). Logistic regression analysis was performed to identify predictors of deterioration. **Results**: Fifteen out of 137 patients experienced clinical deterioration. Age, marital status, smoking status, diabetes mellitus (DM), hypertension, chronic pulmonary disease and chronic liver disease (CLD), and high mean of computed topography (CT score) were more prevalent among deteriorated patients; nevertheless, anosmia and loss of taste were characteristic of non-deteriorated cases. The latter group had relatively low mean lymphocytes, neutrophils/lymphocytes ratio (N/L ratio), albumin, and high mean of inflammatory markers. Logistic regression revealed that only diabetes, chronic liver disease, albumin, LDH, CT score were significant predictors of deterioration. Analysis of the receiver operating characteristic curve revealed that CT score was the most sensitive and specific indicator for prediction of deterioration. **Conclusions**: Many clinical data, laboratory and radiological features were more prominent in deteriorated cases, but DM, CLD, albumin, LDH and CT score were significant predictors of deterioration.

Introduction

COVID-19 is now spreading progressively with a massive accumulation of its burden. To date, there are over 166 million confirmed cases of COVID-19 with nearly 3.5 million deaths worldwide. According to the World Health Organization, there is over 251 thousands confirmed cases of COVID in Egypt, with around 6% mortality rate [1].

Fortunately, around 80% of patients with COVID-19 have mild symptoms, while the rest

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presents with severe symptoms that necessitates hospitalization [2]. Sever illness during COVID-19 infection is linked to many aspects including risk factors and multiple comorbidities. The common medical conditions associated with high mortality are hypertension, metabolic diseases, obesity, cardiovascular and lung diseases [3]. There has been a debate over those predicting factors of severity. While presenting symptoms constitutes a greater importance of determination of severity, progression of the disease and deterioration is widely based on other elements such as laboratory and radiological findings [4].

With the emergence of the third wave, there is an equal collapse of the human and hospital resources as well. Thus, anticipation of potentially critical cases is a must to reduce mortality rate, in addition to overcome shortage of healthcare workers and hospital resources [5, 6]. In this study, we aimed at identification of predictors of deterioration of mild cases of COVID-19 to reduce such burden as early as possible.

Methods

In this nested case control study, we investigated the predictors of deterioration of mild cases with COVID-19 who visited Suez Canal University Hospital at Ismailia city and Suez Canal Private Hospital at Suez city during the period between January to April 2021. This was achieved through retrospective analysis of patients' data including: socio-demographics (age, sex, residence, marital status, occupation, smoking, and BMI), risk factors and comorbidities (diabetes mellitus (DM), hypertension, chronic pulmonary disease, chronic liver disease (CLD), heart failure, renal failure, and positive family history of COVID-19), clinical presentation (constitutional manifestations, respiratory manifestations, gastrointestinal manifestations, anosmia, loss of taste, and insomnia), laboratory findings, computed topography (CT) score, and treatment regimen.

The CT score was calculated as following: "multiplication of four-point scale (to assess the nature of infiltration) by four-point scale (to assess the distribution of infiltration). The first scale ranges from one to four; one is normal attenuation, two is ground glass opacity (GGO), three is mixed GGO and consolidation, and four is consolidation. The latter scale ranges from zero to four; zero as normal, one as <25% abnormality, two as 25%–50% abnormality, three as 50%–75% abnormality, and four as 75% abnormality. Each lung zone-with a total of six lung zones in each patient-was assigned a score on the mentioned scales. Points from all zones were added for a final cumulative score, with a value ranging from zero to 96. This method of assessment was firstly described by **Ooi et al.** in 2004 for assessment of SARS severity" [7].

Clinical deterioration was determined if any of the following was found: oxygen saturation less than 92%, ratio of partial pressure of oxygen to fraction of inspiration O2 (PaO2/FiO2) less than300mmHg, respiratory rate more than 30 breaths/ minute or lung infiltration more than 50%. Participants were divided into two groups: group 1 (cases) were those who witnessed deterioration and group 2 (control) were those who did not witness deterioration.

The study was approved by the institutional review board of Suez Canal University, Faculty of Medicine.

Statistical analysis

All statistical analyses were performed using the *SPSS* statistical package for social science version 22. Descriptive statistics were applied in numerical form (mean, SD or percentages) to describe the quantitative variables. Associations between variables were tested for significance by using Chi-square test for categorical variables and the Student (t) test for continuous variables with normally distributed data. Non-normally distributed data will be tested using Chi-square test for categorical variables and Mann-Witney U tests for continuous variables. Multivariate analysis was used to assess determinants of deterioration. Diagnostic accuracy was assessed through estimation of cutoff values, sensitivity and specificity through ROC curve. Results will be considered statistically significant at a *p*-value of less than or equal 0.05.

Results

We involved 137 patients; about two thirds of them were males. The majority of cases were relatively older than control group. Concerning the socio-demographic data, the majority of participants were urban residents (80%), married (73%), employed (58%), non smokers (69%), and of average BMI. Only fifteen patients witnessed deterioration. Remarkably, there was a significant difference between the patients who deteriorated and those who did not regarding age, marital status, and smoking **(Table 1)**.

When risk factors and comorbidities were compared between those who witnessed deterioration and those who did not, it was noticed that the majority of the former group had DM and hypertension; nevertheless, fewer percent of them had chronic pulmonary disease and CLD. Minority of patients had ischemic heart disease and renal failure **(Table 2)**.

Symptoms and signs of COVID were insignificantly different between patients, except for anosmia and loss of taste which were more common among patients who did not deteriorate **(Table 3)**.

There was a statistically significant difference in many laboratory data of cases than controls. For instance, deterioration was associated with lower lymphocytic count, N/L ratio, albumin, in addition to higher mean of CRP, ESR, LDH, and D dimer). Moreover, mean of CT score was higher among deteriorated patients **(Table 4)**.

Logistic regression analysis revealed that diabetes mellitus (OR 4, CI 1.09-14.97), chronic liver disease (OR 7.6, CI 1.21-47.7), albumin (OR 0.004, CI 0.004-0.50), LDH (OR 0.57, CI 0.09-3.33), and CT score (OR 1.45, CI 1.11-1.90), were significant predictors of deterioration **(Table 6)**.

Analysis of the receiver operating characteristic curve revealed that age and CT score was the most sensitive indicator (sensitivity 92%) followed by LDH and D Dimer (sensitivity 84%) meanwhile CT score and age was the most specific indicator for prediction of deterioration **(Table 7 and figure 1)**.

Table 1. Characteristics of patients.

Variables	Group 1 N = 15	Group 2 N = 122	Total N = 137	P value
Age				
18-34	0 (0)	47 (39)	47 (44)	
35-54	5 (33)	54 (44)	59 (43)	<0.001*
55-75	10 (67)	21 (17)	21 (23)	
Gender				
Male	11 (73)	79 (65)	90 (65)	0.3
Female	4 (27)	43 (35)	47 (35)	
Residence				
Urban	11 (73)	99 (81)	110 (80)	0.3
Rural	4 (23)	23 (19)	27 (20)	
Marital status				
Married	11 (73)	88 (72)	99 (73)	
Single	0 (0)	24 (20)	24 (17)	0.01*
Divorced	0 (0)	3 (2)	3 (2)	
Widow	4 (27)	7 (6)	11 (8)	
Occupation				
Employee	8 (53)	72 (59)	80 (58)	0.5
Worker	0 (0)	10 (8)	10 (7)	
Farmer	1 (7)	4 (3)	5 (4)	
Unemployed	6 (40)	36 (30)	42 (31)	
Smoking				
Yes	8 (53)	34 (28)	42 (31)	0.04*
No	7 (47)	88 (72)	95 (69)	
BMI				
Average	11 (73)	94 (77)	105 (77)	
High	4 (27)	25 (20)	29 (21)	0.7
Low	0 (0)	3 (3)	3 (2)	

Data are presented as number and percent; n (%). Presented percent is column percent.

Table 2. Risk factors and comorbidities.

Variables		Group 1 N = 15	Group 2 N = 122	Total N = 137	*p* value
DM	Yes	9 (60)	22 (18)	31 (23)	0.001*
	No	6 (40)	100 (82)	106 (77)	
HTN	Yes	9 (60)	32 (26)	41 (30)	0.01*
	No	6 (40)	90 (74)	96 (70)	
Chronic pulmonary disease	Yes	3 (20)	5 (4)	8 (6)	0.04*
	No	12 (80)	117 (96)	129 (94)	
CLD	Yes	3 (20)	3 (3)	6 (4)	0.01*
	No	12 (80)	119 (97)	131 (96)	
IHD	Yes	2 (13)	5 (4)	7 (5)	0.1
	No	13 (87)	117 (96)	130 (95)	
Heart failure	Yes	0 (0)	3 (3)	3 (2)	0.7
	No	15 (100)	119 (97)	134 (98)	
Renal failure	Yes	1 (7)	3 (3)	4 (3)	0.3
	No	14 (93)	119 (97)	133 (97)	

Data are presented as number and percent; n (%). Presented percent is column percent.

Table 3. Clinical presentation.

Variables		Group 1 N = 15	Group 2 N = 122	Total N = 137	*p* value
Constitutional manifestations					
Fever	Yes	10 (67)	92 (75)	102 (75)	0.3
	No	5 (33)	30 (25)	35 (25)	
Fatigue	Yes	10 (67)	97 (80)	107 (78)	0.2
	No	5 (33)	25 (20)	30 (20)	
Headache	Yes	5 (33)	58 (47)	63 (46)	0.2
	No	10 (67)	64 (53)	74 (54)	
Bone aches	Yes	8 (53)	75 (62)	83 (61)	0.3
	No	5 (47)	47 (38)	54 (39)	
Respiratory manifestations					
Cough	Yes	10 (67)	77 (63)	87 (64)	0.5
	No	5 (33)	45 (37)	50 (36)	
Dyspnea	Yes	4 (27)	23 (19)	27 (20)	0.3
	No	11 (73)	99 (81)	110 (80)	
Chest tightness	Yes	6 (40)	28 (23)	34 (25)	0.1
	No	9 (60)	94 (77)	103 (75)	
Chest pain	Yes	1 (7)	7 (6)	8 (6)	0.6
	No	14 (93)	115 (94)	129 (94)	
GIT manifestations					
Nausea	Yes	9 (60)	53 (43)	52 (45)	0.1
	No	6 (40)	69 (57)	75 (55)	
Vomiting	Yes	2 (13)	19 (16)	21 (15)	0.5
	No	13 (87)	113 (85)	116 (85)	
Diarrhea	Yes	3 (20)	42 (35)	45 (33)	0.2
	No	12 (80)	80 (65)	95 (92)	
Abdominal pain	Yes	4 (27)	41 (34)	45 (33)	0.4
	No	11 (73)	80 (66)	91 (69)	

Others					
Anosmia	Yes	4 (27)	65 (53)	69 (50)	0.04*
	No	11 (73)	57 (47)	68 (50)	
Loss of taste	Yes	3 (20)	58 (47)	61 (44)	0.03*
	No	12 (80)	64 (53)	76 (55)	
Insomnia	Yes	4 (27)	23 (19)	27 (20)	0.3
	No	11 (73)	99 (81)	110 (80)	

Data are presented as number and percent; n (%). Presented percent is column percent.

Table 4. Laboratory and imaging features.

Variables	Group 1 N = 15	Group 2 N = 122	Total N = 137	*p* value
Hb	11.7±2.4	12.7±1.4	12.6±1.5	0.1
WBC($\times 10^9$)	5.93±2.36	6.09±1.60	6.07±1.69	0.8
Platelets	199±74	241±62	236±65	0.05
Neutrophils	68±9	65±8	66±8	0.3
Lymphocytes	21±11	29±9	28±10	**0.04***
N/L ratio	1.40±0.50	1.73±0.44	1.70±0.46	**0.02***
T-bilirubin	1.41±0.64	1.15±0.10	1.19±0.25	0.1
D-bilirubin	1.00±0.45	0.81±0.12	0.83±0.20	0.1
ALT	36±17	32±14	33±15	0.5
AST	49±29	33±16	35±18	0.05
Albumin	3.8±0.56	4.2±0.22	4.1±0.30	**0.03***
PT	14.2±1.5	13.4±0.7	13.5±0.9	0.07
INR	1.15±0.15	1.08±0.08	1.09±0.09	0.1
Creatnine	1.44±1.66	0.96±1.2	1.02±1.9	0.3
Urea	46±55	26±37	29±40	0.2
CRP	69±52	36±35	40±39	**0.03***
ESR	47±28	28±18	30±20	**0.03***
LDH	412±144	307±100	321±112	**0.02***
Ferritin	455±713	217±152	243±280	0.2
D. Dimer	0.54±0.42	0.28±0.38	0.31±0.39	**0.03***
CT score	11.9±4	7.0±3.6	7.5±3.9	**<0.001***

Data are presented as mean±SD. N/L ratio: neutrophils/lymphocytes ration. T-bilirubin: total bilirubin, D-bilirubin: direct bilirubin. ALT: alanine aminotransferase, AST:aspartate aminotransferase, PT: prothrombin time, INR: International Normalized Ratio, CRP: C reactive protein, LDH: lactate dehydrogenase, CT score: Computed tobography score.

Table 5. Treatment regimen.

Variables	Group 1 N = 15	Group 2 N = 122	Total N = 137	*p* value
Antibiotics				
Alone	4 (27)	78 (64)	82 (60)	0.007*
Combined	11 (73)	44 (36)	55 (40)	
Corticosteroids				
Yes	6 (40)	62 (51)	68 (49)	0.3
No	9 (60)	60 (49)	69 (51)	

Data are presented as number and percent; n (%). Presented percent is column percent.

Table 6. Multivariate logistic regression for determinants of deterioration.

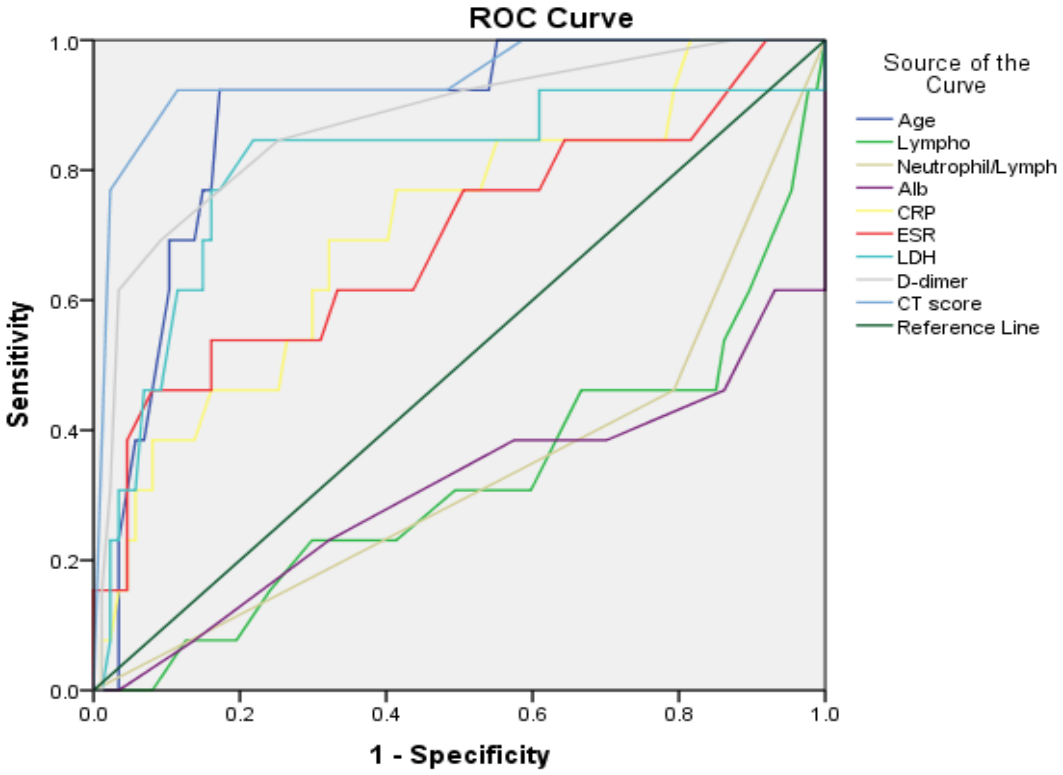
Variables	OR	CI	*p* value
Age	1.05	0.97-1.12	0.2
Smoking	2.9	0.88-9.66	0.07
Anosmia	0.5	0.12-2.1	0.3
Loss of taste	0.4	0.08-1.2	0.2
DM	4.0	1.09-14.97	**0.03**
HTN	2.0	0.5-7.8	0.3
Chronic pulmonary disease	1.8	0.28-11.5	0.5
CLD	7.6	1.21-47.7	**0.03**
Lymphocytes	0.9	0.83-1.11	0.6
N/L ratio	0.7	0.03-14.6	0.8
Albumin	0.004	0.004-0.50	**0.01**
CRP	1.01	0.98-1.03	0.3
ESR	1.02	0.97-1.08	0.3
LDH	1.009	1.00-1.01	**0.03**
D. Dimer	0.57	0.09-3.33	0.5
CT score	1.45	1.11-1.90	**0.006**

Table 7: Accuracy of different predictors of deterioration

Variables	Cutoff value	Sensitivity	Specificity
Age	51	92	83
CRP	56	69	68
ESR	28	61	67
LDH	353	84	79
D. Dimer	0.35	84	75
CT score	12.5	92	89

Highly inaccurate predictors (lymphocytes, Neutrophil/Lymph ratio, Albumin) were excluded.

Figure 1. ROC curve for all quantitative determinants of deterioration.



Discussion

In this case control study, we aimed at investigating the predictors of severity and deterioration of mild cases with COVID. Despite the presence of many associated sociodemographic, laboratory and radiological features, deterioration was determined based upon few of them. In our study, we found that DM, CLD, and CT score were significant predictors of deterioration.

Sociodemographic characteristics of patients were of remarkably different between cases and controls. We found that age, marital status, and smoking status were significantly different between the patients who deteriorated and those who did not. Previous studies agreed upon using advanced age as a predictor for deterioration as old age is associated with many comorbidities including chronic illnesses [8-11].

Similarly, smoking was found to be associated with deterioration. This is well established as smoking is linked to many chronic conditions such as diabetes, hypertension, cardiovascular and respiratory diseases. Those conditions in turn worsen the prognosis of COVID-19 [12]. Many studies supported this opinion as the mortality rate was higher among smokers than non-smokers [13-15].

Among the studied risk factors, we noticed that DM, hypertension, chronic pulmonary disease and CLD were more prevalent among deteriorated patients with a significant difference between those who had deteriorated and those who did not. There are many factors that link these chronic illnesses and deterioration of patients with COVID-19. For example, presence of DM essentially creates a state of immunocompromisation.

In addition to the increased expression of angiotensin-converting enzyme 2 (ACE2), the entry receptor of SARS-CoV-2, that is associated with exacerbated inflammatory reaction due to endothelial cell activation, insulin resistance and disruption of the alveolar-capillary barrier [16]. This is evident by previous studies where need for ICU admission and mechanical ventilation were higher among diabetic patients; OR 5.47 [17]. Moreover, uncontrolled diabetes was associated with poor outcome [18].

Many studies agreed with us that hypertension is one of the predictors of deterioration; OR = 2.72 [19]. Hypertension disrupts

the vasculature, and it predisposes to critical illness in infections such as COVID [12]. Presence of pulmonary diseases predisposes to more severe condition in patients with COVID due to impaired ventilator function and poor pulmonary reserve [16]. This came in agreement with **Ciceri et al.** where COPD was linked to higher mortality rate [10]. Furthermore, **cheng et al.** proved that presence of chronic pulmonary disease was associated with poor prognosis [20]. **Gao et al.** agreed with us that CLD is one of the predictors of deterioration. This is attributed to low immunity; thus patients with liver disease are at higher risk of infection with COVID and subsequent deterioration [16].

Concerning the clinical picture of participants, we noticed that anosmia and loss of taste were the only two symptoms that were more prevalent among patients who did not deteriorate; however they were insignificant indicator of outcome. This is in line with Foster et al who found that smell loss is a positive prognostic factor [21]. Similarly, **Porta-Etessam et al.** reached the same conclusion as they found that olfactory and gustatory dysfunctions were characteristic of mild cases of COVID [22].

The use of laboratory data is no longer used for diagnosis only, but also for risk stratification. We found that deterioration was significantly associated with low lymphocytic count, N/L ratio and serum levels of albumin, in addition to higher common inflammatory markers. This agrees with previous reports where low level of lymphocytic count, N/L ratio, and albumin [19], higher levels of IL-6, ferritin, and CRP were associated with severe cases [23-25]. These findings would be useful for identification of patients who might benefit from immunotherapies [26]. In contrast to many studies, there was no difference between cases and control regarding leukocytic count, neither serum ferritin. This is might be attributed to early presentation when infection had not been yet invaded [20].

Concerning radiological role in prediction of deterioration, it was noticed that the higher the CT score, the higher the risk of deterioration. This is similar to findings by Gallo Marin et al, where they found that increased CT score was higher among severe cases. Aside from its diagnostic value, CT is helpful in detection of findings associated with poor prognosis, such as pulmonary fibrosis which is linked to prolonged hospitalization and ICU admission [27].

Regarding the role of some medications in disease progression, we found that corticosteroids use did not correlate to deterioration, but antibiotics did, which were used more frequent with deteriorated cases. It has been long debated on the effectiveness of corticosteroids use in COVID. On the one hand, many studies augmented their use in critical cases claiming better outcome [28-30], while, on the other hand, others proved negative or nil outcome [31,32]. Unlike the subjects in our study, those studies were conducted in cases with severe illness, which justifies the difference in results.

It is well established that antibiotics do not affect COVID, but the bacterial co-infection if found. What still under investigation is the cost of using antibiotics on the long term. It is evident that overuse of antibiotics could lead to antimicrobial-resistance. Furthermore, administration of high-dose antibiotics facilitates co-infections with drug-resistant bacteria [33].

It is depicted that "10 million people could die from an antibiotic-resistant bacterial infection in the year of 2050" [34]. Inevitably, broad-spectrum antibiotics weaken the immunity, and inhibit the immune system's capability to produce antibodies [35]. Thus, it is confusing whether frequent antibiotic use caused impaired immunity, and introduction of more aggressive strains so deterioration happened or it is more frequent with deterioration because of the primarily poor health condition. To the best of our knowledge, scarce resources investigated the role of antibiotics in prediction of the course of the disease. According to a review and meta analysis by Langford et al, only five studies reported that antibiotic use was more frequently with critically-ill cases [36].

Based on logistic regression analysis, our study showed that two chronic illnesses (DM and CL), two laboratory parameters (albumin and LDH) and radiological findings (CT score) can be useful predictors of deterioration of patients with COVID. This is similar to previous studies**; Shang et al., Gao et al.** and **Zheng et al.** where they found that chronic illnesses such as hypertension and diabetes were significant predictors of deterioration [4,12,16]. Interestingly, CLD is not a commonly studied risk factor despite its importance. Basically, COVID-19 infection causes impairment of liver function; thus, patients with CLD at higher risk of deterioration than healthy ones. Our laboratory deductions came in line with most of previous

studies as LDH is an already recognized one of the laboratory markers of severity of COVID-19. However, we highlighted the role of albumin decrease in prediction of severity of cases, while only few studies investigated its predictive role in COVID-19 [19,20]. Only few studies considered overall CT score as a predictor, instead the majority of them assessed the predictability of specific findings such as consolidation on CT chest. Tabata et al reported that CT findings are paramount in scenarios of negative PCR test with highly suspected cases [37]. Therefore, early detection of these findings would prevents late diagnosis and hence deterioration [38].

Conclusions

To sum up, medical history of patients, their laboratory and radiological data are of paramount role in diagnosis and early detection of severity, but more specifically chronic illnesses (such as DM and CLD), and CT score are good predictors of deterioration.

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Contributions

All authors have made substantial to all of the following: (1) the conception and design of the study , acquisition of data , analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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