# Prognostic significance of ferritin, D-dimer, lymphocyte monocyte ratio and some biochemical markers in patients with SARS-CoV-2

Ali Eser[1]*, Nang Hseng Kyio[2]

1 Bezmialem Vakif University, Department of Hematology, Istanbul, TR
2 Bezmialem Vakif University, Department of Internal Medicine, Istanbul,TR
* **Corresponding Author:** Ali Eser **E-mail:** dralieser@gmail.com

## ABSTRACT

**Objective:** The disease caused by COVID-19 that progress with severe acute respiratory distress syndrome (SARS) and can result in death, spread all over the world emerging from China. It is important to know the cases that expected to show a fatal course beforehand due to the cases resulting in death. In this study we analyzed the changes observed in ferritin, D-dimer, lymphocyte and monocyte levels, which are easily measured in patients, and evaluated how these determinants can be used as prognostic factors of the disease.

**Material and Methods:** One hundred patients who applied to Bezmialem Vakif University Hospital between April 2020 – May 2020, who were COVID-19 PCR positive, and had infiltration in their pulmonary computerized tomography scan, were included in the study. These patients were divided into two groups as normal inpatient and intensive care unit patients. Ferritin, D-dimer, lymphocyte and monocyte levels, ALT, AST, LDH, and CRP levels were recorded at the time of diagnosis. Lymphocyte/monocyte ratio (LMR) was calculated.

**Results:** Ferritin and D-dimer levels, ALT, AST, LDH, and CRP levels were found to be statistically and significantly higher in the exitus group compared to alive group (p<0.05). LMR, on the other hand, was found to be statistically and significantly lower in the mortality group (p<0.05).

**Conclusion:** Ferritin, D-dimer levels and LMR can be determinant laboratory findings in the prognosis of the disease that are detected in the Covid-19 patients at the dime of diagnosis. More studies should be conducted to objectively evaluate disease-related prognostic factors.

**Key words:** Ferritin, D-dimer, LMR, SARS-CoV-2, COVID-19

## INTRODUCTION

COVID-19 (SARS-CoV 2) infection have become a world pandemic in March 2019, emerging from China's state Wuhan, in December 2019 (**1**). SARS-CoV2 can primarily cause respiratory tract infection as well as a clinical picture affecting hematopoietic, gastrointestinal, cardiovascular, neurological and immune systems (**2,3**). Though the outbreak is likely to spread to humans as a result of a zoonotic transmission, there is evidence of person-to-person transmission through direct contact or droplets from an infected person (**4**). The common symptoms of SARS-CoV-2 are as follows; fever, cough, back and joint pain, dyspnea, hemoptysis, and diarrhea. The clinical spectrum of the disease can range from asymptomatic or a mild upper respiratory tract symptom to acute pneumonia, respiratory failure, and death (**5**).

Various hematological and biochemical parameters related to lymphopenia, monocytosis, hyperferritinemia, high lactate dehydrogenase (LDH), C-reactive protein (CRP), fibrinogen and d-dimer levels have been reported in Covid-19 patients (**6-8**). The lymphocyte/ monocyte ratio (LMR) is an appropriate index that can be calculated from a complete blood count, and many studies have shown a prognostic value in a variety of conditions such as sepsis, lymphoma and malignant tumors (**9-11**).

The purpose of this study is to retrospectively examine some of the hematological and biochemical parameters of the patients hospitalized due to Covid-19 infection (inpatient and intensive care patients), and is to evaluate the effect of these parameters on the course of the disease and prognosis.

## MATERIAL AND METHODS

One hundred patients who applied to our center between April 2020 – May 2020, who were Covid-19 PCR positive, and had infiltration in their thorax computed tomography (CT) scan, were included in the study.

These patients were divided into two groups such as alive and exitus according to their last status. Hematological and biochemical parameters such as ferritin, d-dimer, CRP, absolute lymphocyte count (ALC), absolute monocyte count (AMC), alanine aminotransferase (ALT) aspartate aminotransferase (AST), alkaline phosphatase (ALP), and LDH were checked from the peripheral blood.

The baseline hematological and biochemical values of all patients were retrospectively analyzed in the following phases; when they were first hospitalized after treatment and before they were discharged (in patients who survived) and before death (in patients who died). The ratios of lymphocyte and monocyte absolute numbers (LMR) were calculated.

### Statistical Analysis

Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with Kolmogorov-Simirnov test. Independent Samples T test and Mann-Whitney U test were used for the comparison of quantitative data. Wilcoxon test were used for the repeated measurement analysis. Chi-Square test was used for the comparison of the comparison of qualitative data. Logistic Regression was used to show the effect level. SPSS 27.0 was used for statistical analyses.

## RESULTS

One hundred patients who resulted as positive for Covid-19 PCR test were included in the study. All the patients had thorax CT scans consistent with typical viral pneumonia. The follow-up and treatment of the half of the patients who were included in the study were carried out in inpatient clinic, the other half were followed in the intensive care unit (ICU). Fifty nine of the patients were male and 41 of the patients were female.

Median age of the patients was 64,5 (range: 47-89). The laboratory findings of the patients at the time of diagnosis are as follows; ferritin level median 379 (range:19-21130) ng/dl, D-dimer level median 307 (140-6422) ng/ml, ALC median 1,1 (range:0,2-7)x103/ul, AMC median 0,5 (range:0,1-2)x103/ul, LMR median 2,38 (range: 0,34-8,54), CRP median 81,5 (range:2-325) mg/L, ALT median 30 (range:12-930) U/L, AST: median 26 (range: 9-414) U/L, ALP median 62,5 (range:27-555) U/L, LDH median 322 (range:159-870) U/L.

The demographic characteristics, and laboratory findings of the patients at the time of diagnosis are summarized in Table 1.

The age of the patients was significantly higher in exitus group than in the alive group (p<0.05) (Figure 1). There was no significant difference regarding the gender in both groups. The rate of mortality in ICU patients were significantly higher than inpatient clinic patients (p<0.05) (Figure 2).

Ferritin levels before and after treatment were significantly higher in the exitus group than in the alive group (p<0.05). After treatment, ferritin values have shown a significant decrease in the alive group, and increase in the exitus group (p<0.05) (Figure 3).

D-dimer levels before and after treatment were significantly higher in the exitus group than in the alive group (p<0.05). After treatment, D-dimer values have shown a significant decrease in the alive group, and increase in the exitus group (p<0.05). The increase of d-dimer, after treatment, was significantly higher in the exitus group than in the alive group (p<0.05) (Figure 4).

The ALC level before and after treatment was significantly lower in the exitus group when compared to the alive group (0.05). After treatment, the ALC level has shown a significant increase in the alive group, and decrease in the exitus group (p<0.05). After treatment, the change in the ALC level in the exitus significantly differed from the alive group (p<0.05).

The AMC level before and after treatment did not differ significantly between the two groups (p<0.05). After treatment, the AMC level has shown a significant increase in the alive group, and decrease in the exitus (p<0.05). After treatment, the change in the AMC level in the exitus group significantly different from the alive group (p<0.05).

LMR before and after treatment was significantly lower in the exitus group than in the alive group (p<0.05). After treatment, LMR did not show a significant difference in both groups (p>0.05). After treatment, the change in LMR in the exitus group significantly differed from the alive group (p<0.05).

CRP, ALT, AST, and LDH levels before and after treatment were significantly higher in the exitus group when compared to the alive group (p<0.05). ALP level did not show a significant difference in both groups.

In the univariate model, a significant (p<0.05) difference was observed between the exitus and alive groups in terms of age, pre-treatment and post-treatment ferritin, D dimer, LMR, CRP, ALT, AST and LDH values (Table 3).

In the multivariate model, a significant difference (p <0.05) was observed between CRP and post-treatment ferritin and LMR between exitus and alive groups (Table 3).

**Table 1:** Patient characteristics

| | | Min-Max | | Median | Mean±sd/n-% |
|---|---|---|---|---|---|
| **Age** | | 47,0 | 89,0 | 64,5 | 66,3±10,6 |
| **Gender** | **Female** | | | | 41 (41,0%) |
| | **Male** | | | | 59 (59,0%) |
| **Intensive Care Hospitalization** | (-) | | | | 50 (50,0%) |
| | (+) | | | | 50 (50,0%) |
| **Ferritin** | | 19,0 | 21130 | 379,0 | 1196,8±2527,0 |
| **D-Dimer** | | 140,0 | 6422 | 307,0 | 887,3±1218,7 |
| **ALC** | | 0,2 | 7 | 1,1 | 1,4±1,1 |
| **AMC** | | 0,1 | 2 | 0,5 | 0,5±0,3 |
| **LMR** | | 0,34 | 8,54 | 2,38 | 2,88±1,73 |
| **CRP** | | 2,0 | 325,0 | 81,5 | 94,1±76,0 |
| **ALT** | | 12,0 | 930,0 | 30,0 | 62,1±116,5 |
| **AST** | | 9,0 | 414,0 | 26,0 | 45,0±61,7 |
| **ALP** | | 27,0 | 555,0 | 62,5 | 86,2±78,9 |
| **LDH** | | 159,0 | 870,0 | 322,0 | 357,9±159,4 |

ALC: Absolute lymphocyte count, AMC: Absolute monocyte count, LMR: Lymphocyte/Monocyte ratio , CRP: C-reaktif protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphataseLDH: Lactate dehydrogenase
Normal laboratory values: Ferritin: 21-274 mg/dl, D-Dimer: 0-300 ng/ml, ALC: 0,6-3,4x103/ul, AMC: 0,19-0,77x103/ul, ALT: 0-55 U/L, AST: 5-34 U/L, ALP: 40-150 U/L, LDH: 125-220 U/L

**Table 2:** Pre-treatment and post-treatment laboratory values of patients

| | | | Mortality (-) | | | Mortality (+) | | | p | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mean±sd | | Median | Mean±sd | | Median | | |
| | Age | | 62,3 ± | 9,2 | 61,0 | 70,5 ± | 10,5 | 71,0 | **0,000** | m |
| | Gender | Female | 20 | 39,2% | | 21 | 42,9% | | 0,711 | x² |
| | | Male | 31 | 60,8% | | 28 | 57,1% | | | |
| | Intensive Care Hospitalization | (-) | 50 | 98,0% | | 0 | 0,0% | | **0,000** | x² |
| | | (+) | 1 | 2,0% | | 49 | 100,0% | | | |
| *Ferritin* | Before Treatment | | 375,4 ± | 506,5 | 271,0 | 2051,7 ± | 3382,3 | 886,0 | **0,000** | m |
| | After Treatment | | 268,6 ± | 220,2 | 222,0 | 5909,3 ± | 11928,2 | 2560,0 | **0,000** | m |
| | Intra Goup Difference | | -106,8 ± | 409,5 | -19,0 | 3857,6 ± | 11212,7 | 400,0 | **0,000** | m |
| | Intra Group p | | | **0,034** | w | | **0,000** | w | | |
| *D-Dimer* | Before Treatment | | 644,9 ± | 1049,4 | 262,0 | 1139,7 ± | 1337,5 | 497,0 | **0,001** | m |
| | After Treatment | | 435,5 ± | 535,3 | 263,0 | 2500,6 ± | 4070,0 | 1568,0 | **0,000** | m |
| | Intra Goup Difference | | -209,4 ± | 911,0 | -14,0 | 1360,9 ± | 3907,0 | 525,0 | **0,000** | m |
| | Intra Group p | | | **0,253** | w | | **0,000** | w | | |
| *ALC* | Before Treatment | | 1,4 ± | 0,7 | 1,3 | 1,4 ± | 1,4 | 0,9 | **0,008** | m |
| | After Treatment | | 1,6 ± | 0,6 | 1,6 | 1,3 ± | 1,1 | 1,0 | **0,001** | m |
| | Intra Goup Difference | | 0,2 ± | 0,7 | 0,3 | -0,1 ± | 1,5 | -0,1 | 0,122 | m |
| | Intra Group p | | | **0,051** | w | | **0,612** | w | | |
| *AMC* | Before Treatment | | 0,5 ± | 0,2 | 0,5 | 0,6 ± | 0,4 | 0,6 | 0,069 | m |
| | After Treatment | | 0,5 ± | 0,2 | 0,5 | 0,7 ± | 0,5 | 0,5 | 0,141 | m |
| | Intra Goup Difference | | 0,03 ± | 0,19 | 0,01 | 0,12 ± | 0,47 | 0,07 | 0,456 | m |
| | Intra Group p | | | 0,370 | w | | 0,258 | w | | |
| *LMR* | Before Treatment | | 3,37 ± | 1,74 | 2,97 | 2,36 ± | 1,57 | 1,86 | **0,000** | m |
| | After Treatment | | 3,70 ± | 1,78 | 3,41 | 2,16 ± | 1,42 | 1,82 | **0,000** | m |
| | Intra Goup Difference | | 0,32 ± | 1,90 | 0,40 | -0,20 ± | 1,73 | -0,21 | 0,063 | m |
| | Intra Group p | | | 0,097 | w | | 0,395 | w | | |
| | CRP | | 58,8 ± | 50,4 | 42,0 | 130,8 ± | 81,0 | 125,0 | **0,000** | m |
| | ALT | | 31,0 ± | 17,5 | 26,0 | 94,4 ± | 160,0 | 42,0 | **0,000** | m |
| | AST | | 29,5 ± | 22,2 | 23,0 | 61,2 ± | 82,5 | 38,0 | **0,008** | m |
| | ALP | | 80,0 ± | 78,0 | 60,0 | 92,6 ± | 80,0 | 72,0 | 0,345 | m |
| | LDH | | 292,2 ± | 93,2 | 289,0 | 426,2 ± | 184,4 | 379,0 | **0,000** | m |

ᵐ : Mann-whitney u test, x²: Chi-square test **ALC:** Absolute lymphocyte count, **AMC:** Absolute monocyte count, **LMR:** Lymphocyte/Monocyte ratio, **CRP:** C-reactive protein, **ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **ALP:** Alkaline phosphatase, **LDH:** Lactate dehydrogenase

**Table 3:** Univariate and multivariate logistic regression of risk factors associated with mortality

| | Univariate Model | | | | Multivariate Model | | | |
|---|---|---|---|---|---|---|---|---|
| | OR | % 95 CI | | p | OR | % 95 CI | | p |
| **Age** | 1,086 | 1,039 - 1,135 | | *0,000* | | | | |
| **Ferritin (BT)** | 1,002 | 1,001 - 1,002 | | *0,001* | | | | |
| **Ferritin (AT)** | 1,004 | 1,002 - 1,006 | | *0,001* | 1,006 | 1,002 - 1,009 | | *0,002* |
| **D-Dimer (BT)** | 1,000 | 1,000 - 1,001 | | *0,052* | | | | |
| **D-Dimer (AT)** | 1,002 | 1,001 - 1,003 | | *0,000* | | | | |
| **LMR (BT)** | 0,678 | 0,516 - 0,891 | | *0,005* | | | | |
| **LMR (AT)** | 0,524 | 0,379 - 0,724 | | *0,000* | 0,223 | 0,087 - 0,571 | | *0,002* |
| **CRP** | 1,017 | 1,009 - 1,025 | | *0,000* | 1,016 | 1,002 - 1,031 | | *0,027* |
| **ALT** | 1,031 | 1,010 - 1,053 | | *0,004* | | | | |
| **AST** | 1,017 | 1,001 - 1,034 | | *0,041* | | | | |
| **LDH** | 1,007 | 1,003 - 1,010 | | *0,000* | | | | |

Logistic Regression (Forward LR), **BT:** Before treatment,   **AT:** After treatment, **LMR:** Lymphocyte/Monocyte ratio**, CRP:** C-reactive protein**, ALT:** Alanine aminotransferase, **AST:** Aspartate aminotransferase, **ALP:** Alkaline phosphatase, **LDH:** Lactate dehydrogenase
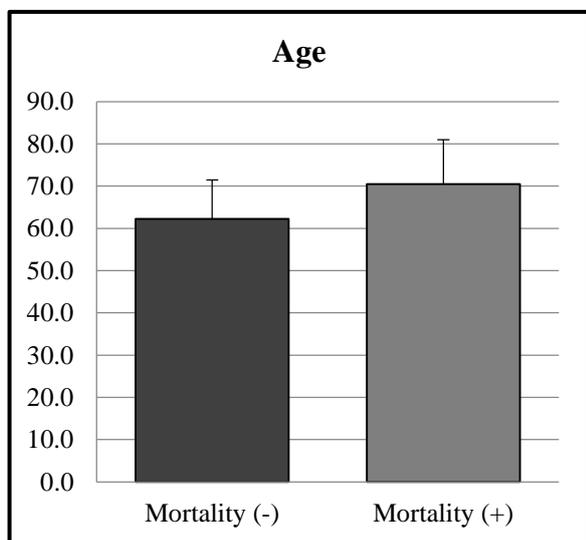

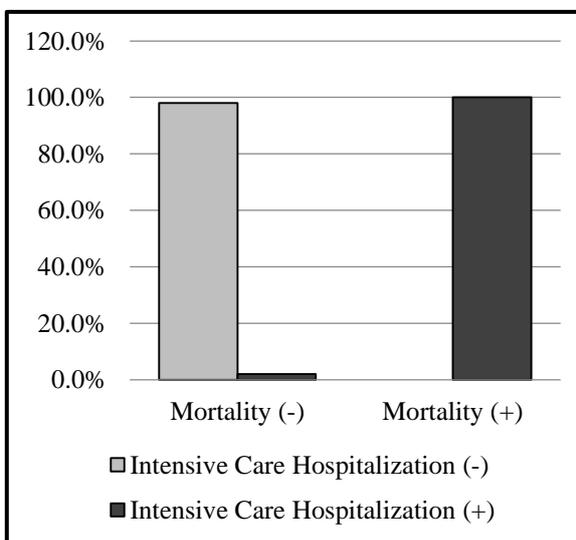
**Figure 1:** Age and mortality relationship in C-19 patients



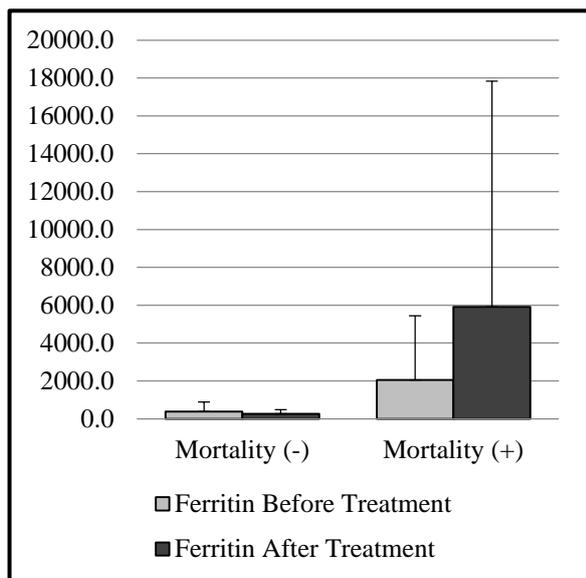**Figure 2:** Intensive care and mortality relationship in C-19 patients



**Figure 3:** Ferritin level and mortality relationship in C-19 patients
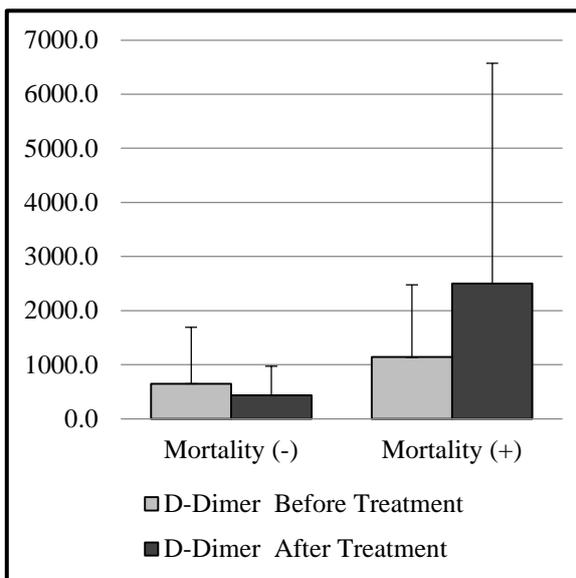


Figure 4: D-Dimer level and mortality relationship in C-19 patients

# DISCUSSION

In Covid-19 patients, cytokine storm occurs in 7-14 days after the first symptoms begin, with an increase in cytokine and inflammatory mediators (12). Cytokine secretion in actively infected areas, especially in the macrophages in pulmonary parenchyma, can cause serum ferritin secretion (13). Previous studies show that ferritin is associated with poor prognosis in severe Covid-19 patients and hyperferritinemia may be a new parameter in SARS-CoV-2(6,14).

In this study, we examined CRP and ferritin levels between two groups as inflammatory parameters. There was a significant difference in CRP and Ferritin levels in the groups with and without mortality. Mean ferritin levels in the alive group were found to be two times the normal at the initial examination. In the exitus group, basal mean ferritin levels were > 2000 ng/dl. So, it was 10 times higher compared to the alive group. The prognosis and mortality of the patience is related to high level of ferritin. Early and intensive anti-inflammatory treatments can be planned by looking at basal ferritin levels. Plasma exchange that decreases cytokine and ferritin levels, can be useful for severe Covid-19 patients.

D-dimer level in COVID-19 patients can be high due to reasons such as intense inflammation, insufficient anti-inflammatory response, endothelial damage, sepsis, and disseminated intravascular coagulation (DIC) (15). High D-dimer level indicates hypercoagulability or thrombosis. The study by Litao and ark. showed that patients with mortality had > four times the increase in D-dimer, in hospital admissions (16). In our study, D-dimer level showed a mean two times the increase in the alive group as well, but in the exitus group the increase was four times. This increase was statistically significant (p<0.05). While there was a significant decrease in the D-dimer level after treatment in the alive group, there was a significant increase in the exitus group. Severe Covid-19 patients may develop increased coagulability and thrombosis together with DIC. This situation causes high risk of venous thromboembolism (VTE) (17). D-dimer levels in predicting VTE in patients with severe SARS-CoV-2 (18).

If 1.5 µg/mL was used as the cut-off value for D-dimer to predict VTE, the sensitivity, specificity, Positive predictive value, and Negative predictive value were 85.0%, 88.5%, 70.8%, and 94.7%, respectively (18). In severe Covid-19 patients who present with high D-dimer value, administration of anticoagulants at therapeutic dose instead of prophylaxis dose may have a positive effect on mortality. Covid-19 can directly infect angiotensin converting enzyme-2 (ACE-2) receptors on lymphocytes' surfaces. As a result of the cytokine storm that develops secondary to excessive inflammation with the lysis of these cells, the increase in interleukins such as IL-1, IL-6, TNF-alpha induce apoptosis and develop lymphopenia (19,20). It was detected in our study that in the alive group, the lymphopenia the treatment, improved after treatment. In the exitus group lymphopenia was significantly lower than in the alive group, and higher decrease was detected in the follow-up period. It was thought that the degree of lymphopenia may be directly related to mortality, therefore, early initiation of anticytokines such as IL-1 receptor blocker anakinra and IL-6 receptor blocker tocilizumab may improve the prognosis of the disease.

Though LMR has been shown as a parameter related to prognosis in patients with sepsis, lymphoma and cancer, there is not enough information regarding Covid-19 patients (9,10). In a study conducted by Russel et al., LMR was detected to be lower in patients who, previously, had respiratory tract involvement due to influenza virus (9). In our study, although ALC was lower in the exitus group than in the alive group, no significant difference was found between the two groups in AMC. Therefore, LMR in exitus group was detected to be significantly lower than the alive group. In the exitus group, the mean LMR as 2,36 cut-off value is acceptable. It was thought that the LMR  at initial diagnosis could be used as a predictive value for  prognosis and mortality of the patients.

COVID-19 virus can connect to ACE-2 receptors on cholangiocytes, leading to liver damage secondary to cholangiocyte dysfunction and systemic inflammatory response (21). The liver postmortem biopsy of a patient who deceased due to COVID-19 indicated microvesicular steatosis that showed liver damage, mild lobular and portal activity (22). In our study, ALT, AST, LDH levels in the exitus group were found to be significantly higher (p<0.05) compared to the alive group. Liver test abnormalities can be used as a determinant for disease severity, and mortality risk. A recent study revealed that patients with elevated AST level were at great risk of progressing to severe disease those require close monitoring (23). Studies conducted in patients with symptomatic COVID-19 showed a decrease in interferon (IFN) expression in both human bronchial cells and circulating mononuclear blood cells (24). Therefore, interferon therapy may be life-saving in patients with low LMR, high ferritin and D-dimer levels at the time of diagnosis.

# CONCLUSION

Covid-19 is a new entity for everybody and there are still many things unknown. It is essential to know the biochemical indicators that show poor prognosis beforehand, as some of the cases result in death with a rapid course. In patients with high ferritin and D-dimer levels and low LMR at the time of diagnosis, early initiation of treatments such as immune plasma therapy, IL-1 and IL-2 inhibitors, and interferon may reduce mortality rates.

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