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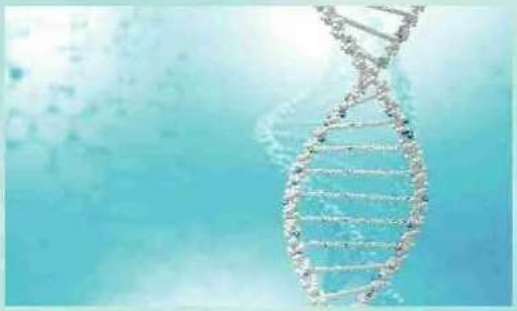

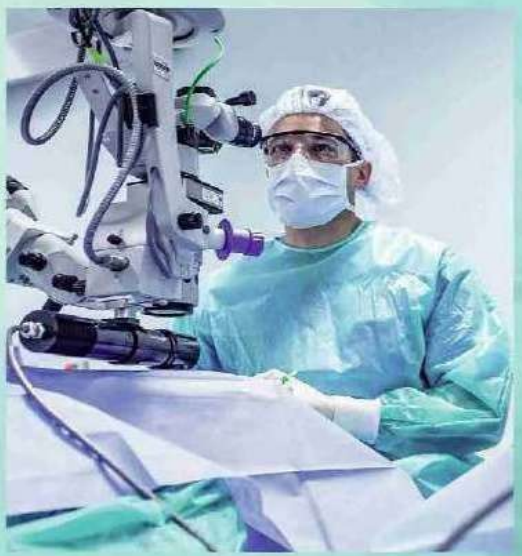

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ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

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Май

www.bsmi.uz
https://newdaymedicine.com E:
ndmuz@mail.ru
Тел: +99890 8061882

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EVALUATION OF THE ROLE OF FERRITIN IN THE COURSE OF CORONAVIRUS INFECTION

H.H.Mammadova, J.P.Isayev

Azerbaijan Medical University, Department of Infectious Diseases, Baku, Azerbaijan

✓ ***Resume***

In this article, the level of ferritin in the blood of patients infected with Covid-19 infection was evaluated according to the degree of complications. Research was conducted among 212 patients diagnosed with Covid-19. Patients were divided into 2 groups, those with complications and those without complications, male and female. Increased ferritin levels due to cytokine storm and secondary hemophagocytic lymphohistiocytosis were found in observed patients. The analysis of the obtained results showed that the level of ferritin in the blood increased more in the group of female patients with complications than in the other group, and this was statistically honest with the Mann-Whitney test. Analysis of blood samples showed that the mean level of ferritin in the blood was 742.5±65.2 μg/L. In conclusion, changes in blood ferritin levels were found to be of prognostic importance in the course of infection and should be shown to have a special role among inflammatory markers.

Key words: Covid-19, complication rate, pneumonia; the inflammatory cytokines; ferritin

Relevance

As is known, since December 2019, the SARS-CoV-2 virus, which causes severe acute respiratory syndrome, has rapidly become a global epidemic characterized by human-to-human transmission [15,17]. On March 11, 2020, WHO declared COVID-19 a pandemic. The new coronovirus infection has spread widely in Azerbaijan, causing 831,983 confirmed cases, including 10,288 deaths by August 2023 [14]. It should also be pointed out that the risk of severe complications and even death is high in those with diabetes, cardiovascular, especially respiratory system and other diseases of the COVID-19 infection. In this regard, the COVID-19 infection is a global crisis and requires the joint efforts of all mankind to fight it.

Cytokine storm is an immune response that is uncontrolled and leads to many severe dysfunctions in the immunopathogenesis of COVID-19. In severe disease, massive secretion of inflammatory cytokines, including TNF-α, IL-6, IL-12, and IL-8, ultimately leads to potential acute respiratory distress syndrome (ARDS) and multiorgan failure [8, 11, 16]. Studies show that serum levels of ferritin, d-dimer, IL-6, and lactate dehydrogenase increase during disease progression, which provides an indicator of mortality risk [16].

Ferritin is an iron-storing protein; its serum level reflects normal iron levels and is a diagnostic indicator of iron deficiency anemia. During viral infections, the level of ferritin in the blood increases, which can be seen as an indicator of the virus growing and multiplying in the blood [1, 9]. Increased ferritin levels have also been shown in severe COVID-19 patients due to cytokine storm [5, 13]. During the severe course of the COVID-19 infection, during the cytokine storm, the synthesis of many inflammatory cytokines is accelerated, including IL-6, TNF-α, IL-1β, IL-12, and IFN-γ, which stimulate hepatocytes, Kupffer cells, and macrophages to synthesize ferritin [12]. Uncontrolled and dysfunctional immune macrophage activation, hyperferritinemic syndrome, and a thrombotic storm-related response eventually lead to multiorgan damage. Studies have shown that ferritin synthesis is not only a consequence of excessive inflammation, but also plays a pathogenic role in the inflammatory process by binding to T-cell immunoglobulin and mucin domain 2 (TIM-2) [7]. In addition, some studies have shown that the H chain of ferritin activates macrophages to secrete inflammatory cytokines [2].

In infectious diseases, hyperferritinemia caused by a severe inflammatory process is associated with the admission of patients to the intensive care unit and mortality. It is also an indication for managing inflammation and identifying patients with high risk of complications [2, 3, 7]. Ferritin, a feature of hemophagocytic lymphohistiocytosis, a complication of viral infection, is associated with delayed recovery in patients with COVID-19 infection, and individuals with lung changes are more likely to have increased ferritin levels [6, 10, 16]. Thus, as a pro-inflammatory factor in an uncontrolled cytokine

storm, the predictive role of ferritin levels in patients with COVID-19 with a likely poor outcome warrants further investigation.

In addition to clinical examinations, laboratory tests can allow clinicians to quickly assess the patient's condition in order to make the optimal approach and make the right decision in patients with COVID-19. In this study, ferritin is of particular interest because of its potential diagnostic and prognostic role. The main objective of this study was to determine the potential relationship of ferritin with severe course and critical conditions of COVID-19 patients

Purpose of the study: assessment of the role of ferrıtın durıng coronavırus ınfectıon.

Material and methods

The data used in this study included data from 212 patients hospitalized and treated for COVID-19 at the Clinical Medical Center between August and December 2021. Patients under the age of 18 and pregnant women who were not diagnosed with COVID-19 on the indicated dates were excluded from the study. In our hospital, only cases with SARS-CoV-2 detected from nasopharyngeal or oropharyngeal smears were diagnosed with COVID-19 by RT-PCR. Age and gender characteristics of detected COVID-19 patients were recorded. Immunological test records of these patients from admission to discharge, as well as clinical course, i.e. severity, were examined. Patient data were divided into two groups: those without complications (n = 110) and those with complications from COVID-19 (n = 102). We included the comorbidity data of the majority of patients included in our study. Hypertension, diabetes and kidney failure were investigated as comorbidities.

Categorical variables were expressed in frequency and percentage, median and quartile values of continuous variables were presented. In the comparison of continuous variables, normally distributed variables were analyzed by independent sample t-test, and non-normally distributed variables were analyzed by Mann-Whitney U test. Categorical variables were analyzed using the $\chi 2$ test. SPSS (version 20.0, SPSS Inc, Chicago) package programs were used for statistical analysis of data. $P<0.05$ was considered statistically significant.

Result and discussion

Demographic characteristics of patients with and without complications treated with a diagnosis of COVID-19 and inflammatory blood values of all patients at the time of admission to the hospital were investigated. 212 (43.6%) of the participants in this study were men and 117 (56.4%) were women. The average age of patients without complications is 55.0±2.2 years, and the average age of patients with complications is 76.0-±2.6 years. It was clarified that the level of ferritin in the blood was 539.3 x mcg/L versus 805.7 mcg/L, higher than the patients without complications. Also, when we evaluate gender indicators, we observe that the number of complications is higher among women compared to men (53.9%). When comparing the age group, more patients with a diagnosis of Covid-19 with complications are seen in the group of patients over 65 years of age, which can be associated with the presence of more co-morbidities. The result obtained by the Mann-Whitney test was P=0.043, which is a statistically significant result $p< 0.05$ (Table 1).

In the course of the study, inflammatory blood indicators were compared with 3 examinations in accordance with the duration of the inpatient stay in the patients. First of all, the length of stay of patients in the hospital attracted special attention. Thus, in the groups of patients with complications, the length of stay - the number of bed days was relatively higher (>14 days). In particular, changes in the level of ferritin were detected as inflammatory markers in all the examined blood samples. P = 0.018. Thus, although the level of ferritin was increased in 10 patients without complications during the 1st measurement during all 3 examinations, this indicator was noted as high in 35 patients with complications. The obtained results suggest that ferritin provides more informative information in assessing the severity of the disease.

As mentioned above, ferritin levels were analyzed in male patients diagnosed with Covid-19. The obtained results showed an increase in the ferritin index - 682.9 x mcg/L in 31 male patients without complications, while this indicator was determined at 1740.3 x mcg/L in 38 patients with complications. The results of the subsequent examinations were 1172.7 x mcg/L and 1546.5 x mcg/L, respectively. At the same time, statistical integrity was not observed when calculating the results using the Mann-Whitney method in 95 male patients with complications (Table 3).

Table 1

Mann-Whitney Test

Ranks

Aggravation		N	Mean Rank	Sum of Ranks
	yes	110	107.75	11852.00
	no	102	105.16	10726.00
	Total	212		

Test Statistics[a]

	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Ferritin	2796.500	5722.500	-2.021	0.043
Ferritin2	606.000	859.000	-1.156	0.248
Ferritin3	34.000	814.000	-1.197	0.231

Aggravation

Mann-Whitney analysis of ferritin levels in critically ill patients

Table 2

Wilcoxon Signed Ranks Test

Ranks[a]

		N	Mean Rank	Sum of Ranks
Ferritin2 - Ferritin	Negative Ranks	31[ct]	34.48	1069.00
	Positive Ranks	35[cu]	32.63	1142.00
	Ties	0[cv]		
	Total	66		
Ferritin3 - Ferritin	Negative Ranks	25[cw]	22.36	559.00
	Positive Ranks	14[cx]	15.79	221.00
	Ties	0[cy]		
	Total	39		

Analysis of the ferritin indicator in 3-day blood samples taken from patients with severe complications with a diagnosis of Covid-19

When examining the ferritin indicators obtained during the examination of women, different results were found. During the measurement by Student's criterion, the ferritin indicator in the blood was shown to be statistically honest, unlike men. Pt-=0.010 In 45 female patients with complications, the average ferritin indicator was 512.6 x μg/L. In particular, during the comparative analysis of routine blood samples, it was known that the level of ferritin in the blood fluctuates at high levels in the peak stage of the disease in women, and the statistic was estimated as Pu=0.004 (Table 4).

Several studies have also found that increased ferritin levels are associated with worsening of the course of COVID-19 [6]. A cytokine storm and an active immune response of the infected organism (ie, ferritin) are involved in the development of acute respiratory failure, and its progression is accompanied by increased mortality. Higher ferritin levels have been reported in such groups of patients with severe or ARDS compared to less severe patients [4].

Table 3

Analysis of ferritin levels in men by the Mann-Whitney method

sex - male				
Mann-Whitney Test				
Ranks[a]				
Aggravation		N	Mean Rank	Sum of Ranks
	yes	8	48.00	2304.00
	no	47	48.00	2256.00
	Total	95		
a. sex = male				
Test Statistics[a,b]				
	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Ferritin	543.500	1284.500	-0.549	0.583
Ferritin2	136.000	202.000	-0.562	0.574
Ferritin3	20.000	26.000	-0.447	0.655
a. sex = male				
b. Grouping Variable: Aggravation				

Table 4

Analysis of ferritin levels in women using the Mann-Whitney method

sex = female				
Mann-Whitney Test				
Ranks[a]				
Aggravation		N	Mean Rank	Sum of Ranks
	yes	62	59.00	3658.00
	no	55	59.00	3245.00
	Total	117		
a. sex = female				
Test Statistics[a,b]				
	Mann-Whitney U	Wilcoxon W	Z	Asymp. Sig. (2-tailed)
Ferritin	770.000	1805.000	-2.894	0.004
Ferritin2	123.000	189.000	-2.061	0.039
a. sex = female				
b Grouping Variable: Aggravation				

Conclusion

Given the results obtained in this study, it is recommended that the ferritin test be used in patients with COVID-19 to assess the presence of hyperinflammation, predict deterioration of hospitalized patients with COVID-19 infection, and predict lethal outcomes. At the same time, it was observed that the level of ferritin was higher in women than in men. Future clinical-laboratory studies are considered appropriate to comprehensively clarify its pathogenetic and prognostic role in COVID-19, its potential therapeutic value for the purpose of controlling inflammation before organ and system damage.

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