Research Article

Investigation of the Relationship between Serum Ferritin Levels, Lung Involvement and Treatment Methods in COVID 19 Patients: A Retrospective Study

COVID19 Hastalarında Serum Ferritin Düzeyleri, Akciğer Tutulumu ve Tedavi Yöntemleri Arasındaki İlişkinin Araştırılması: Retrospektif Bir Çalışma

Seyda Tuba Savrun, Atakan Savrun

Ordu University, Faculty of Medicine, Department of Emergency Medicine, Ordu, Turkey

Abstract

Aim: COVID-19 disease was identified as cases of pneumonia of unknown origin in China in 2019. It has been reported that after the Covid 19 virus entered the body, the immune system cell was over-activated and there was an intense release of cytokines and the clinical picture worsened accordingly. In addition there is a relationship between ferritin level and cytokine release. In the present study, it was aimed to examine the relationship between the presence of lung involvement and treatment and ferritin levels in cases diagnosed with Covid 19 in the emergency department.

Material and Methods: Cases aged 18 years and older who applied to the emergency department with positive SARS-CoV-2 PCR analysis were included in the study. Demographic characteristics, serum ferritin levels, lung tomography reports (according to the Co-Rads Classification) and treatment modalities (outpatient treatment, inpatient treatment in the service and treatment in the intensive care unit) of the cases were examined.

Results: It was determined that patients with pulmonary involvement had an increased treated in intensive care (p<0.001). It was determined that the serum ferritin level of the patients treated in the service was significantly higher than those of the outpatients (p<0.001). The serum ferritin levels of the patients treated in the intensive care unit were also found to be significantly higher than the serum ferritin levels of the inpatient group (p<0.001).

Conclusion: Cytokine storm is seen in Covid 19 patients. This situation worsens the clinical condition of the patients and causes an increase ferritin level. Serum ferritin levels are increased in patients with lung involvement and increased with severity of the disease. It is recommended to measure serum ferritin levels in the routine follow-ups of Covid 19 patients.

Keywords: Covid-19, lung tomography, ferritin, Covid 19 treatment

Öz

Amaç: COVID-19 hastalığı, 2019 yılında Çin'de menşei bilinmeyen pnömoni vakaları olarak tanımlanmıştır.

Covid 19 virüsü vücuda girdikten sonra ,bağışıklık sistemi hücreleri aşırı aktif hale gelir, yoğun sitokin salınımına sebep olur ve buna bağlı klinik tablo kötüleştiği bildirilmiştir. Ayrıca ferritin düzeyi ile sitokin salınımı arasında da bir ilişki vardır. Sunulan çalışmada acil serviste Covid 19 teşhisi konulan olguların akciğer tutulumu varlığı, tedavi şekilleri ile ferritin düzeyleri arasındaki ilişkinin incelenmesi amaçlanmıştır.

Materyal ve Metot: Acil serviste SARS-CoV-2 PCR pozitifliği saptanan, 18 yaş ve üzeri olgular çalışmaya dahil edilmiştir. Olguların demografik özellikleri, serum ferritin seviyeleri, akciğer tomografı raporları (Co-Rads Sınıflandırması) ve tedavi yöntemleri (ayakta tedavi, serviste yatarak tedavi ve yoğun bakımda tedavi) bakım ünitesi incelenmiştir.

Bulgular: Akciğer tutulumu olan hastaların yoğun bakımda tedavi edilme oranlarının arttığı belirlendi (p<0,001). Hastanede serviste yatarak tedavi edilen hastaların serum ferritin düzeyi,ayaktan tedavi edilen hastalara göre anlamlı derecede dah yüksek olduğu saptandı (p<0,001). Yoğun bakımda yatarak tedavi gören olguların serum ferritin düzeyleri de serviste yatarak tedavi olan diğer olgulara göre anlamlı derecede yüksek bulundu (p<0,001).

Sonuç: Covid 19 hastalarında sitokin fırtınası görülür. Bu durum hastaların klinik durumlarının kötüleşmesine ve serum ferritin seviyesinin artmasına sebep olur. Akciğer tutulumu olan hastalarda serum ferritin seviyeleri yükselir ve hastalığın şiddeti ile artar. Covid 19 hastalarının rutin takiplerinde serum ferritin düzeylerinin ölçülmesi önerilir.

Anahtar Kelimeler: Covid-19, akciğer tomografisi, ferritin, Covid 19 tedavisi

INTRODUCTION

COVID-19 disease was identified as pneumonia cases of unknown origin in China in 2019 (1). In a short time, it spread all over the world and became a pandemic. The disease that caused deaths affected more than 200 countries, more than 6,000,000 confirmed cases and more than 370,000 patients were reported (2).

The clinics of those infected with COVID 19 may differ from patient to patient. The treatment of patients is planned according to their clinical status and lung involvement. In cases such as myalgia, fever, sore throat and dry cough that do not impair the general health of the people; are treated on an outpatient basis. It was reported that she was hospitalized in the service in cases accompanied by severe symptoms such as shortness of breath and / or hypoxemia.It has even been reported that they are treated in intensive care units in cases where clinical conditions with high mortality such as septic shock and acute respiratory distress syndrome (ARDS) develop (3).

After the COVID 19 virus enters the body, the immune system cell becomes over-activated, causing the release of intense amounts of cytokines. This situation worsens the clinical picture of the patients. In addition it has been reported that there is a relationship between ferritin level and cytokine release (4). In this direction, the present study aimed to examine the relationship between the presence of lung involvement and treatment (outpatient treatment, inpatient treatment in the service and treatment in the intensive care unit) and serum ferritin levels in cases diagnosed with COVID 19 in the emergency department.

MATERIAL AND METHOD

The presented study is a cross-sectional and retrospective study. Before starting the study, approval was obtained from the Ethics Committee of Ordu University Faculty of Medicine (2022/51 date: 25.02.2022). The study was conducted in accordance with the Declaration of Helsinki.

Patient data were accessed through the patient registration system. Age, gender, serum ferritin levels, lung tomography reports (according to the Co-Rads Classification) and treatment modalities (outpatient treatment, inpatient treatment in the service and treatment in the intensive care unit) of the patients were examined..

Study populastion

Cases aged 18 years and older who applied to the emergency department between 01/03/2020 and 01/06/2021, whose SARS-CoV-2 PCR analysis was positive and whose data were accessed from the patient information system, were included in the study.

Patients whose data could not be accessed from the patient information system, SARS-CoV-2 PCR analysis was not performed, ferritin level and lung tomography examination were not performed, those under 18 years of age, those with a history of liver malignancy, liver failure,

cirrhosis, hepatitis, those receiving medical treatment that cause deterioration in liver function tests, pregnant women patients with immunodeficiency and cancer were excluded from the study.

Lung Tomography Analysis

The pulmonary tomography reports of the patients included in the study were recorded retrospectively. In the hospital where the study was conducted, the lung tomography reports of COVID 19 patients were evaluated according to the Corads scoring. Cases reported as having a corads score of 3 and above were accepted as having lung involvement (5).

Co-Rads Classification		
Level	**Suspicion Level**	**Findings**
CO-RADS 0	Not evaluated	The review is technically inadequate.
CO-RADS 1	Very low	Normal or non-infectious findings (mild or severe emphysema, perifissural nodules, lung tumor or fibrosis)
CO-RADS 2	low	Typical findings for other infections (Budded branch, centrlobular pattern, lobar or segmental consolidation, cavitation)
CO-RADS 3	Medium/ uncertain	Findings in both COVID-19 and other diseases (central ground glass opacities, pulmonary edema, Homogeneous, diffuse ground-glass appearance with interlobular septal thickening or pleural effusion suggestive ground glass nodules that are not centrlobular or adjacent to the visceral pleura)
CO-RADS 4	High	Suspicious / possible findings for COVID-19
CO-RADS 5	Very high	Typical findings for COVID-19 (bilateral and multifocal, including fissure, adjacent to the visceral pleura, with or without consolidation, ground glass opacities)
CO-RADS 6	Definitive diagnosis	RT-PCR** positive patient

Statistical Analysis

Data were collected retrospectively and analyzed with the IBM SPSS for Windows 22.0 Program. Data are given in numbers and percentages are indicated. Demographic information of the patients and the relationship between thorax tomography involvement and treatment method were examined. The relationship between the patients' serum ferritin levels at the time of admission and their pulmonary involvement and treatment modalities was analyzed using the Mann-Whitney U test. Data were tested for normality using analysis first and than descriptive statistics (number of samples, percentage, mean, standard deviation, median, minimum/maximum) were made. Kolmogorov-Smirnov test and Levene test for variance homogeneity were used. $p < 0.05$ was accepted as significant in the statistical evaluation.

RESULTS

In the study, 580 cases with positive COVID 19 test in the emergency room were included.

It was determined that 53.4% (n=310) of the patients were female and 46.6% (n=270) were male. Median and IQR values were used because the age group of the patients did not fit normal distribution. The median age of all Covid cases was 46/year (IQR 28), the median age of female patients was 44/year (IQR 27), while the median age of male patients was 48/year (IQR 26). No correlation was found between them according to age groups (p>0.05).

The treatment modalities of the patients were examined; 51.9% (n=301) were treated as outpatients, 44.5% (n=258) were hospitalized in the service and 3.6% (n=21) were in the intensive care unit has been treated.

Lung tomography reports of the patients who applied to the emergency department were reported as corads of 3 and above were considered positive. It was determined that 82.2% (n=477) patients had negative CT scans and 17.8% (n=103) patients had positive CT scans. Treatment modalities according to involvement were analyzed using the chi-square test.

Positive tomography uptakes increased the inpatient treatment requirements of the patients (p<0.001). Tomography involvement was detected in 6.3% (n=19) of 301 outpatients, 25.2% (n=65) of 258 hospitalized patients were treated in the service and 90% of 21 patients treated in the intensive care unit. It was determined that; 5 (n=19) of them had tomography involvement. Accordingly a statistically significant relationship was found between tomography involvement and treatment modalities of covid patients (p<0.05).

Serum ferritin levels were measured in all patient groups. Median values were used because they did not fit the normal distribution. The median serum ferritin was 103.45 ml/l (IQR 210.8).

The relationship between serum ferritin levels and lung tomography involvement of COVID 19 patients was investigated. While the median ferritin level of the patients without lung tomography involvement was 266.9ml/l, the median ferritin level of the patients with lung tomography involvement was 399.8ml/l. It was determined that there was a significant difference between the patient groups with and without lung tomography involvement (p<0.001).

The relationship between serum ferritin levels and treatment modalities of COVID 19 patients was investigated. Ferritin level of the patients receiving outpatient treatment was 229.80ml/l, the serum ferritin levels of the patients treated in the service were found to be 338.57ml/l and there was a statistically significant relationship between them (p<0.001). Serum ferritin levels of patients receiving outpatient treatment and patients receiving intensive care inpatient treatment were 152.79ml/l and 286.33ml/l respectively. It was found that there was a statistically significant relationship between them (p<0.001). In addition, the serum ferritin levels of COVID 19 patients receiving inpatient treatment in the service and inpatient treatment in the intensive care unit were found respectively 133.33ml/l and 221.90ml/l. It was found that there was a statistically significant relationship between them (p<0.001)

DISCUSSION

PIn line with the source information; the mechanism of disease in humans how the disease progresses and the effect of the cases on the immune system are still not fully known. However, some opinions have been focused on. The most common among them; it is thought to be associated with the inflammatory cytokine storm during the period of COVID 19 infection. Cytokine storm is an uncontrolled and dysfunctional immune response due to the immunopathogenic mechanism of COVID-19. Meanwhile, many inflammatory cytokines such as TNF-α, IL-6, IL-12 and IL-8 are released (6). It has been reported that cytokine storm causes negative effects on many tissues in the body. Most affected structure among these tissues is the lung tissue (2). In patients with lung involvement; diffuse alveolar epithelial destruction, hyaline membrane, capillary damage, capillary bleeding, alveolar septal fibrous proliferation and/or pulmonary hypertension may occur (7). It may have an effect on acute respiratory distress syndrome (ARDS) and systemic organ failure and even mortality in the further stages of the disease (8). Another study reported that COVID 19 causes different levels of damage to the lungs depending on the severity of the disease (9). In presented study; the pulmonary involvement status of patients diagnosed with COVID 19 in the emergency department was examined and it was found that a large proportion of 17.8% had lung involvement, similar to the literature. Presence of lung involvement and degree of disease guide the planning of treatment modalities. Treatment modalities also differ from patient to patient. While some cases are treated as an outpatient, some are treated in the hospital COVID 19 service and some are treated in intensive care units (2). The presence of lung tomography involvement is among the important determinants of treatment modalities (10). In a similar

study, it was stated that lung imaging plays an important role in detecting the lung involvement of COVID 19, determining the severity of the disease and even planning the treatment of the patient (11). In another study, it was reported that the co-rads classification is useful in detecting the degree of lung involvement of the COVID 19 disease and in making decisions in the treatment of the disease (12). In the presented study; The relationship between pulmonary tomography involvement and hospitalization was examined. It was found that patients with lung involvement were more likely to receive inpatient treatment (p<0.001).The treatment of patients in the Covid service or intensive care unit while receiving inpatient treatment was examined and a significant correlation was found with lung

involvement (p<0.001). This can be explained by the high rate of treatment in patients with lung involvement in the covid service and intensive care units.

Many systems in the body are affected due to COVID 19 infection. Among these systems, iron homeostasis and ferritin levels were also found to be related (13). It has been reported that serum ferritin levels increase and serum ferritin levels can be used to predict mortality, especially in the case of worsening of the disease due to cytokine storm (14). Ferritin is an iron-storing protein. In clinical practice, it is often used for the diagnosis of iron deficiency anemia as it is associated with serum iron levels (15). Ferritin consists of two different subunits; H and L. In particular, it is known that H-ferritin has both proinflammatory and immunosuppressive functions and even the level of ferritin increases in viral infections as a marker of viral replication (16). Colafrancesco et al. reported that there is a correlation between high ferritin level and disease severity in COVID 19 patients (17). Taneri et al. reported that as the severity of the disease in COVID 19 patients increased the ferritin level also increased (18). Similarly, in the presented study; serum ferritin levels of patients with lung tomography involvement were found to be statistically significantly higher than those of patients without lung involvement (p<0.001). In addition, the patients receiving outpatient treatment and inpatient treatment in the service are compared; it was determined that the serum ferritin level of the group receiving inpatient treatment in the service was significantly higher than the other group (p<0.001). The serum ferritin levels of the patients receiving treatment in the intensive care unit were also found to be significantly higher than the serum ferritin levels of the inpatient group (p<0.001). This situation can be explained as the increase in cytokine storm in patients worsens the clinical condition and causes an increase in ferritin level.

CONCLUSION

In COVID 19 patients, the presence of lung involvement adversely affects the clinical course of the disease.

It has been determined that serum Feritin levels increase in diseases such as COVID 19 in which cytokine storms occur. In addition, it can be said that in cases with lung involvement of COVID 19 serum ferritin levels increase and the severity of the disease increases. It is thought that serum ferritin levels should be checked in the routine follow-ups of COVID 19 patients and the change of serum ferritin levels can give an idea about the course of the disease.

REFERENCES

1. Zhou P, Yang X, Wang X, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. nature 2020; 579;7798:270-3.

2. Saribas MS, Tomakin M, Ozkay I. Retrospective analysis of lactate levels, lung involvement and treatment methods of patients with COVID-19 who applied to the emergency department. Int Target Med J. 2022;1:5-9.

3. Akcay S, Özlü T, Yılmaz A. Radiological approaches to COVID-19 pneumonia. Turk J Med Sci. 2020;50:604-10.

4. Gormüs Uzay. Covid-19: Molecular and Clinical Approach. Istanbul University Press, Istanbul.2020;47-55.

5. Pekcevik Y, Belet U. Patient management in the radiology department, the role of chest imaging during the SARS-CoV-2 pandemic and chest ct findings related to COVID-19 Pneumonia. J Tepecik Education Research Hospital. 2020;30:195-212.

6. Mehta P, McAuley DF, Brown M, et al. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020; 395:1033–34.

7. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;55.

8. Moore BJB, June CH. Cytokine release syndrome in severe COVID 19. Science. 2020;368:473-4.

9. Fan L, Liu S. CT and COVID-19: Chinese experience and recommendations concerning detection, staging and follow-up. Eur Radiol. 2020;30:5214-6.

10. Bao C, Liu X, Zhang H, et al. Coronavirus Disease 2019 (COVID-19) CT Findings: a systematic review and meta-analysis. J Am Coll Radiol. 2020;17:701-9.

11. Prokop M, van Everdingen W, van Rees Vellinga T, et al. COVID-19 standardized reporting working group of the dutch radiological society. Radiology. 2020;296:97-104.

12. Bellini D, Panvini N, Rengo M, et al. Diagnostic accuracy and interobserver variability of CO-RADS in patients with suspected coronavirus disease-2019: a multireader validation study. Eur Radiol. 2021;31:1932-40.

13. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood. 2019;133:40–50.

14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID 19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.

15. Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe or critical type 2019 novel coronavirus pneumonia. Lab Invest. 2020;100:794-800.

16. Kernan KF, Carcillo JA. Hiperferritinemi ve inflamasyon. Int Immünol. 2017; 29:401-9.

17. Colafrancesco S, Alessandri C, Conti F, Priori R. COVID-19 has gone bad: A new character on the spectrum of hyperferritinemic syndrome? autoimmune. Rev. 2020;19:102573.

18. Taneri PE, Gómez-Ochoa SA, Llanaj E, et al. Anemia and iron metabolism in COVID-19: A systematic review and meta-analysis. Avro.J Epidemiol. 2020;35:763-73.