

Alteration of Ferritin Levels and Lymphocytes Counts in Saudi Patients with COVID-19 Infection in Al Madinah Al Munawarah

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Abstract: It is an essential to evaluate the potential biomarkers affecting the progression of disease in COVID-19 patients. Therefore, we investigated the relationship between Ferritin levels and hematological parameters and severity of COVID-19 to explore its role in predicting the severity of COVID-19. This retrospective study was conducted in different Hospitals at Madinah region, Saudi Arabia. In the present study, a total of 112 cases of COVID-19 patients. The patient records included the clinical and laboratory data that was used for analysis by using the GraphPad Prism Software. Data presented as mean (SD), all differences were statistically significant at the level of $P \leq 0.05$ or ≤ 0.001 . There were significantly increased levels of ferritin, neutrophil and leukocyte counts in severe COVID-19 cases (1857 (50.9), 9.9 (2.8), 9.9 (2.8) respectively) compared with non-sever cases. Additionally, there were significantly reduction in lymphocytes counts in COVID-19 patients (1.3 (9.5), $P=0.001$). There were also strong correlations between elevation of ferritin levels or reduction of lymphocytes and the severity COVID-19 infection ($r=0.53$, OR: 5.88 and $r=-0.55$, OR: 3.98 respectively). The results demonstrate that high values for neutrophil, leukocyte counts and Ferritin levels, and low values for lymphocyte counts may have diagnostic properties concerning COVID-19 in severe cases.

Keywords: Neutrophil, Leukocyte, Ferritin, Lymphocyte, COVID-19

1. Introduction

The coronavirus disease (COVID-19) is initiated by a large family of coronaviruses (CoV's) that are found varying in animal species. The COVID-19 has led to the outbreak of respiratory syndrome that noticed and reported in Wuhan, China in December 2019. Globally it has affected over 210 countries. The World Health Organization (WHO) declared it a Public Health Emergency of International Concern in January [1]. The infection spreads by human to human transmission. The symptoms include high fever, persistent dry cough, myalgia, pneumonia, headache, diarrhea. There

has been prompt outpouring of research after the outbreak of COVID-19, on the epidemiology, clinical features, and diagnosis [1].

A study on early virus transmission has reported that the median age of patients is 59 years, between 15 to 89 years, with the majority (59%) being male [2]. It was further reported that the people with weak immune system like older people and those with underlying medical condition like cardiovascular, diabetic, renal and hepatic dysfunction are at higher risk [3-5]. The association between clinical parameters and the severity of COVID-19 is crucial in understanding their role and in predicting the severity of disease. In the recent past, several clinical parameters have been studied that

could help in distinguishing between mild and severe disease and possibly may be used as prognostic markers. One of the crucial laboratory investigations are the hematological parameters. A prior study indicated that white blood cell neutrophil count, lymphocyte count and albumin were risk factors for intensive care unit (ICU) care in patients with COVID-19 [6]. Similarly, hyperferritinemia or hyperferritinemia syndrome has been linked with increased illness and fatal outcomes. Hyperferritinemia, indicates the occurrence of viruses and bacteria in the body [7]. Ferritin is a main intracellular iron storage protein in all organisms. It combines free ions of the trace element, neutralizing its toxic properties and enhancing its solubility. In the soluble structure, the body can expend iron as required, in particular for regulation of cellular oxygen metabolism. Low ferritin levels result in decrease iron concentrations and iron deficiency anemia. Hyperferritinemia, is a disorder where high levels of intracellular iron storage protein, called ferritin are found, that lead to the activation of macrophages resulting in increased cytokine secretion [7, 8]. Cytokines are a type of signaling molecules that mediate and regulate immunity. At low concentrations, they are safe for the body and assist to defend it against viruses and bacteria [9]. At high levels, the so called "cytokine storm" develops, which can be deadly for half of the patients, particularly for the elderly [8, 9].

Therefore, it is an essential to assess the potential factors influencing the progression of disease in COVID-19 patients. We investigated the relationship between Ferritin levels and hematological indicators and severity of COVID-19 to explore its role in predicting the severity of COVID-19.

2. Methods

2.1. Study Design and Data Collection

This retrospective study was conducted in the Ohud Hospital and King Fahd Hospital of Madinah region, Saudi Arabia. In the current study, a total of 112 cases of COVID-19 patients. The patient files contained the clinical and laboratory data that was used for analysis. All cases were evaluated based on the inclusion and exclusion criteria; the inclusion criteria were patients with confirmed COVID-19 disease. However, those patients were excluded who were having the history of endocrine diseases or history of renal, liver, heart, or neurological disease. Patients with confirmed Covid-19 were categorized as severe and non-severe according to the clinical characteristics and symptoms and chest radiography results [10].

The study was accepted by the Ethics Committee of the Faculty of Applied Medical Sciences at Taibah University and Saudi Arabia Ministry of Health, General Administration for Research & Studies.

2.2. Statistical Analysis

Data was evaluated using the GraphPad Prism Software (version 5.01). Quantitative data was presented as percentages,

mean, standard deviation and range. One-way Anova test was applied to compare between the patient's groups (severe and non-severe). Also, Multivariate analysis was applied based on the Multiple Logistic Regression (severity of COVID-19 infection is dependent parameter tested against the biochemical markers). The odds ratio (OR) was determined with 95% confidence intervals. All differences were statistically significant at the level of $P \leq 0.05$ or ≤ 0.001 . Receiver-Operating Characteristic (ROC) curve was created, the Youden's index (J) applied for cut-off values in the diagnosis of COVID-19 and the area under the curve (AUC) was determined by using Epitools - Epidemiological Calculators [11].

3. Results

3.1. Evaluations the Hematological Parameters Levels for Severe and Non-severe Coronavirus Infection

When compared between two study groups (severe and non-severe), the study indicated that 57.2% of COVID-19 patients are severe cases and have high mean age (78 ± 13.8), whereas 42.8% are non-severe patients with low mean age (54 ± 12.01 , $P < 0.05$) (Table 1). Comparisons made also according to the severity of infection showed that a statistically significant difference ($P < 0.001$) was found between the two groups regarding leukocyte, neutrophil and Ferritin values. In patients with severe infection, it was noticed that leukocyte, neutrophil and Ferritin values were higher, whereas lymphocyte was observed to be lower, comparing to non-severe cases (Table 1). While no statistically significant difference was observed between two groups regarding Hemoglobin values ($P > 0.05$).

Table 1. Hematological markers Characteristics of the Study Patients ($n=112$), According to Disease Severity.

Parameters	Severe group, 64 (57.2%)	Non-severe group, 48 (42.8%)	P-Value
Sex			
Male	37 (57.8%)	25 (52.1%)	
Female	27 (42.2%)	23 (47.9%)	
Age (Y)	78 (13.8)	54 (12.01)	0.02*
Leukocyte ($10^3/L$)	12 (3.57)	7.4 (2.4)	0.002**
Neutrophil ($10^3/L$)	9.9 (2.8)	6.7 (2.3)	0.01*
Hemoglobin (g/L)	12.5 (2.28)	13 (1.7)	>0.05
Platelet ($10^3/L$)	120 (20.7)	221 (33.6)	0.03*
Lymphocyte ($10^3/L$)	1.3 (9.5)	4.8 (9.9)	0.001**
S. Ferritin (ng/mL)	1857 (50.9)	313 (24.8)	<0.001**

Data presented as number (percentage%) for sex. One-way Anova test was used to compare between the levels of CBC markers in severe and non-severe Covid-19 infected patients. Data presented as mean (SD), $P < 0.05^*$, 0.001^{**} . The value in bold font has a statistically significant difference.

3.2. Evaluation the Risk Factors for COVID-19 in Severe Cases

Multiple regression was applied to evaluate whether age or gender were risk factors and as a result, it was determined that age of the patients was a risk factor for COVID-19 in severe cases ($P=0.02$; OR: 2.998; 95% CI: 0.997–3.802). Whereas

the patient's gender was not a risk factor for COVID-19 ($P=0.08$; OR: 0.6598; 95% CI: 0.771–1.322, Data did not show).

Table 2. Multivariate analysis for hematological markers in severe Covid-19 cases.

Variables	Multivariate analysis			
	<i>r</i>	OR	95% CI	<i>P</i> value
Leukocyte ($10^3/L$)	0.68	4.55	2.45 to 6.17	0.002**
Neutrophil ($10^3/L$)	0.75	6.87	1.88 to 7.18	0.001**
Hemoglobin (g/L)	0.21	1.03	0.8930 to 1.055	0.57
Platelet ($10^3/L$)	0.12	0.59	0.07610 to 3.283	0.84
Lymphocyte ($10^3/L$)	-0.55	3.98	1.83 to 4.77	0.03*
S. Ferritin (ng/mL)	0.53	5.88	1.00 to 6.01	0.01*

Data presented as r =Pearson correlation coefficients, OR=odd ratio, 95%CI=95% confidence interval. All differences were statistically significant at the level of $P \leq 0.05$ or ≤ 0.001 **.

Furthermore, the Multiple Logistic Regression in which severity was the dependent variable and the hematological markers were the independent variables revealed higher significant odds ratio for leukocytes, neutrophils, and Ferritin (OR: 4.55, OR: 6.87 and OR: 5.88 respectively, Table 2). Also, the associations between severity and the alteration of hematological markers levels were examined by Pearson correlation coefficients (r). The severity of infection

associated positively with increasing Leukocyte ($r=0.68$), Neutrophil ($r=0.75$) and Ferritin ($r=0.53$). Whereas a negative association between severity and decreasing of lymphocytes ($r=-0.55$) was indicated.

3.3. Cut-off Values for Significant Indicators in the Prediction of Coronavirus Infection in Severe Cases

Receiver-Operating Characteristic (ROC) curve was produced, the Youden's index (J) applied for cut-off values in the diagnosis of COVID-19 and the area under the curve (AUC) was calculated. There was a statistically significant variation between severe and non-severe groups according to parameters (leukocyte, neutrophil, Ferritin and lymphocytes), they were then analyzed with ROC analyses. Related to the results yielded by ROC analyses, the following information regarding patients with severe COVID-19 infection were noticed (Table 3 & Figure 1A, B, C and D): The cut-off point for leukocyte values was observed to be ≤ 11.2 (AUC=0.572; $p > 0.001$; 95% CI: 0.465–0.679). The cut-off point for neutrophil values was found to be ≤ 10.8 (AUC=0.733; $p < 0.001$; 95% CI: 0.63–0.836). The cut-off point for Ferritin was found to be ≤ 955 (AUC=0.937; $p < 0.001$; 95% CI: 0.886–0.987). The cut-off point for lymphocytes values was found to be ≤ 6.9 (AUC=0.833; $p < 0.001$; 95% CI: 0.751–0.915) (Table 3 & Figure 1).

Table 3. Recommended cut-off values for significant markers in the prediction of Coronavirus Disease in severe cases.

Parameters	AUC	Cut off	Sensitivity	Specificity	95% CI	P
Leukocyte	0.572	11.2	0.118	0.83	0.465-0.679	> 0.001
Neutrophil	0.733	10.8	0.922	0.604	0.63-0.836	< 0.001
Lymphocyte	0.833	6.9	0.906	0.729	0.751-0.915	< 0.001
S. Ferritin	0.937	955	0.891	0.896	0.886-0.987	< 0.001

Diagnostic cut off values derived from the ROC curve (Receiver operating characteristic curve). AUC: Area under the curve, 95%CI=95% confidence interval. The values in bold font have a statistically significant difference.

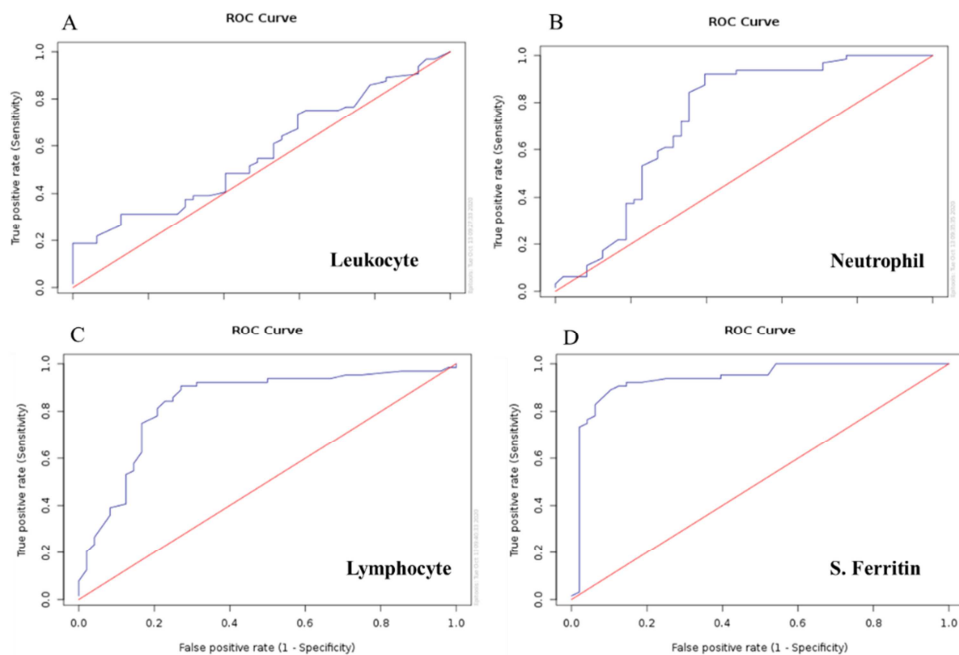


Figure 1. Receiver-operating characteristic curve for significant markers in the prediction of Coronavirus Disease in severe cases.

4. Discussion

The prevalence of COVID-19 infection was enlarged during the last months and distributed overall the world [12]. Consequently, all countries need to evaluate the disease severity and mortality and identify the effective therapy that may limit the spreading of this pandemic [13]. A varied of abnormal laboratory parameters containing biochemical, hematological, inflammatory, and immunological markers considered to be altered during COVID-19 outbreak and lead to the severity of the infection [14, 15]. In this retrospective study, our team attempted to clarify and determine the various alteration in Ferritin, hematological parameters related to the severity and mortality of COVID-19. The initiation of this study, the investigation different hematological levels were done on 112 patients diagnosed with COVID-19. Current findings indicated that reduction in the number of lymphocytes count but augmentation in the number of leukocytes, neutrophil is directly related to the severity of COVID-19 infection. In patients with the COVID-19 epidemic, the WBC count can vary [16]. Some studies indicated that leukocytosis, and lymphopenia were indicated, and lymphopenia occurred frequently in infected patients [17, 18]. Additional study advocated that lymphopenia is an efficient marker for the severity of COVID-19 [19], which is confirmed in our study. Furthermore, a retrospective study observed some variations in WBC levels between severe and non-severe COVID-19 patients [20]. Both groups have high count numbers in leucocytes and neutrophil but in the severe group having a considerably greater increase (5.6 vs $4.9 \times 10^9/L$; $P < 0.001$). The levels of lymphocytes were less in severe COVID-19 patients [14, 20, 21] is considered as marker for inflammatory conditions which may be used to indicate disease severity. In the results of our study, which are also consistent with former research, high leukocyte and neutrophil counts and low lymphocytes counts were shown in COVID-19 severe patients. Nevertheless, a bigger study is required to clarify the effectiveness of lymphocytes count as a good marker for early detection of severe COVID-19. In this respect, we may possibly speculate the prospective role of high WBC count with lymphopenia as diagnostic and prognostic marker for severe status of COVID-19.

Concerning the Ferritin levels correlated with the COVID-19 pandemic, this retrospective study detected a higher concentration of Ferritin among severe patients with COVID-19. Recently, a study for 20 patients with COVID-19 found that individuals with severe COVID-19 had increase serum ferritin level, actuality serum ferritin in the severe COVID-19 group significantly greater than in non-severe COVID-19 group (1006.16 ng/ml vs 291.13 ng/ml respectively) [22]. In agreement with this, another study showed that by severe COVID-19 patients, ferritin levels were elevated when admission to the hospital and throughout their staying [23], also the serum ferritin levels exceeded the high limit of detection in these patients until they died.

Furthermore, Chen et al. evaluated the levels of biochemical indicators in 99 patients with COVID-19, indicating elevation in ferritin levels in 12 patients who were died by severe COVID-19 infection [24]. An investigation of the peripheral blood of 69 patients with severe COVID-19 showed raised levels of ferritin compared with patients with non-severe disease, suggesting that serum ferritin levels were strongly correlated to the severity of COVID-19 [25-27]. Our current study showed increased levels of serum ferritin among sever infected patients compared with non-severe patients, and this significant outcome was observed in previous studies. We also indicated a strong association between the elevation of ferritin levels and the severity of COVID-19. In this regard, we may possibly consider the potential role of ferritin as a prognostic biomarker during the severe status of COVID-19. The area under the ROC curve greater than 0.9 has high precision, while 0.7 – 0.9 indicates moderate precision, 0.5–0.7 low precision test [28]. Based on this, Ferritin level was found to be significantly high for patients with severe COVID-19 infection, meaning that it can also be used for diagnosing COVID-19. The cut-off value for Ferritin was observed as being=955, and the AUC=0.937 with a sensitivity of 89.1%, and a specificity of 89.6%. Our results also indicated that low lymphocytes levels can probably be used as a diagnostic indicator for COVID-19, because the resulting for lymphocytes were AUC=0.833, cut-off=6.9, specificity=0.729 and sensitivity=0.906. Ferritin is a vital mediator for dysregulation the immune system, particularly under severe hyperferritinemia, through its directly suppressing the immune functions and stimulating the pro-inflammatory factors, causing the cytokine storm [29, 30, 31]. It has been informed that serious outcomes by COVID-19 are associated with cytokine storm syndrome, suggesting that disease severity is related to the cytokine storm syndrome [5, 32].

5. Conclusion

Our findings supported the hypothesis that ferritin levels may possibly be an important factor affecting the severity of COVID-19. But the limitation of this study was the insufficient number of patients. Studies performed on a larger patient group may obviously identify the importance biomarkers from peripheral blood tests in the diagnosis of COVID-19 patients. However, we supposed that monitoring of ferritin during hospitalization might help to detect severe patients and predict the progression of COVID-19 infection. Several of biochemical and hematological parameters may possibly associate with the severity and mortality of COVID-19 infection and must be examined and evaluated continuously during the progression of this deadly disease. These parameters contained WBCs count, lymphocytes count, and ferritin levels. Because their alterations may lead to vital damage in infected patients and early detection may reduce the progression of COVID-19 severity.

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Competing Interests

None declared.

Ethical Approval

The study was approved by the Ethics Committee of the Faculty of Applied Medical Sciences at Taibah University and Saudi Arabia Ministry of Health, General Administration for Research & Studies.

Author Contributions

WM and AS: Conceptualization, study design, software, data curation, analysis and interpretation, original draft preparation and formal analysis, reviewing and editing. Author has critically reviewed and approved the final draft and is responsible for the content and similarity index of the manuscript. HH and MA: Providing the samples, collecting the data. NS: Original draft preparation. Editing language and proof-reading the article. All authors significantly contributed to this research and hold responsibility for its quality and content.

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