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The Association of C-Reactive Protein and Ferritin Levels with the Severity of COVID-19 in Ajman, UAE

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Abstract

Background: SARS-Cov-2, a new strain of coronavirus first identified in Wuhan city, China, has spread worldwide, causing severe illnesses and a high mortality rate. Many studies have shown the association of elevated levels of pro-inflammatory markers, such as ferritin and C-reactive protein (CRP), with the severe course of coronavirus disease The aim of this research was to investigate the association between CRP and ferritin levels, and the severity of COVID-19.

Methods and Results: This cross-sectional study was performed in Thumbay Hospital, Ajman, United Arab Emirates, from January 2021 to October 2021. A total of 100 COVID-19 positive patients were included in this study. Serum CRP and ferritin were measured by immunoturbidimetric assay. We found statistically significant differences between ferritin levels and disease severity (P=0.005), age category (P=0.030), and the clinical wards (P=0.016). Statistically significant differences were found between the ferritin levels in mild to moderate cases (P=0.023) and mild to severe cases (P=0.007). There were significant differences in CRP in mild to moderate cases (P=0.012), and in mild to severe cases (P=0.000). Thus, the results obtained showed that CRP and ferritin levels are considerably greater in severe cases than in mild and moderate cases of COVID-19. The findings of the current study indicate that CRP and serum ferritin levels might be considered as an essential indication of the progression and severity of COVID-19.(**International Journal of Biomedicine. 2022;12(2):237-241.**)

Key Words: SARS-Cov-2 • C-reactive protein • ferritin

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Introduction

SARS-Cov-2, a new strain of coronavirus first identified in Wuhan city, China, has spread worldwide, causing severe illnesses and a high mortality rate.[1-3] Patients with SARS-CoV-2 infection can experience a range of clinical manifestations, from no symptoms to critical conditions.[4-6] Many studies have shown the association of elevated levels of pro-inflammatory markers, such as ferritin and C-reactive protein (CRP), with the severe course of coronavirus disease.[7,8] Ferritin is a protein that binds iron molecules and stores iron. It comprises two subunits: light chain and heavy chain. Typically, in response to inflammation, ferritin levels increase in blood, whereas hyperferritinemia is associated with a significantly increased mortality in infected patients. Iron availability in the blood is the main modulator of ferritin levels.[9,10] CRP is the first inflammatory marker that increases significantly at the early stage of the disease. It plays an important role in cases of infections and inflammations.[11] Many studies have shown a positive correlation between increased CRP and ferritin levels and COVID-19 severity.[12,13]

The aim of this research was to investigate the association between CRP and ferritin levels, and the severity of COVID-19.

Materials and Methods

This cross-sectional study was conducted in Thumbay Hospital, Ajman, United Arab Emirates, from January 2021 to October 2021. A total of 100 COVID-19 positive patients were included in this study. Written informed consent was obtained from all participants.

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Serum CRP and ferritin were measured by immunoturbidimetric assay using Beckman Coulter AU Chemistry Analyzers. The validation procedure was done according to CAP and CLIA for precision, accuracy, and linearity. The severity and diagnosis of pneumonia and the severity of the illness (mild, moderate, or severe) were assessed according to WHO recommendations. Participants without symptoms or with mild symptoms did not require hospitalization, but they were included in the study as they tested positive for SARS-CoV-2.

Clinical symptoms in the mild group included nausea, headaches, stomach pain, and vomiting. The moderate group was hospitalized due to symptoms such as fever, cough, and pneumonia. The severe group of patients who presented with high temperatures, coughing, pneumonia, and shortness of breath required intensive care.

Statistical analysis was performed using the statistical software package SPSS version 16.0 (SPSS Inc, Chicago, IL). Variables were presented as the mean (M) and standard deviation (SD). A 95% confidence interval (CI) was calculated. For data with normal distribution, inter-group comparisons were performed using Student's t-test. Multiple comparisons were performed with one-way ANOVA. Pearson's correlation coefficient (r) was used to determine the strength of the relationship between the two continuous variables. A probability value of $P<0.05$ was considered statistically significant.

Results

Among 100 COVID-19 positive patients, men accounted for 77.0%. Age subgroups were as follows: 26-35 yrs – 19(19.0%), 36-45 yrs – 40(40%), and >45 yrs – 41(41.0%). A total of 45(45%) patients had no chronic diseases. Sixty-one (61.0%) patients were admitted to the Internal Medicine Ward (IMW), 24(24.0%) to the Pulmonary Ward (PW), and 15(15.0%) patients were admitted to the Intensive Care Unit (ICU). The mild, moderate, and severe courses of the disease were found in 29(29%), 25(25.0%), and 46(46.0%) cases, respectively (Table 1). Summary of patients' symptoms: 58(58.0%) patients had shortness of breath, 88(88.0%) - fever, 58(58.0%) - pneumonia, 76(76.0%) - cough, 58(58.0%) - fatigue, 77(77.0%) - headache. A few patients experienced nausea and vomiting, diarrhea, loss of taste & smell, sore throat, and abdominal pain (Table 2). We observed a statistically significant difference between clinical course groups and CRP (Table 3).

We also found significant differences in CRP in patients of IMW to ICU (P=0.001). At the same time, there were no statistically significant differences between the PW and IMW patients (P=0.950) (Table 4). There were significant differences in CRP in mild to moderate cases (P=0.012), and in mild to severe cases (P=0.000); but there were no statistically significant differences between the moderate and severe groups of patients cases (P=0.283) (Table 5). We found statistically significant differences between ferritin levels and disease severity (P=0.005), age category (P=0.030), and the clinical wards (P=0.016). There were no associations between comorbidities and ferritin levels (Table 6). There were significant differences in ferritin levels in patients of PW and ICU (P=0.012) but no statistically significant differences between IMW and ICU (P=0.165) patients (Table 7). Statistically significant differences were found between the ferritin levels in mild to moderate cases (P=0.023) and mild to severe cases (P=0.007). However, there were no statistically significant differences between the moderate and severe cases (P=1.000) (Table 8). There were associations between ferritin levels and age subgroups (Table 9). We found weak positive correlations between ferritin and CRP levels (r=0.273, P=0.006), ferritin levels and age (r=0.239, P=0.017), and CRP levels and age (r=0.246, P=0.014) (Table 10). The ferritin and CRP levels did not differ between men and women (Tables 11 and 12).

Table 1.
Baseline characteristics of the patients included in the study

Variables	Group	Frequency	Percentage
Gender	Males	77	77.0 %
	Females	23	23.0 %
Age Category	26 – 35	19	19.0 %
	36 – 45	40	40.0 %
	> 45	41	41.0 %
Comorbidities	DM	20	20.0 %
	HTN	8	8.0 %
	DM & HTN	12	12.0 %
	Multiple comorbidity	3	3.0 %
	Other	14	14.0 %
	No Chronic Diseases	43	43.0 %
Ward	IMW	61	61.0 %
	PW	24	24.0 %
	ICU	15	15.0 %
Disease Severity	Mild	29	29.0 %
	Moderate	25	25.0 %
	Severe	46	46.0 %
Contentious Variables			
Variable	Mean±SD	Minimum	Maximum
Age	44.39±11.892	26	84
Length of Stay,day	10.310±8.3566	2.0	70.0
CRP, mg/L	82.343±76.5985	5.0	518.8
Ferritin, ng/mL	561.096±516.8643	8.8	2616.0

Table 2.
Summary of Patients' Symptoms

Variables	Group	Frequency	Percentage
Abdominal Pain	No	98	98.0 %
	Yes	2	2.0 %
Sore throat	No	97	97.0 %
	Yes	3	3.0 %
Loss of taste & Smell	No	91	91.0 %
	Yes	9	9.0 %
Nausea	No	94	94.0 %
	Yes	6	6.0 %
Vomiting	No	97	97.0 %
	Yes	3	3.0 %
Diarrhea	No	94	94.0 %
	Yes	6	6.0 %
Headache	No	77	77.0 %
	Yes	23	23.0 %
Fatigue	No	42	42.0 %
	Yes	58	58.0 %
Cough	No	24	24.0 %
	Yes	76	76.0 %
Pneumonia	No	42	42.0 %
	Yes	58	58.0 %
Fever	No	12	12.0 %
	Yes	88	88.0 %
SOB	No	42	42.0 %
	Yes	58	58.0 %

Table 3.

Analysis of variance (ANOVA) of CRP with Severity, Age Category, Comorbidities, and Wards

Variables		Sum of Squares	Df	Mean Square	F	Sig.
Severity	Between Groups	118260.683	2	59130.342	12.399	0.000
	Within Groups	462604.442	97	4769.118		
	Total	580865.125	99			
Age Category	Between Groups	30898.900	2	15449.450	2.725	0.071
	Within Groups	549966.225	97	5669.755		
	Total	580865.125	99			
Co-morbidities	Between Groups	56303.745	5	11260.749	2.018	0.083
	Within Groups	524561.380	94	5580.440		
	Total	580865.125	99			
Ward	Between Groups	79802.979	2	39901.490	7.724	0.001
	Within Groups	501062.146	97	5165.589		

Table 4.

Multiple comparisons (Post-Hoc) of CRP with Wards

Dependent Variable: CRP						
Tukey HSD						
(I) Ward	(J) Ward	Mean Difference (I-J)	Std. Error	Sig	95% CI	
					Lower Bound	Upper Bound
IMW	PW	-5.2903	17.3180	0.950	-46.511	35.930
	ICU	-80.3686	20.7136	0.001	-129.672	-31.066
PW	IMW	5.2903	17.3180	0.950	-35.930	46.511
	ICU	-75.0783	23.6560	0.006	-131.385	-18.772
ICU	IMW	80.3686	20.7136	0.001	31.066	129.672
	PW	75.0783	23.6560	0.006	18.772	131.385

Table 5.

Multiple comparisons (Post-Hoc) of CRP with Disease Severity

Dependent Variable: CRP						
Tukey HSD						
(I) Severity	(J) Severity	Mean Difference (I-J)	Std. Error	Sig	95% CI	
					Lower Bound	Upper Bound
Mild	Moderate	-55.1719	18.8472	0.012	-100.032	-10.311
	Severe	-81.3606	16.3746	0.000	-120.336	-42.385
Moderate	Mild	55.1719	18.8472	0.012	10.311	100.032
	Severe	-26.1888	17.1593	0.283	-67.032	14.654
Severe	Mild	81.3606	16.3746	0.000	42.385	120.336
	Moderate	26.1888	17.1593	0.283	-14.654	67.032

Table 6.

Analysis of variance (ANOVA) of Ferritin with Severity, Age Category, Comorbidities, and Wards

Variables		Sum of Squares	df	Mean Square	F	Sig.
Severity	Between Groups	2702780.636	2	1351390.318	5.521	0.005
	Within Groups	23744937.223	97	244793.167		
	Total	26447717.858	99			
Age Category	Between Groups	1838445.278	2	919222.639	3.623	0.030
	Within Groups	24609272.581	97	253703.841		
	Total	26447717.858	99			
Co-morbidities	Between Groups	2419822.403	5	483964.481	1.893	0.103
	Within Groups	24027895.455	94	255615.909		
	Total	26447717.858	99			
Ward	Between Groups	2152206.232	2	1076103.116	4.296	0.016
	Within Groups	24295511.626	97	250469.192		
	Total	26447717.858	99			

Table 7.

Multiple comparisons (Post-Hoc) of Ferritin with Wards

Dependent Variable: Ferritin						
Tukey HSD						
(I) Ward	(J) Ward	Mean Difference (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
IMW	PW	216.1854	120.5913	0.177	-70.849	503.219
	ICU	-264.0230	144.2359	0.165	-607.336	79.290
PW	IMW	-216.1854	120.5913	0.177	-503.219	70.849
	ICU	-480.2083	164.7245	0.012	-872.289	-88.128
ICU	IMW	264.0230	144.2359	0.165	-79.290	607.336
	PW	480.2083	164.7245	0.012	88.128	872.289

Table 8.

Multiple comparisons (Post-Hoc) of Ferritin with disease severity

Dependent Variable: Ferritin						
Tukey HSD						
(I) Severity	(J) Severity	Mean Difference (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
Mild	Moderate	-363.0014	135.0291	0.023	-684.401	-41.602
	Severe	-361.9283	117.3147	0.007	-641.163	-82.693
Moderate	Mild	363.0014	135.0291	0.023	41.602	684.401
	Severe	1.0730	122.9362	1.000	-291.542	293.688
Severe	Mild	361.9283	117.3147	0.007	82.693	641.163
	Moderate	-1.0730	122.9362	1.000	-293.688	291.542

Table 9.

Multiple comparisons (Post-Hoc) of Ferritin levels with age category

Dependent Variable: Ferritin						
Tukey HSD						
(I) Age	(J) Age	Mean Difference (I-J)	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
26 - 35	36 - 45	-232.7158	140.3404	0.227	-566.757	101.325
	> 45	-374.9402	139.7882	0.023	-707.667	-42.213
36 - 45	26 - 35	232.7158	140.3404	0.227	-101.325	566.757
	> 45	-142.2244	111.9397	0.415	-408.666	124.217
> 45	26 - 35	374.9402	139.7882	0.023	42.213	707.667
	36 - 45	142.2244	111.9397	0.415	-124.217	408.666

Table 10.
Relationship between CRP levels, Ferritin levels, and age

		Age in years	CRP	Ferritin
Age in years	Pearson Correlation		0.246	0.239
	Sig. (2-tailed)		0.014	0.017
	N		100	100
CRP	Pearson Correlation	0.246		0.273
	Sig. (2-tailed)	0.014		0.006
	N	100	100	100
Ferritin	Pearson Correlation	0.239	0.273	
	Sig. (2-tailed)	0.017	0.006	
	N	100	100	

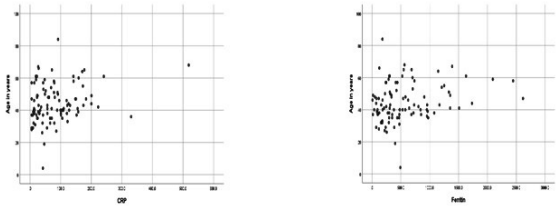

Table 11.
Group Statistics of Gender with CRP and Ferritin

Group Statistics					
	Gender	N	Mean	Std. Deviation	Std. Error
Ferritin	Male	77	622.565	537.1310	61.2118
	Female	23	355.309	384.7094	80.2175
CRP	Male	77	84.634	64.5451	7.3556
	Female	23	74.674	109.2301	22.7761

Table 12.
Comparison between Gender with CRP and Ferritin

Variable	Group	N	Mean±SD	Mean Difference	95% CI		Sig.
					Lower	Upper	
Ferritin	Male	100	622.565 ± 537.1310	267.2562	28.2147	506.2978	0.226
	Female	100	355.309 ± 384.7094				
CRP	Male	100	84.634 ± 64.5451	9.9599	18.2666	-26.2896	0.224
	Female	100	74.674 ± 109.2301				

Discussion

The results obtained showed that CRP and ferritin levels are considerably greater in severe cases than in mild and moderate cases of COVID-19. A high ferritin level was associated with admission to ICU. The current findings are consistent with data obtained by Cheng et al.[5] The close positive association between CRP values and severity of tissue damage in many different pathologies, notably including COVID-19, was illustrated by Smilowitz et al.[11] CRP bound to tissues damaged by the virus and/or host response activates a complement locally, thereby exacerbating damage and promoting systemic complement activation. A novel small-molecule drug that inhibits CRP binding in vivo is currently being developed to test whether this CRP-complement mechanism significantly contributes to the severity of COVID-19 and other diseases.[12] The findings of the current study indicate that serum ferritin levels might be considered as an essential indication of the progression and severity of COVID-19.[13] Henry et al.[14] found that ferritin levels were high at admission to the hospital and during the hospital stay in patients who died from COVID-19. In a study by Liu et al.,[9] an analysis of the peripheral blood of 69 patients with severe COVID-19 revealed elevated ferritin levels, compared with patients with a non-severe course of the disease. In addition, a positive correlation between ferritin and IL-6 was noted. A retrospective study of over 900 patients admitted with COVID-19 showed that higher ferritin levels were associated with all-cause mortality.[8] Thus, multiple publications are showing that higher ferritin levels, along with other pro-inflammatory markers, including CRP and IL-6, are correlated with worse outcomes and may even help predict these outcomes of COVID-19.[15-21] Zhou et al.[7] found that a combination test of hepcidin and serum ferritin provided the best specificity and sensitivity in the prognosis of COVID-19 severity. Hepcidin and serum ferritin tandem testing predicted COVID-19 severity with 94.6% specificity. It is quite obvious that iron homeostasis had a robust association with the occurrence of severe COVID-19.

Conclusion

The findings of the current study indicate that CRP and serum ferritin levels might be considered as an essential indication of the progression and severity of COVID-19.

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Competing Interests

The authors declare that they have no competing interests.

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