International Journal of Biomedicine 13(4) (2023) 286-295
http://dx.doi.org/10.21103/Article13(4)_OA9

ORIGINAL ARTICLE

COVID-19

INTERNATIONAL JOURNAL OF BIOMEDICINE

The Association of Prolactin and CRP Biomarkers with the Severity of COVID-19 in Thumbay Hospital, Ajman, UAE

Aisha Abdulkrim Nur, Ahmed L. Osman, Praveen Kumar Kandakurti, Ayman H. Alfeel, Marwan Ismail, Asaad Ma. Babker, Abdelgdair A. Altoum*

College of Health Sciences, Gulf Medical University, Ajman, UAE

Abstract

Background: This study aimed to estimate the levels of C-reactive protein (CRP) and prolactin (PRL) in SARS-CoV2 infection and their association with the severity of COVID-19 among patients in Ajman, UAE.

Methods and Results: This cross-sectional study was conducted in Thumbay Hospital from 2020 to 2021. The study included 71 patients (55 males and 16 females) with positive SARS-CoV-2 test results. Nasal swab specimens were collected for the COVID-19 test on the day of admission or after one day of admission. COVID-19 diagnoses and severity levels were determined according to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission of China (2020).

Serum samples were collected from the patients upon admission. The PRL level was determined using the immune chemiluminescent method by the DXI 800 Beckman Coulter analyzer. The CRP level was determined using the immunoturbidimetric method by the DXC 700 AU chemistry analyzer.

Among 71 COVID-19 patients, the great majority were men 55(77.5%), 38(53.5%) being of Indian nationality. In this study, most participants (50.7%) had no history of chronic illnesses. In terms of COVID-19 severity, 24(33.8%) of patients had mild cases, 27(38.0%) had moderate cases, and 20(28.2%) had severe cases. Twenty (28.2%) patients were transferred to the ICU, and 19(26.8%) were intubated. The patients' average age was 47.58±13.63, CRP level - 74.30±71.46 mg/L, and PRL level - 205.1946±168.52 ng/mL. The mean CRP level was highest in severe cases, compared to mild and moderate cases, with a statistically significant difference between mild and severe groups (P=0.000) and mild and moderate groups (P=0.004). The mean PRL level was highest in severe cases compared to mild and moderate cases; however, the differences between the groups were not significant. CRP and PRL levels were greater in the ICU patients than non-ICU patients, with statistically significant differences only for CRP. We found a moderate positive correlation between CRP level and age (r=0.458, P=0.000); a weak positive correlation between PRL level and age was not statistically significant (r=0.201, P=0.093). A moderate positive correlation between CRP level and PRL level (r=0.461, P=0.03) was statistically significant.

Conclusion: The current study implies that serum CRP levels might be an important indication of COVID-19 development and severity. A more extensive study with a larger sample size is needed to validate the significance of PRL in disease severity. **(International Journal of Biomedicine. 2023;13(4):286-295.)**

Keywords: COVID-19 • prolactin • C-reactive protein

For citation: Nur AA, Osman AL, Kandakurti PK, Alfeel AA, Ismail M, Babker AMa, Altoum AA. The Association of Prolactin and CRP Biomarkers with the Severity of COVID-19 in Thumbay Hospital, Ajman, UAE. International Journal of Biomedicine. 2023;13(4):286-295. doi:10.21103/Article13(4)_OA9

Abbreviations

BP, blood pressure; **BMI**, body mass index; **CRP**, C-reactive protein; **COVID-19**, coronavirus disease 2019; **DM**, diabetes mellitus; **GH**, growth hormone; **hs-CRP**, high-sensitivity CRP; **HPT**, Hypertension; **ICU**, intensive care unit; **LH**, luteinizing hormone; **PRL**, prolactin; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus-2.

Introduction

Coronaviruses (CoVs), enveloped positive-strand RNA viruses from the *Coronaviridae* family, are associated with upper respiratory tract infections that occasionally spread to the lungs and other organs. As well as the common cold, CoVs can cause more severe diseases, including SARS-CoV disease, MERS-CoV, and COVID-19, which was caused by SARS-CoV-2. As of 20 August 2023, over 769 million confirmed cases of COVID-19 and over 6.9 million deaths have been reported globally[1] Typical manifestations include flu-like symptoms such as fever, cough, fatigue, and shortness of breath. However, in approximately 20% of patients, the infection progresses to severe interstitial pneumonia and can cause an uncontrolled host immune response, leading to a life-threatening condition called cytokine storm;[2] it is critical to identify early and treat this subgroup of patients. The degree of severity and mortality of patients with COVID-19 may be associated with altered levels of some blood markers.

One such marker is C-reactive protein (CRP). It is one of the clinical parameters that indicates more severe infection and has been used as an indicator of COVID-19 disease severity.[3] CRP is a plasma protein produced by the liver and induced by various inflammatory mediators, such as IL-6. Clinically, CRP is used as a biomarker for various inflammatory conditions, so any rise in its level indicates an increased disease severity but not specific to a particular disease.[4] CRP has been recognized as one of the most, if not the most, sensitive acute phase reactants. CRP levels in plasma can rise dramatically after myocardial infarction, stress, trauma, infection, or neoplastic proliferation. The CRP marker was found to be significantly increased in the initial phases of the infection for severe COVID-19 patients. Importantly, CRP has been associated with disease development and is an early predictor for severe COVID-19.[5] There are two tests that measure CRP, and each test measures a different range of CRP levels in the blood for different purposes: The standard CRP test measures markedly high protein levels to detect diseases that cause significant inflammation. It measures CRP in the range from 10 to 1000 mg/L. This test may be used to detect inflammation. However, hs-CRP test is more sensitive than a standard CRP test. The hs-CRP test accurately detects lower protein levels than the standard CRP test. It measures CRP in the range from 0.5 to 10mg/L. This test is used to evaluate individuals for the risk of cardiovascular disease. Many studies have indicated that CRP levels can help predict the severity and presence of COVID-19 infections.[6]

Hormonal homeostasis has a major impact on achieving competent and healthy immune system function. Prolactin (PRL) has a bioactive function, acting as a hormone and cytokine.[7] Hyperprolactinemia has been detected in many patients with different autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, multiple sclerosis, autoimmune thyroid disease, systemic sclerosis, and others. High PRL levels have been shown in patients with severe sepsis and infants with severe respiratory infections. At the same time, long-term hypoprolactinemia can cause death from opportunistic infections in patients with HIV infection.[8] PRL has both pro-inflammatory and anti-inflammatory roles, depending on certain conditions.[9-12]

High blood PRL level is known to provide an immunological advantage in many pathological conditions (with some exceptions like autoimmune diseases), and women, because of their higher blood PRL level, get an advantage in this regard. It has been reported that enhancement of PRL serum level toward the physiological values by dopamine antagonists may improve the immunological profile and survival in various critical statuses.[13,14] PRL acts through specific PRL receptors (PRLRs) belonging to the class I cytokine receptor family, which includes more than 30 receptors, such as the PRLR, GH receptor, thrombopoietin receptor, IL-6 receptor, and others.[15] PRLRs can also act as function receptors for GH and placental lactogen.[16] Also, PRL may serve as a cytokine-like action via the activation of cytokine receptors in the regulation of the immune system.[17]) PRL stimulates T and B cells, natural killer cells, macrophages, neutrophils, CD34+ hematopoietic cells, and antigen-presenting dendritic cells.[18] It influences the modulation of the immune system, mainly by inhibiting the negative selection of autoreactive B lymphocytes.[7]

SARS-CoV-2 infection can impair the hypothalamic–pituitary–gonadal axis and, by this mechanism, may increase the secretion of PRL from the anterior pituitary in COVID-19.[19] The underlying mechanisms of high serum PRL levels in COVID-19 are poorly understood. However, stress and immune dysregulation may be potential mechanisms, as stressful conditions in COVID-19 may trigger PRL release.[20-22] The reduction in brain dopamine levels by SARS-CoV-2 may remove the inhibitory effects on prolactinemia, leading to the hyperprolactinemia observed in patients with COVID-19. In addition, high pro-inflammatory cytokine levels, including IL-6, in COVID-19 are considered a potent stimulator of PRL from the anterior pituitary gland.[23,24] High arginine-vasopressin and angiotensin II serum levels during COVID-19 might be another mechanism for COVID-19-induced hyperprolactinemia.[25]

In general, PRL production is increased in SARS-CoV2 infection. While PRL can trigger the production of proinflammatory cytokines, it also has several anti-inflammatory effects[14] that can reduce hyperinflammation. The exact mechanism of PRL's contribution to the severity of COVID-19 is unknown.

This study aimed to estimate the levels of CRP and PRL in SARS-CoV2 infection and their association with the severity of COVID-19 among patients in Ajman, UAE.

Materials and Methods

This cross-sectional study was conducted in Thumbay Hospital from 2020 to 2021. The study included 71 patients (55 males and 16 females) with positive SARS-CoV-2 test results. The information for all patients, including demographic data, clinical characteristics, laboratory parameters, and outcomes, was collected prospectively. Nasal swab specimens were collected for the COVID-19 test on the day of admission or after one day of admission. RT-PCR assay was used as per the manufacturer's instructions.

Serum samples were collected from the patients upon admission. The PRL level was determined using the immune chemiluminescent method by the DXI 800 Beckman Coulter analyzer. Hyperprolactinemia was defined when fasting PRL serum levels were more than 25 ng/mL in females and 20 ng/mL in males.[26] The CRP level was determined using the immunoturbidimetric method by the DXC 700 AU chemistry analyzer. Normal CRP levels were defined as below 3.0 mg/L.[27]

The validation procedure was done according to CAP and CLIA for precision, accuracy, and linearity.

COVID-19 diagnoses and severity levels were determined according to the New Coronavirus Pneumonia Prevention and Control Program (7th edition) published by the National Health Commission of China.[28] Briefly, mild disease was defined as mild symptoms without radiographic features. Moderate disease was defined as fever, respiratory symptoms, and radiographic features. Severe cases met one of the following three criteria: (a) dyspnea, with a respiratory rate ≥ 30 times/min, (b) oxygen saturation ≤ 93% at rest, or (c) PaO_2/FiO_2 ≤ 300mmHg. Critical cases met one of the following three criteria: (a) respiratory failure, (b) septic shock, or (c) multiorgan failure.

In this study, we defined the moderate group as the mild and moderate cases, and we defined the severe group as the severe and critical cases. The duration of viral shedding was defined as the time from symptom onset to a SARS-CoV-2 RNA throat swab turning negative. 'Long-term positive' cases were defined as cases with a duration of viral shedding > 50 days, and the other cases were assigned to the normal-term group. Data was stored and retrieved from the laboratory information system (Thumbay Labs, Ajman, UAE).

Statistical analysis was performed using the statistical software package SPSS version 26.0 (SPSS Inc, Armonk, NY: IBM Corp). For the descriptive analysis, results are presented as mean (M) ± standard deviation (SD). The two-sample z-test and independent t-test were used to test the difference between the means of two groups, whereas a one-sample z-test was used to test the difference between a single group and the hypothesized population value. Multiple comparisons were performed with one-way ANOVA and Tukey HSD post-hoc test. Pearson's correlation coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A value of $P<0.05$ was considered significant.

Results

Among 71 COVID-19 patients, the great majority were men 55(77.5%), 38(53.5%) being of Indian nationality. In this study, most participants (50.7%) had no history of chronic illnesses. In terms of COVID-19 severity, 24(33.8%) of patients had mild cases, 27(38.0%) had moderate cases, and 20(28.2%) had severe cases. Twenty (28.2%) patients were transferred to the ICU, and 19(26.8%) were intubated.

The disease's signs and symptoms are presented in Table 1. The patients' average age was 47.58±13.63, CRP level - 74.30±71.46 mg/L, and PRL level - 205.1946±168.52 ng/mL (Table 2).

Table 1.
Baseline characteristics of the study group.

Variables	Group	Frequency	Percentage
Gender	Males	55	77.5%
	Females	16	22.5%
Nationality	Arab	17	23.9%
	Indian	38	53.5%
	Pakistani	7	9.9%
	Other	9	12.7%
Comorbidities	No Comorbidities	36	50.7%
	Diabetes	10	14.1%
	HPT	6	8.5%
	HPT & DM	11	15.5%
	Other	8	11.3%
Severity	Mild	24	33.8%
	Moderate	27	38.0%
	Severe	20	28.2%
ICU admission	Yes	20	28.2%
	No	51	71.8%
Mechanical Ventilator (Intubation)	Yes	19	26.8%
	No	52	73.2%
Patients' outcome	Alive	62	87.3%
	Dead	9	12.7%
Descriptive Statistics of Patients Symptoms			
Headache	Yes	30	42.3%
	No	41	57.7%
Fever	Yes	67	94.4%
	No	4	5.6%
Cough	Yes	66	93.0%
	No	5	7.0%
Fatigue	Yes	52	73.2%
	No	19	26.8%
Pneumonia	Yes	22	31.0%
	No	49	69.0%
Shortness of breath	Yes	40	56.3%
	No	31	43.7%

The mean CRP level was highest in severe cases (122.895±76.3050 mg/L), compared to mild (25.154±25.6865 mg/L) and moderate cases (81.993±69.1761 mg/L) (Table 3), with a statistically significant difference between mild and severe groups (P=0.000) and mild and moderate groups (P=0.004) (Table 4 and Table 5).

Table 2.

Characteristics of clinical parameters.

Parameters	N	Minimum	Maximum	Mean	SD
Age, yrs.	71	24	78	47.58	13.629
BMI, kg/m^2	71	15.70	41.02	28.0906	4.47115
Oxygen saturation, %	71	70.00	99.00	94.1972	5.05009
Respiratory rate, breaths per minute	71	18	44	24.93	5.680
Temperature, °C	71	36.5	39.0	37.794	0.6618
Diastolic BP, mmHg	71	43	100	73.87	10.105
Systolic BP, mmHg	71	80	179	120.79	15.059
CRP, mg/L	71	5.0	278.2	74.301	71.4158
White blood count, $\times10^9$/L	71	1.8	22.8	8.338	4.0439
Neutrophils, $\times10^9$/L	71	0.68	21.73	6.5023	4.14271
Lymphocytes, $\times10^9$/L	70	0.11	4.50	1.1789	0.74152
PRL, ng/mL	71	57.68	1218.45	205.1946	168.52532

Table 3.

CRP level and COVID-19 severity.

COVID-19 severity	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
Mild	24	25.154	25.6865	5.2432	14.308	36.001	5.0	84.5
Moderate	27	81.993	69.1761	13.3129	54.627	109.358	6.0	249.5
Severe	20	122.895	76.3050	17.0623	87.183	158.607	18.6	278.2
Total	71	74.301	71.4158	8.4755	57.398	91.205	5.0	278.2

Table 4.

Analysis of variance (ANOVA) of CRP level with COVID-19 severity.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	106794.742	2	53397.371	14.511	0.000
Within Groups	250220.628	68	3679.715		
Total	357015.370	70			

Table 5.

Multiple Comparisons (Post-Hoc) of CRP level with COVID-19 severity.

Dependent Variable: CRP						
(I) Severity	(J) Severity	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Mild	Moderate	-56.8384	17.0178	0.004	-98.611	-15.066
	Severe	-97.7408	18.3659	0.000	-142.823	-52.659
Moderate	Mild	56.8384	17.0178	0.004	15.066	98.611
	Severe	-40.9024	17.8961	0.076	-84.831	3.026
Severe	Mild	97.7408	18.3659	0.000	52.659	142.823
	Moderate	40.9024	17.8961	0.076	-3.026	84.831

The mean PRL level was highest in severe cases (255.975±263.56 ng/mL) compared to mild (187.990±104.361 ng/mL) and moderate cases (182.8726±115.28912 ng/mL) (Table 6). However, the differences between the groups were not significant (Table 7 and Table 8).

Table 6.

Prolactin level and COVID-19 severity.

COVID-19 severity	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
Mild	24	187.9900	104.36156	21.30272	143.9220	232.0580	71.40	527.96
Moderate	27	182.8726	115.28912	22.18740	137.2657	228.4795	57.68	553.49
Severe	20	255.9750	263.56291	58.93446	132.6238	379.3262	62.80	1218.45
Total	71	205.1946	168.52532	20.00028	165.3054	245.0839	57.68	1218.45

CRP and PRL levels were greater in the ICU patients than non-ICU patients (Table 9), with statistically significant differences only for CRP (Table 10). No statistically significant difference in PRL and CRP levels with gender was found (Tables 11 and 12).

We found a moderate positive correlation between CRP level and age (r=0.458, *P*=0.000) (Table 13, Figure 1); a weak positive correlation between PRL level and age was not statistically significant (r=0.201, *P*>0.093) (Table 14, Figure 2).

Table 7.

Analysis of variance (ANOVA) of Prolactin level with COVID-19 severity.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	72130.283	2	36065.142	1.280	0.285
Within Groups	1915924.563	68	28175.361		
Total	1988054.846	70			

Table 8.

Multiple Comparisons (Post-Hoc) of Prolactin level with COVID-19 severity.

Dependent Variable: prolactin						
(I) Severity	(J) Severity	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Mild	Moderate	5.11741	47.09039	1.000	-110.4728	120.7076
	Severe	-67.98500	50.82068	0.556	-192.7317	56.7617
Moderate	Mild	-5.11741	47.09039	1.000	-120.7076	110.4728
	Severe	-73.10241	49.52070	0.434	-194.6582	48.4533
Severe	Mild	67.98500	50.82068	0.556	-56.7617	192.7317
	Moderate	73.10241	49.52070	0.434	-48.4533	194.6582

Table 9.

Group statistics of CRP and Prolactin with ICU admission.

	ICU Admission	N	Mean	Std. Deviation	Std. Error Mean
CRP	Yes	20	123.295	71.0223	15.8811
	No	51	55.088	62.3446	8.7300
PRL	Yes	20	254.4780	263.95167	59.02139
	No	51	185.8678	109.24183	15.29692

Table 11.

Group statistics of CRP and Prolactin with gender.

	Gender	N	Mean	Std. Deviation	Std. Error Mean
CRP	Male	55	79.260	70.2936	9.4784
	Female	16	57.256	74.9177	18.7294
PRL	Male	55	194.3769	174.86898	23.57933
	Female	16	242.3806	143.34554	35.83638

Table 10.

Independent samples t-test of CRP and Prolactin with ICU admission.

		Levene's Test for equality of variances		t-test for equality of means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
CRP	Equal variances assumed	0.868	0.355	3.98	69	0.000	68.2068	17.1096	34.0741	102.3394
	Equal variances not assumed			3.76	31.1	0.001	68.2068	18.1224	31.2525	105.1610
PRL	Equal variances assumed	7.82	0.007	1.55	69	0.124	68.6101	44.0152	- 19.1979	156.4182
	Equal variances not assumed			1.12	21.6	0.273	68.6101	60.9714	- 57.9724	195.1927

Table 12.

Independent samples t-test of CRP and PRL with gender.

		Levene's Test for equality of variances		t-test for equality of means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
CRP	Equal variances assumed	0.069	. 0.794	1.08	69	0.281	22.0038	20.2594	- 18.412	62.4201
	Equal variances not assumed			1.04	23.2	0.305	22.0038	20.9912	- 21.394	65.4022
PRL	Equal variances assumed	0.002	0.961	-1.0	69	0.319	- 48.003	47.8668	- 143.49	47.4881
	Equal variances not assumed			-1.1	29.2	0.272	- 48.003	42.8979	- 135.70	39.6965

Table 13.

Pearson correlation between CRP and age.

		CRP	Age
CRP	Pearson correlation	1	0.458
	Sig. (2-tailed)		0.000
	N	71	71
Age	Pearson correlation	0.458	1
	Sig. (2-tailed)	0.000	
	N	71	71

Table 14.

Pearson correlation between PRL and age.

		Age	Prolactin
Age	Pearson correlation	1	0.201
	Sig. (2-tailed)		0.093
	N	71	71
PRL	Pearson Correlation	0.201	1
	Sig. (2-tailed)	0.093	
	N	71	71

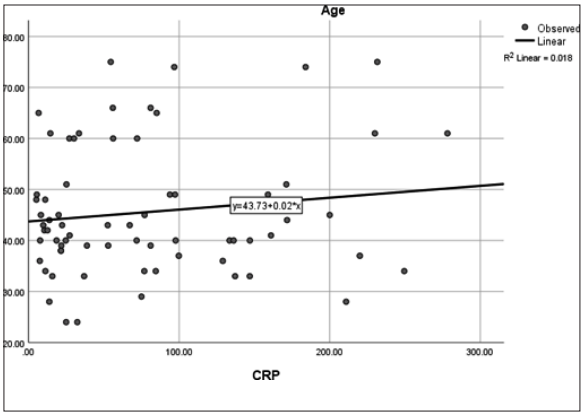

Fig. 1. *Scatterplot: Relationship between CRP and age.*

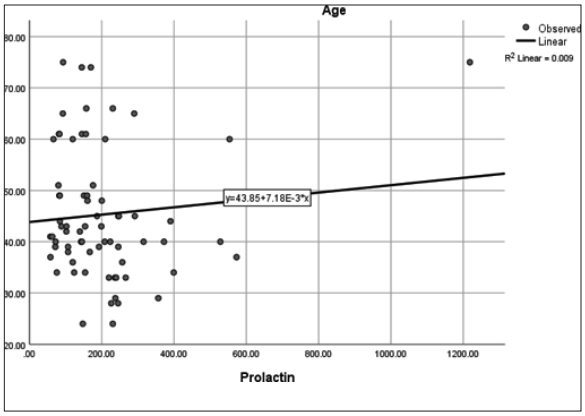

Fig. 2. *Scatterplot: Relationship between PRL and age.*

We found a moderate positive correlation between CRP level and PRL level age (r=0.461, *P*=0.03) (Table 15, Figure 3).

Table 15.

Pearson correlation between CRP and PRL.

		CRP	PRL
CRP	Pearson correlation	1	0.461
	Sig. (2-tailed)		0.03
	N	71	71
PRL	Pearson correlation	0.461	1
	Sig. (2-tailed)	0.03	
	N	71	71

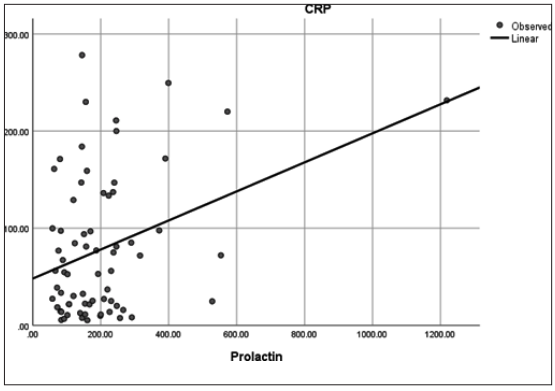

Fig. 3. *Scatterplot: Relationship between PRL and CRP.*

Discussion

The current research found that severe cases of COVID-19 had considerably higher CRP levels than mild cases, and moderate cases had considerably higher CRP levels than mild cases. However, the results revealed that the PRL level was not associated with the severity of the condition.

This study differs from other studies in the field due to the different races and nationalities. The country of the United Arab Emirates has a culture of variety. Other studies were carried out in a homogeneous nationality. The effect of PRL on COVID-19 severity has not been thoroughly researched. As indicated in the analysis performed above, the severity of COVID-19 disease was not associated with PRL levels. Similarly, another study found that infected patients with COVID-19 have similar susceptibility to infection and disease severity irrespective of their PRL levels.[29] In contrast, Zare-Zardini et al.[30] performed a study to determine the influence of PRL on COVID-19 infection susceptibility and severity. According to the study, lower blood PRL levels in patients enhance their susceptibility to and severity of COVID-19 infection. The low frequency of COVID-19 among children and women has been attributed to various molecular and physiological factors.[30,31] Although pregnant women have high PRL levels, they are more susceptible to COVID-19 than the general population.[32] Other studies reported that pregnant and non-pregnant women have similar susceptibility to COVID-19.[33] However, higher PRL levels during pregnancy may give pregnant women an advantage in fighting COVID-19. Thus, in a study by Liu et al.,[34] all cases of COVID-19 pneumonia in pregnant women were mild. While men and women have the same prevalence, men with COVID-19 are more at risk for worse outcomes and death, independent of age.[35] It is known that women have higher blood PRL levels than men, and their levels do not fall after menopause.[36] Yamaji et al.[37] demonstrated that PRL secretion is enhanced in female subjects throughout life after puberty and that aging, per se, is not associated with an alteration in the rate of secretion of this hormone in human subjects. Therefore, higher PRL levels in women may explain the gender difference in COVID-19. Early studies suggested that cigarette smokers were more resistant to coronavirus, possibly due to nicotine's ability to increase serum PRL levels.[38]

Many COVID-19 patients in this research had increased CRP levels, consistent with findings from prior investigations. Furthermore, severe cases in this research had considerably higher CRP levels than mild and moderate cases, suggesting that CRP might be a serum marker for severe COVID-19 patients. The current findings are consistent with those of Chen et al.,[39] who demonstrated that the plasma CRP level was positively correlated to the severity of COVID-19 pneumonia.

The close positive association between CRP values and the severity of tissue damage in many different pathologies, notably including COVID-19, illustrated by Smilowitz et al.[40] in the exemplary study, is equally consistent with a pathogenic role for CRP. CRP associated with tissues damaged by the virus and/or the host response locally activates complement, guaranteeing aggravation of the damage, as well as promoting systemic activation of complement. A new small molecule drug that inhibits CRP binding in vivo is currently being developed to test whether this CRP-complement mechanism contributes significantly to the severity of COVID-19.[41]

A large cohort study of 1275 COVID-19 patients showed that high CRP and D-dimer levels at admission (≥150 mg/L and ≥1000 ng/ml, respectively) and a peak D-dimer ≥6000 ng/ml during hospital stay were independent factors associated with pulmonary embolism.[42] Along with high levels of CRP, the progressive increase in leukocyte count and sustained lymphopenia and eosinopenia in severe COVID-19 patients may be associated with the progression of inflammatory status, which might progress to a fatal clinical outcome.[43,44]

Accumulating evidence has indicated that CRP is not only an excellent biomarker of inflammation but also acts as a direct participant in the SARS-CoV-2 infection.[45] Several studies have proposed CRP as a marker of cytokine

storm in COVID-19 patients.[46,47] Moreover, increased CRP levels in the blood can be detected in the earliest stages of the disease,[47-50] even before lung lesions.[46,51] Thus, CRP represents a very useful tool for identifying patients in need of immediate attention and closer clinical follow-up.[52] CRP levels are not only an early marker of disease stratification, but also a valuable tool for predicting the development of COVID-19.[46,51] Today, it is generally accepted that COVID-19 can manifest itself in different ways, from mild to critical conditions leading to death. In this context, the discovery of reliable biomarkers and therapeutic targets merits further targeted research.[52] CRP and serum ferritin levels might be considered as an essential indication of the progression and severity of COVID-19.[53]

Limitations

There are several limitations to this study. First, it is single-center retrospective research with a limited sample size, which limits the data's generalizability. Second, missing data was discovered in many cases. Third, only hospitalized patients were documented. Children and pregnant women should be included in future studies to examine their PRL levels and compare them to the general population.

Conclusion

The current study implies that serum CRP levels might be an important indication of COVID-19 development and severity. A more extensive study with a larger sample size is needed to validate the significance of PRL in disease severity.

Ethical Considerations

The study protocol was reviewed and approved by the Ethics Committee of the Gulf Medical University, Ajman, UAE**.** Written informed consent was obtained from all the participants.

Competing Interests

The authors declare that they have no competing interests.

References

1. WHO: Weekly epidemiological update on COVID-19 - 25 August 2023. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---30-august-2023
2. Picchianti Diamanti A, Rosado MM, Pioli C, Sesti G, Laganà B. Cytokine Release Syndrome in COVID-19 Patients, A New Scenario for an Old Concern: The Fragile Balance between Infections and Autoimmunity. Int J Mol Sci. 2020 May 8;21(9):3330. doi: 10.3390/ijms21093330.
3. Ali N. Elevated level of C-reactive protein may be an early marker to predict risk for severity of COVID-19. J Med Virol. 2020 Nov;92(11):2409-2411. doi: 10.1002/jmv.26097.
4. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018 Apr 13;9:754. doi: 10.3389/fimmu.2018.00754.
5. Ahnach M, Zbiri S, Nejjari S, Ousti F, Elkettani C. C-reactive protein as an early predictor of COVID-19 severity. J Med Biochem. 2020 Oct 2;39(4):500-507. doi: 10.5937/jomb0-27554.
6. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. Life Sci. 2020 Aug 1;254:117788. doi: 10.1016/j.lfs.2020.117788.
7. Borba VV, Zandman-Goddard G, Shoenfeld Y. Prolactin and autoimmunity: The hormone as an inflammatory cytokine. Best Pract Res Clin Endocrinol Metab. 2019 Dec;33(6):101324. doi: 10.1016/j.beem.2019.101324.
8. Zaid D, Greenman Y. Human Immunodeficiency Virus Infection and the Endocrine System. Endocrinol Metab (Seoul). 2019 Jun;34(2):95-105. doi: 10.3803/EnM.2019.34.2.95.
9. Williams LM, Sarma U, Willets K, Smallie T, Brennan F, Foxwell BM. Expression of constitutively active STAT3 can replicate the cytokine-suppressive activity of interleukin-10 in human primary macrophages. J Biol Chem. 2007 Mar 9;282(10):6965-75. doi: 10.1074/jbc.M609101200.
10. Tripathi A, Sodhi A. Prolactin-induced production of cytokines in macrophages in vitro involves JAK/STAT and JNK MAPK pathways. Int Immunol. 2008 Mar;20(3):327-36. doi: 10.1093/intimm/dxm145.
11. Abramicheva PA, Smirnova OV. Prolactin Receptor Isoforms as the Basis of Tissue-Specific Action of Prolactin in the Norm and Pathology. Biochemistry (Mosc). 2019 Apr;84(4):329-345. doi: 10.1134/S0006297919040011.
12. Del Vecchio Filipin M, Brazão V, Santello FH, da Costa CMB, Paula Alonso Toldo M, Rossetto de Morais F, do Prado Júnior JC. Does Prolactin treatment trigger imunoendocrine alterations during experimental T. cruzi infection? Cytokine. 2019 Sep;121:154736. doi: 10.1016/j.cyto.2019.154736.
13. Pinoli M, Marino F, Cosentino M. Dopaminergic Regulation of Innate Immunity: a Review. J Neuroimmune Pharmacol. 2017 Dec;12(4):602-623. doi: 10.1007/s11481-017-9749-2.
14. Sen A. Repurposing prolactin as a promising immunomodulator for the treatment of COVID-19: Are common Antiemetics the wonder drug to fight coronavirus? Med Hypotheses. 2020 Nov;144:110208. doi: 10.1016/j.mehy.2020.110208.
15. Gong N, Ferreira-Martins D, McCormick SD, Sheridan MA. Divergent genes encoding the putative receptors for growth hormone and prolactin in sea lamprey display distinct patterns of expression. Sci Rep. 2020 Feb 3;10(1):1674. doi: 10.1038/s41598-020-58344-5.
16. Liu Y, Jiang J, Lepik B, Zhang Y, Zinn KR, Frank SJ. Subdomain 2, Not the Transmembrane Domain, Determines the Dimerization Partner of Growth Hormone Receptor and

***Corresponding author**: Dr. Abdelgdair A. Altoum, Medical Laboratory Sciences Program, College of Health Sciences, Gulf Medical University Ajman, United Arab Emirates. E-mail: gadoora1977@live.com*

Prolactin Receptor. Endocrinology. 2017 Oct 1;158(10):3235-3248. doi: 10.1210/en.2017-00469.
17. Ihedioha O, Blanchard AA, Balhara J, Okwor I, Jia P, Uzonna J, Myal Y. The human breast cancer-associated protein, the prolactin-inducible protein (PIP), regulates intracellular signaling events and cytokine production by macrophages. Immunol Res. 2018 Apr;66(2):245-254. doi: 10.1007/s12026-018-8987-6.
18. Ochoa-Amaya JE, Malucelli BE, Cruz-Casallas PE, Nasello AG, Felicio LF, Carvalho-Freitas MI. Acute and chronic stress and the inflammatory response in hyperprolactinemic rats. Neuroimmunomodulation. 2010;17(6):386-95. doi: 10.1159/000292063.
19. Al-Kuraishy HM, Al-Gareeb AI, Butnariu M, Batiha GE. The crucial role of prolactin-lactogenic hormone in Covid-19. Mol Cell Biochem. 2022 May;477(5):1381-1392. doi: 10.1007/s11010-022-04381-9.
20. Song E, Bartley CM, Chow RD, Ngo TT, Jiang R, Zamecnik CR, et al. Divergent and self-reactive immune responses in the CNS of COVID-19 patients with neurological symptoms. Cell Rep Med. 2021 May 18;2(5):100288. doi: 10.1016/j.xcrm.2021.100288.
21. Lennartsson AK, Jonsdottir IH. Prolactin in response to acute psychosocial stress in healthy men and women. Psychoneuroendocrinology. 2011 Nov;36(10):1530-9. doi: 10.1016/j.psyneuen.2011.04.007.
22. Wang S, Zhang A, Pan Y, Liu L, Niu S, Zhang F, Liu X. Association between COVID-19 and Male Fertility: Systematic Review and Meta-Analysis of Observational Studies. World J Mens Health. 2023 Apr;41(2):311-329. doi: 10.5534/wjmh.220091.
23. Tomaszewska-Zaremba D, Haziak K, Tomczyk M, Herman AP. Inflammation and LPS-Binding Protein Enable the Stimulatory Effect of Endotoxin on Prolactin Secretion in the Ovine Anterior Pituitary: Ex Vivo Study. Mediators Inflamm. 2018 Aug 14;2018:5427089. doi: 10.1155/2018/5427089.
24. Sanli DET, Altundag A, Kandemirli SG, Yildirim D, Sanli AN, Saatci O, Kirisoglu CE, Dikensoy O, Murrja E, Yesil A, Bastan S, Karsidag T, Akinci IO, Ozkok S, Yilmaz E, Tuzuner F, Kilercik M, Ljama T. Relationship between disease severity and serum IL-6 levels in COVID-19 anosmia. Am J Otolaryngol. 2021 Jan-Feb;42(1):102796. doi: 10.1016/j.amjoto.2020.102796.
25. Al-Kuraishy HM, Al-Gareeb AI, Qusti S, Alshammari EM, Atanu FO, Batiha GE. Arginine vasopressin and pathophysiology of COVID-19: An innovative perspective. Biomed Pharmacother. 2021 Nov;143:112193. doi: 10.1016/j.biopha.2021.112193.
26. Vilar L, Vilar CF, Lyra R, Freitas MDC. Pitfalls in the Diagnostic Evaluation of Hyperprolactinemia. Neuroendocrinology. 2019;109(1):7-19. doi: 10.1159/000499694.
27. Nehring SM, Goyal A, Patel BC. C Reactive Protein. 2023 Jul 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: 28722873.
28. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition). Available from: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html
29. Mirzaei F, Tavilani A, Asefy Z, Abbasi E. Prolactin and susceptibility to COVID-19 infection. Medical Hypotheses. 2021;155:110662.
30. Zare-Zardini H, Soltaninejad H, Ferdosian F, Hamidieh AA, Memarpoor-Yazdi M. Coronavirus Disease 2019 (COVID-19) in Children: Prevalence, Diagnosis, Clinical Symptoms, and Treatment. Int J Gen Med. 2020 Jul 28;13:477-482. doi: 10.2147/IJGM.S262098.
31. Li Y, Jerkic M, Slutsky AS, Zhang H. Molecular mechanisms of sex bias differences in COVID-19 mortality. Crit Care. 2020 Jul 9;24(1):405. doi: 10.1186/s13054-020-03118-8.
32. Mirzaei F, Tavilani A, Asefy Z, Abbasi E. Prolactin and susceptibility to COVID-19 infection. Med Hypotheses. 2021 Oct;155:110662. doi: 10.1016/j.mehy.2021.110662.
33. Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020 Jun;139:103122. doi: 10.1016/j.jri.2020.103122.
34. Liu D, Li L, Wu X, Zheng D, Wang J, Yang L, Zheng C. Pregnancy and Perinatal Outcomes of Women With Coronavirus Disease (COVID-19) Pneumonia: A Preliminary Analysis. AJR Am J Roentgenol. 2020 Jul;215(1):127-132. doi: 10.2214/AJR.20.23072.
35. Jin JM, Bai P, He W, Wu F, Liu XF, Han DM, Liu S, Yang JK. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. Front Public Health. 2020 Apr 29;8:152. doi: 10.3389/fpubh.2020.00152.
36. Sawin CT, Carlson HE, Geller A, Castelli WP, Bacharach P. Serum prolactin and aging: basal values and changes with estrogen use and hypothyroidism. J Gerontol. 1989 Jul;44(4):M131-5. doi: 10.1093/geronj/44.4.m131.
37. Yamaji T, Shimamoto K, Ishibashi M, Kosaka K, Orimo H. Effect of age and sex on circulating and pituitary prolactin levels in human. Acta Endocrinol (Copenh). 1976 Dec;83(4):711-9. doi: 10.1530/acta.0.0830711.
38. Wilkins JN, Carlson HE, Van Vunakis H, Hill MA, Gritz E, Jarvik ME. Nicotine from cigarette smoking increases circulating levels of cortisol, growth hormone, and prolactin in male chronic smokers. Psychopharmacology (Berl). 1982;78(4):305-8. doi: 10.1007/BF00433730.
39. Chen W, Zheng KI, Liu S, Yan Z, Xu C, Qiao Z. Plasma CRP level is positively associated with the severity of COVID-19. Ann Clin Microbiol Antimicrob. 2020 May 15;19(1):18. doi: 10.1186/s12941-020-00362-2
40. Smilowitz NR, Kunichoff D, Garshick M, Shah B, Pillinger M, Hochman JS, Berger JS. C-reactive protein and clinical outcomes in patients with COVID-19. Eur Heart J. 2021 Jun 14;42(23):2270-2279. doi: 10.1093/eurheartj/ehaa1103.
41. Pepys MB. C-reactive protein predicts outcome in COVID-19: is it also a therapeutic target? Eur Heart J. 2021 Jun 14;42(23):2280-2283. doi: 10.1093/eurheartj/ehab169.
42. Benito N, Filella D, Mateo J, Fortuna AM, Gutierrez-Alliende JE, Hernandez N, Gimenez AM, Pomar V, Castellvi I, Corominas H, Casademont J, Domingo P. Pulmonary Thrombosis or Embolism in a Large Cohort of Hospitalized Patients With Covid-19. Front Med (Lausanne). 2020 Aug 25;7:557. doi: 10.3389/fmed.2020.00557.
43. Zhang JJ, Cao YY, Tan G, Dong X, Wang BC, Lin J, Yan YQ, Liu GH, Akdis M, Akdis CA, Gao YD. Clinical, radiological, and laboratory characteristics and risk factors for severity and mortality of 289 hospitalized COVID-19 patients. Allergy. 2021 Feb;76(2):533-550. doi: 10.1111/all.14496.

44. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, Shi J, Zhou M, Wu B, Yang Z, Zhang C, Yue J, Zhang Z, Renz H, Liu X, Xie J, Xie M, Zhao J. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020 Jul;146(1):110-118. doi: 10.1016/j.jaci.2020.04.006.
45. Luan YY, Yin CH, Yao YM. Update Advances on C-Reactive Protein in COVID-19 and Other Viral Infections. Front Immunol. 2021 Aug 10;12:720363. doi: 10.3389/fimmu.2021.720363.
46. Li Y, Li H, Song C, Lu R, Zhao Y, Lin F, Han D, Chen L, Pan P, Dai M. Early Prediction of Disease Progression in Patients with Severe COVID-19 Using C-Reactive Protein to Albumin Ratio. Dis Markers. 2021 Dec 3;2021:6304189. doi: 10.1155/2021/6304189.
47. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, Ye L, Xiong J, Jiang Z, Liu Y, Zhang B, Yang W. Prognostic Value of C-Reactive Protein in Patients With Coronavirus 2019. Clin Infect Dis. 2020 Nov 19;71(16):2174-2179. doi: 10.1093/cid/ciaa641.
48. Bouayed MZ, Laaribi I, Chatar CEM, Benaini I, Bouazzaoui MA, Oujidi Y, Berrichi S, El Aidouni G, Bkiyar H, Abda N, Housni B. C-Reactive Protein (CRP): A poor prognostic biomarker in COVID-19. Front Immunol. 2022 Nov 14;13:1040024. doi: 10.3389/fimmu.2022.1040024.
49. Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, Quinn TJ, Vilches-Moraga A, Stechman MJ, Pearce L, Moug S, McCarthy K, Hewitt J, Carter B; COPE Study Collaborators. The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol. 2021 May 17;50(2):420-429. doi: 10.1093/ije/dyab012.
50. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020 Jun;50(4):332-334. doi: 10.1016/j.medmal.2020.03.007.
51. Zhang JN, Gao Y, Wang XT, Li NN, Du X, Tang YJ, Lai QQ, Chen PF, Yue CS, Wu JH, Kang K, Zhao MY. Lymphocyte-C-reactive protein ratio can differentiate disease severity of COVID-19 patients and serve as an assistant screening tool for hospital and ICU admission. Front Immunol. 2022 Sep 23;13:957407. doi: 10.3389/fimmu.2022.957407.
52. Rizzi M, D'Onghia D, Tonello S, Minisini R, Colangelo D, Bellan M, Castello LM, Gavelli F, Avanzi GC, Pirisi M, Sainaghi PP. COVID-19 Biomarkers at the Crossroad between Patient Stratification and Targeted Therapy: The Role of Validated and Proposed Parameters. Int J Mol Sci. 2023 Apr 12;24(8):7099. doi: 10.3390/ijms24087099.
53. Obaid KG, Hussein SEO, Osman AL, Abdmomen NK, Ismail M, Kandakurti PK, Altoum AA. The Association of C-Reactive Protein and Ferritin Levels with the Severity of COVID-19 in Ajman, UAE. International Journal of Biomedicine. 2022;12(2):237-241. doi:10.21103/Article12(2)_OA6