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Research Article
The Correlation of Serum Periostin Level with Disease Severity in Patients with Covid -19

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is an emerging zoonotic disease caused by the new respiratory virus SARS-CoV2. It has a tropism in the lung tissues where excess target receptors exist. Periostin plays a role in subepithelial fibrosis associated with bronchial asthma. Since the Coronavirus's target is the human respiratory system, Periostin has been recently described as a valuable new biomarker in the diagnosis and evaluation of disease in patients with COVID-19 lung involvement.
Objectives: To assess the level of Periostin in the serum of COVID-19 patients and to correlate its role in disease severity and prognosis.
Subjects and Methods: Periostin serum levels were measured for 63 patients attending three main COVID-19 Control Centers in Baghdad, compared to 25 healthy subjects, using an enzyme-linked immunosorbent assay (ELISA) from January 2021 to April 2022.
Results: Serum levels of Periostin among studied groups with (mild - moderate, severe - critical, post-COVID, and controls) were (17.3, 664, 597, and 48) ng/dl respectively. The serum concentration of Periostin was highly significant in (severe- critical and post-COVID) than in other groups.
Conclusions: The elevated level of serum Periostin in COVID-19 patients correlated with disease severity and post-COVID lung complications. The high Periostin level is consistent with high inflammatory markers, which might be used as an indicator of COVID-19 severity and predict a bad prognosis.

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS CoV-2) is one of the shocking medical challenges that has already had enormous economic and communal impacts (1-3). Infection with SARS-Cov-2 is not limited to the respiratory system but may activate a massive immune reaction, ending in multiple organ failure and death (4). Compared to other coronaviruses, especially SARS and MERS-related diseases, the lethal ability of SARS-CoV-2 is lesser, but it has easier transmission than other respiratory viruses, making COVID-19 more concerning (5,6). Severe and seriously ill patients develop an acute systemic inflammatory state termed cytokine release syndrome (CRS), characterized by rapid and prolonged systemic elevation of more than twenty inflammatory cytokines and chemokines (7). Periostin has been linked with many respiratory disorders. It has been recently shown to be an indication of disease progression in idiopathic pulmonary fibrosis (8). It is one of the non-structural extra-cellular matrix proteins (9) that interacts with other proteins to facilitate tissue re-modeling, and they combine many growth factors and cytokines to modulate their activities (10). The interaction between Periostin and several molecules participated in signal cascades to modify the expression of genes, such as those that encode collagens and chemokines (11). POSTN Expression, the gene that codes the human Periostin, can be stimulated by the cytokines transforming growth

factor beta (TGFβ), interleukin-4, and interleukin -13 (12, 13). This study aimed to assess the level of Periostin in the serum of COVID-19 patients and to correlate its role in disease severity and prognosis.

Subjects and Methods

A case-control study was conducted in COVID-19 Control Centers, including (Dar Al-Salam Hospital, Dar-Alshifaa Hospital, and Al-Imamian Al-Kadhimain Teaching Hospital) in Baghdad, Iraq. The study extended from January 2021 to April 2022. Eighty-eight participants enrolled in this study; their ages ranged from 43 to 71. Sixty-three were COVID-19 cases confirmed by RT-PCR positive for SARS-CoV-2 and clinically evaluated by respiratory specialist. They grouped into three subgroups according to the severity of symptoms, oxygen saturation (Spo2), and C-T scan for lung involvement: mild to moderate COVID-19 subgroup that includes patients who had mild symptoms and those who showed oxygen saturations above 95%, respiratory rate of less than 22 /minute with 0-25% lung infiltrates on C-T scan, while the severe to critical subgroup those admitted to the COVID-19 centers for treatment because of severe shortness of breath with respiratory rate of more than 30/minute, oxygen saturations below 93% with more than 50% lung infiltrates on C-T scan and those with end-organ failure and requiring intensive care unit admission, most of the latter group had comorbid hypertension and diabetes but not with vascular or kidney diseases, or with any autoimmune or asthma. The post-COVID subgroup who presented with severe dyspnea and marked C-T scan lung changes after six months of confirmed COVID-19 are not smokers and have no previous history of respiratory diseases (such as asthma or chronic obstructive pulmonary disease). Compared to 25 persons whose healthy control age and sex-matched, they were non-smokers and did not have any history of allergic rhinitis, asthma, or any autoimmune diseases. Ethical approval for the study was obtained the ethical committee in the Department of Microbiology and from the Council of College of Medicine, University of Baghdad. The agreement of health authorities in the included centers was also obtained. All patients received a written and verbal information sheet explaining the aim of the study. Each individual participating in the study was assigned written consent.

From each individual, 5ml of blood was drawn via venipuncture under a strict aseptic technique; the blood was drawn into a gel tube and maintained at room temperature for 2 hours, and centrifugation of samples was made for 15 minutes at 1000xg. The serum was pipetted in Eppendorf tubes and stored at -20°C until used. The quantitative sandwich enzyme immunoassay technique was employed as directed by the manufacturer.

For statistical analysis, the results were organized into tables and figures after being calculated using Microsoft Excel sheet 2016 and loaded into SPSS -version 26 statistical program. Median with interquartile range (IQR) using (the Mann-Whitney U test) to compare two non-normally distributed data and (the Kruskal-Wallis HI) test to compare more than two abnormally scattered data. Periostin variables are tested by receiver operating characteristic (ROC) curves to determine sensitivity and specificity performance characteristics. A statistically significant difference was defined as a two-tailed test. A P value less than 0.05 was considered statistically significant.

Results

The COVID-19 patients' group was divided according to disease severity into three subgroups: mild to moderate, which comprised 18 patients (20%); critical to severe, which comprised 40 (46%) of cases; and post-COVID-19, which comprised only 5 cases (6%).

Data in table 1 show that the Inter quartile medians of periostin serum levels among subjects' groups (mild- moderate, severe- critical, post COVID-19, and control groups) were (17.3, 664, 597, 48) ng/ml, respectively. The mean concentration of serum periostin in the first group (mild-moderate) was 31.50 ng/ml, whereas in the second group (severe-critical) was 66.63 ng/ml. In the post-COVID-19 group, the mean serum level of periostin was 57.80 ng/ml, compared to 15.80 ng/ml of the control group.

Pairwise comparisons were clearly demonstrated, as the mean concentration of periostin in the severe to critical group was significantly higher than that of the mild to moderate group (p-value=0.001), with the post-COVID-19 group, the p-value was equal to 0.01 compared to mild-moderate group, and that of control group p-value was equal to 0.001 in comparison with mild-moderate group.

Table 1: Differences between mean of periostin serum level according to studied groups

Study Groups	serum periostin (ng/ml)								
	*IQR Medians	Mean ±SD	P-value	**Pairwise comparison between subgroups					
				1-2	1-3	1-4	2-3	2-4	3-4
Mild-moderate	17.3	31.50± 19.23	0.001	0.001	0.011	0.001	0.049	0.401	0.008
Severe-critical	664	66.63± 57.09							
Post COVID	597	57.80± 51.13							
Control	48	15.80± 3.99							

*IQR:interquartile

**(1=mild-moderate, 2=Severe to critical, 3=Post COVID, 4= Control).

Clinical sensitivity of periostin level by (ROC) curves to identify patients with COVID-19: Roc curve analysis shows that at a periostin cutoff point of 112ng/ml, one can diagnose COVID-19 cases with sensitivity equal to 95% and specificity of 87.5%. (Total area under the curve was 0.961, standard error was equal to 0.020, and p-value=0.001). Figure-1
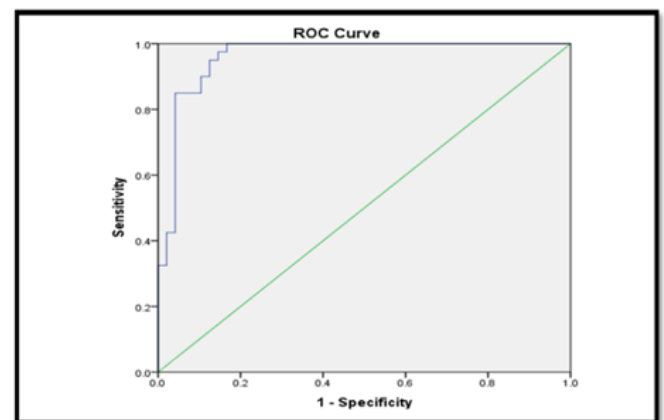

Figure 1: ROC curve analysis of serum periostin cut off value

Table 2 demonstrates serum periostin level in association with sex and age of including subjects. No statistically significance differences were noticed between sex, age with level of serum periostin with p value for both (0.095,0.91) respectively

Table 2: Differences between Periostin serum levels according to age and sex among study groups

Variables		No.	*IQR median (ng/ml)	P- value **NS
Sex	Male	52	170	0.095
	Female	36	647	
Age groups/yrs	≤40	10	657	0.091
	41-60	37	594	
	>60	41	142	

*IQR:interquartile; **NS=non statistical significance

Correlation between Periostin and measured variables:

In Table 3, a significant positive correlation was noticed between; D. dimer, S. ferritin, S. LDH, CRP, WBC count with serum periostin concentrations. P value< 0.05 in all variables and the correlation coefficient (r) of them were (0.609, 0.556, 0.556, 0.307, 0.265) respectively. Significant negative correlation was noticed between lymphocyte count and serum level of periostin and the P value=0.001 with correlation coefficient of (-0.610).

Table 3: Correlations between serum periostin levels and measured variables.

Variables *Normal value	Serum Periostin Levels		
	Correlation Coefficients	P -value	Statistical significant
D.Dimer	R	0.609	NS
* 0-0.5 ug/ml	p-value	0.000	S
Serum. Ferritin	R	0.556	NS
* 11-363 ng\ml	p-value	0.000	S
Serum LDH	R	0.556	NS
*135-225U\L	p-value	0.000	S
CRP	R	0.307	NS
* 0-10mg\m	p-value	-0.014	S
Lymphocyte count	R	-0.610	S
1-4.8*1000/ul	p-value	0.001	S

CRP=C-Reactive Protein, LDH= Lactate Dehydrogenase, r=correlation coefficient, NS=non-significant, S=significant

Periostin serum levels and the degree of Lung involvement:

According to CT scan findings of lung involvement with COVID-19, scoring system (14) was applied accordingly. As demonstrated in (table 4). The Lung involvement scores were classified into; Score-0: no score-1: 1-5% score- 2: 6-25%, score-3: 26-49%, score- 4: 50-74%, and score-5: >75%. In this study, the mean concentration of periostin in score 5 was significantly higher than that found in score 0, 1, 2, 3

and 4. Also the mean concentration of periostin in score 4 was statistically significantly higher than that found in score 0 and 1.

Table 4: Differences between Periostin serum levels according to Lung involvement in patients' groups

Lung involvement score	serum periostin (ng/ml)			
	No.	*IQR Median	Mean ±SD	P-Value
0	4	16	4.25±3.12	0.001
1	4	15.5	6.25±5.62	
2	5	2	10.0±8.23	
3	5	8	15.80±13.73	
4	22	109	29.64±26.94	
5	23	150	51.87±30.33	

*IQR: interquartile

Discussion

The Coronavirus Disease 2019 (COVID-19) pandemic is a hastily emerging disease that continues to pressure healthcare institutions worldwide. A sophisticated investigation identifies many patient factors, including demographic, clinical, immunological, hematological, biochemical, and radiological results; these findings may be valuable for physicians in predicting the severity of COVID-19 and mortality (15). The quick and persistent systemic rise of many serum inflammatory cytokines and chemokines, a syndrome termed cytokine storm, has been developed in many cases with severely ill COVID-19 patients (7). Injuries to lung epithelia are a usual phenomenon in most respiratory illnesses, including infections, causing secretion, among others, of periostin, which is implicated afterward in the re-modeling of airways and other characteristics in the pathophysiology of the respiratory tract (10).

This study revealed high levels of serum periostin level in severe and critical COVID-19 cases with a concentration of 664 ng/ml. Those with mild to moderate severity with 17.3 ng/ml were compared to a control group with a 48 ng/ml concentration. This difference was statistically significant. So, the periostin level can be used to predict disease severity, as in (16), who suggests using periostin as a new biomarker for detecting COVID-19 infection severity. Regarding post-COVID-19 patients included in this study, five patients complained of respiratory distress 4 to 8 weeks after COVID-19 infection. The serum concentration of periostin in those patients was high, with a registered concentration of 597ng/ml in comparison to mild-moderate and control groups, but it was lower than those with severe and critical cases; these differences in results between post-COVID-19 and currently infected groups are attributed to the immunomodulation and intense stress. It has been clearly found that many cytokines, such as IL-4. IL-13 and TGF-ß are released from inflammatory cells during COVID-19, and they activate and regulate the production of periostin from the epithelial cells of respiratory airways in patients with COVID-19 (16).

Furthermore, the POSTN gene is fully expressed and up-regulated in bronchial epithelium under the effect of the released cytokines. therefore: serum periostin might be of prognostic value for an increased threat of disease exacerbations and gradual decline in lung function, and it has been estimated to identify patients with an increased therapeutic advantage with anti-IL13 (such as lebrikizumab.

tralokinumab) and anti-Ige (omalizumab) treatment (17). Notably, in the current study, the level of periostin was increased significantly with increasing concentrations of other inflammatory markers such as (D-dimer. ferritin. L.DH, and CRP) indicating that the high serum periostin concentration was consistent with other factors determining the onset of severe symptoms. The opposite correlation was clearly observed between periostin level, inflammatory markers, and disease severity with lymphocyte count (as most of the infected patients had lymphopenia or lymphocytopenia). Although the number of T-lymphocytes could be initially increased at the onset of COVID-19, patients are prone to have lymphopenia, a status of an abnormally low lymphocyte count that usually correlates with clinical deterioration among COVID-19-infected patients. Moreover, it has been confirmed that those who died from COVID-19 had significantly lower lymphocyte counts than survivors (18).

In the present study, higher concentrations of periostin serum level were recorded in the ages of less than 40 years compared to other age groups, similar data were reported by (19). That might be attributed to the higher turnover rate and some heterogeneity of skeletal modeling and maturity at an early age, but these differences in our study are not significant, with a P value of 0.091. Moreover, the mean concentration of periostin level was 49.96 ng/ml in females compared to males, with a mean concentration of 40.72 ng/ml, as agreed with the previous study (20).

A recent study reviewed the challenges associated with post-COVID sequelae, highlighting many risk factors induced by pulmonary fibrosis, including advanced age, female patients, chronic diseases, and duration of mechanical ventilation. The study suggested the use of pathological biomarkers for the diagnosis besides clinic-radiological examinations, indicating the use of anti-fibrotic agents for respiratory distress patients that might avert fibroproliferative course (21).

This study focused on the association between serum level of periostin and lung injury due to COVID-19, as this infection tends to possess the ability to cause subsequent lung fibrosis, according to lung involvement score evaluated by CT scan. Serum periostin levels in patients with scores 4 and 5 were higher than 0, 1, 2, and 3 scores, and this supports an aforementioned result concerning the relation of higher concentration of periostin with bad disease prognosis. Periostin was strongly expressed in lung parenchyma due to interstitial pneumonia and idiopathic pulmonary fibrosis; therefore, periostin was considered as a potential biomarker to distinguish interstitial pneumonia from lung fibrosis (22). In support of the present findings, a previous study concluded that periostin played an important role in fibrogenesis, suggesting that it was a significant predictor of disease severity and lung fibrosis and can be applied as a routine biomarker and may, therefore, present a potential goal to prevent disease progression and fibrotic process (22).

As a limitation of this study, difficulties were raised during sample collection and patient follow-up, especially for severe and critical patients and those with post-covid lung fibrosis. Collecting saliva or sputum from studied subjects would be more useful for a clearer explanation.

Conclusion

Measuring the Periostin level in COVID-19 patients can identify high-risk cases with a severe and critical course of the disease and can guide healthcare providers in treatment and medical attention. Additional studies are necessary to explore the vital role of periostin, its clinical usefulness as a biomarker in COVID-19, and even its prospective application as a therapeutic goal in the disease.

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