Original Article / Özgün Araştırma

The Relationship Between Inflammatory Indicators and the Severity of the Disease in Coronavirus Disease

Koronavirüs Hastalığında Hastalık Şiddeti ve Enflamasyonla İlgili Göstergeler Arasındaki İlişki

Recai Aci[1], Mukadder Erdem[1], Göksenin Ünlügüzel Üstün[1], Utku Duran[2], Adem Keskin[3], Melek Bilgin[4]

[1]University of Health Sciences Turkey, Samsun Training and Research Hospital, Department of Biochemistry, Samsun, Turkey
[2]Zonguldak Bülent Ecevit University, Çaycuma Food and Agriculture Vocational School, Veterinary Department, Zonguldak, Turkey
[3]Aydın Gynecology and Pediatrics Hospital, Clinic of Biochemistry, Aydın, Turkey
[4]University of Health Sciences Turkey, Health Sciences University, Samsun Training and Research Hospital, Department of Microbiology, Samsun, Turkey

Keywords
Coronavirus disease, C-reactive protein, ferritin, procalcitonin, neutrophil-lymphocyte ratio, inflammation

Anahtar Kelimeler
Koronavirüs hastalığı 2019, C-reaktif protein, ferritin, prokalsitonin, nötrofil-lenfosit oranı, enflamasyon

Received/Geliş Tarihi : 10.11.2020
Accepted/Kabul Tarihi : 09.11.2021

doi:10.4274/meandros.galenos.2021.65477

Address for Correspondence/Yazışma Adresi:
Mukadder Erdem MD,
University of Health Sciences Turkey, Samsun Training and Research Hospital, Clinic of Biochemistry, Samsun, Turkey
Phone : +90 362 311 15 00
E-mail : dr.mukadder@hotmail.com
ORCID ID: orcid.org/0000-0001-7796-3671

Abstract

Objective: The complete blood count parameters and biochemical biomarkers important for the follow-up of patients in the inflammatory process of coronavirus disease 2019 (COVID-19) inpatients in the ward, and intensive care were analysed retrospectively.

Materials and Methods: One hundred thirty inpatients in the intensive care and 147 inpatients in the COVID-19 ward were included in this study. Additionally, 47 healthy people were added as a control group. Whole blood parameters [white blood cell (WBC), lymphocyte, monocytes, platelet, neutrophil, monocyte/lymphocyte (MLR), neutrophil/lymphocyte (NLR)], ferritin, C-reactive protein (CRP), procalcitonin, erythrocyte sedimentation ratio (ESR) and albumin values of these patients and individuals were analyzed retrospectively. Obtained laboratory values were compared.

Results: The procalcitonin, CRP, ESR, WBC, neutrophil, NLR, MLR, ferritin and procalcitonin values of the patients the intensive care patients were higher than the other two groups ($p<0.001$). However, the albumin and lymphocyte levels of the patients in the intensive care unit were lower ($p<0.001$). Additionally, the CRP and ESR values of the inpatients in the ward were higher than those in the control group ($p<0.001$).

Conclusion: Hematological findings such as lymphocytes, NLR, WBC and inflammatory findings such as procalcitonin, ESR, CRP, and ferritin are associated with disease severity. Additionally, increased NLR levels may indicate aggravation of the inflammatory process and the possibility of intensive care admission. Therefore, monitoring of inflammatory findings, and NLR, can help predict and treat the prognosis of COVID-19.

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) servis ve yoğun bakım ünitelerinde takip edilen hastaların tam kan parametreleri ile enflamatuvar süreçte hastalığın prognozu açısından önemli olan biyokimyasal biyobelirteçlerin değerleri retrospektif olarak incelendi.

Gereç ve Yöntemler: Bu çalışmaya, COVID-19 yoğun bakımda yatan 130 hasta ve COVID-19 serviste yatan 147 hasta dahil edilmiştir. Ayrıca çalışmaya, kontrol grubu olarak sağlıklı 47 birey eklenmiştir. Bu hastaların ve bireylerin tam kan parametreleri [WBC (beyaz kan hücresi), lenfosit, monosit, nötrofil, trombosit, nötrofil/lenfosit

(NLR), monosit/lenfosit (MLR)] ile C-reaktif protein (CRP), prokalsitonin, ferritin, eritrosit sedimantasyon oranı (ESR) ve albümin değerleri retrospektif olarak incelendi. Elde edilen laboratuvar sonuçları karşılaştırıldı.

Bulgular: Yoğun bakımda yatan hastaların prokalsitonin, CRP, ESR, WBC, nötrofil, NLR, MLR, ferritin ve prokalsitonin ortalama değerleri, hem serviste yatan hastalardan hem de kontrol grubundan daha yüksekti (p<0,001). Diğer taraftan yoğun bakımda yatan hastaların albümin ve lenfosit ortalama değerleri, diğer iki gruba göre daha düşüktü (p<0,001). Ayrıca serviste yatan hastaların CRP ve ESR ortalama değerleri, kontrol grubundan daha yüksekti (p<0,001).

Sonuç: WBC, lenfosit, NLR gibi hemotolojik parametreler ile prokalsitonin, CRP, ESR ve ferritin gibi immün-enflamatuvar parametrelerin hastalık şiddeti ile ilişkili olduğu ve hastalığın ilerlemesi için potansiyel olarak önemli risk faktörleri olarak kullanılabileceği görülmüştür. Ayrıca artmış bir enflamatuvar süreci yansıtan artmış NLR seviyeleri yoğun bakıma yatış ihtimalini gösterebilir. Bu nedenle, immün-enflamatuvar parametrelerin, özellikle NLR'nin sürveyansı, COVID-19'un teşhisinde, erken taramasında ve tahmininde ve ciddi hastalıkların tedavisinde yardımcı olabilir.

Introduction

Coronavirus disease-2019 (COVID-19) outbreak, which arose in China in the last months of 2019, quickly caused a pandemic. Although measures were taken to prevent spread, the number of people caught with COVID-19 reached approximately 37 million worldwide as of October, while the number of people who died of this disease exceeded 1 million (1). COVID-19 can cause respiratory failure, severe pneumonia, high fever, joint pain and even death (2). Studies conducted to date on inflammation markers in viral respiratory infections have played an major role in the rapid progress of our knowledge about the prognosis of COVID-19 (3).

C-reactive protein (CRP) is a biomarker of acute phase-response in inflammation, infection and tissue damage that can be used as a marker of inflammation (4). Procalcitonin levels have a more important role than CRP and white blood cell (WBC) count in separating one bacterial infection from other inflammatory process. In studies conducted on COVID-19 disease, a significant increase has been found in procalcitonin levels of groups whose disease had a severe course (5). Erythrocyte sedimentation rate (ESR) is not specific for any disease; however, it is used in combination with other tests to find out the presence of increased inflammatory activity. ESR has been long been used as a "disease indicator" due to its repeatability and low cost (6). Ferritin is an acute phase protein as demonstrated in both infectious and non-infectious diseases. High serum ferritin is a useful marker for a possible disease progression towards the critical development of COVID-19 (7).

A large number of studies have shown an increase in neutrophils with the decrease in lymphocyte in patients with COVID-19 (8-10). The neutrophil/lymphocyte ratio (NLR), obtained by the ratio of rising neutrophils to falling lymphocytes in infection, is a very strong indicator of the systemic inflammatory state (11).

The aim of our study is to evaluate the relationship between the hematological and inflammatory biomarkers and the severity of the disease that are important in the course of the COVID-19 disease. This evaluation was made as a result of comparing the whole blood and inflammatory parameters of inpatients with COVID-19 followed in the intensive care and ward with each other and with healthy individuals. As a result, whole blood and inflammatory biomarkers that come to the forefront in the hospitalization process of inpatients with COVID-19 both in the intensive care and ward are determined.

Materials and Methods

Our study was carried out after obtaining 2020/13 session numbered and 2020.13.6 decision numbered University of Health Sciences Turkey, Samsun Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (date: 09.09.2020). Three groups were formed in the study.

Criteria of Groups

First of all, patients with positive COVID-19 real-time polymerase chain reaction test were included in the study. Patients with COVID-19 diagnosed with radiological or clinical findings but negative polymerase chain reaction test were not included in the study. Patients with COVID-19 were divided into two groups according to the unit they were hospitalized in. Inpatients in the ward were determined as a group, and inpatients in the intensive care as a group. In addition, a control group consisting of healthy individuals was added to the study.

Biochemical Process

After the ethics committee approval, with the authorization from Hospital Information Management system, the inpatients followed in COVID-19 ward and intensive care with a suspicion of coronavirus in May, June and July months of 2020 were found and their complete blood count parameters [WBC, lymphocyte, monocyte, neutrophil, platelet, monocyte/lymphocyte ratio (MLR), NLR] and CRP, procalcitonin, ferritin, ESR and albumin values, which are important biomarkers in the inflammatory process in terms of the prognosis of the disease, were examined retrospectively. Complete blood count parameters had been studied in Beckman Coulter DXH800 device, procalcitonin and ferritin were studied in Roche Cobas E411 device, CRP was studied in Beckman Coulter AU5800 device by using suitable kits and materials.

Statistical Analyses

SPSS 22.0 Windows Program was used for statistical analysis. It was determined that the data were not normally distributed. For this reason, non-parametric analyzes were used. Mann-Whitney U test was used for pairwise comparison of the groups.

Results

One hundred thirty inpatients diagnosed with COVID-19 from the intensive care and 147 inpatients from the ward were included in this study. In addition, 47 healthy individuals were added as a control. Of the inpatients in the intensive care, 46 (35.38%) were female and 84 (64.62%) were male. Of the inpatients in the ward, 74 (50.34%) were female and 73 (49.66%) were male. Twenty (42.55%) of the control group were female and 27 (57.45%) were male. While the average age of the inpatients in the intensive care was 68.28±14.22, the average age of the inpatients in the ward was 54.96±16.66, and the average age of the control group is 46.72±10.82. While the average day of hospital stay of the inpatients in the intensive care was 19.85, the average day hospital stay of the inpatients in the ward was 7.56. While 77 of the inpatients in the intensive care died, the others were discharged. Whole blood and inflammatory parameter mean ± standard deviations of the groups are given in Table 1.

In the comparison of the whole blood parameter values of the groups, the values of WBC, neutrophil, NLR and MLR of the inpatients in the intensive care was found to be higher than the values of the inpatients in the ward and the control group ($p<0.001$) (Figure 1). Additionally, the values of lymphocytes of the inpatients in the intensive care was found to be lower than the values of the inpatients in the ward and the control group ($p<0.001$) (Figure 1).

In the comparison of the inflammatory parameter levels of the groups, the values of CRP, ESR, ferritin and procalcitonin of the inpatients in the intensive care was found to be significantly higher than the values of the inpatients in the ward and the control group ($p<0.001$) (Figure 2). Additionally, the values of albumin of the inpatients in the intensive care was found to be lower than the values of the inpatients in the ward and the control group ($p<0.001$) (Figure 2). In addition, the values of CRP and ESR of the inpatients in the ward were found to be higher than the control group ($p<0.001$) (Figure 2).

Discussion

Haematological parameters which are used to classify COVID-19 inpatients include WBC, neutrophil, lymphocyte, monocyte, thrombocyte, eosinophil, MLR, NLR and haemoglobin. In addition to being very important component in the immune of the body, lymphocytes are also the main executers of all immune functions and at the same time a cellular component on the forefront to fight external infections. Lymphopenia has an important prognostic value in COVID-19 disease. While lymphopenia has been reported in 80% of the critical inpatients (12), this rate has been reported as 25% in mild inpatients (13). In a meta-analysis which included 758 COVID-19 positive cases that had severe disease and 1688 COVID-19 positive cases that had mild disease, a significant increase was found in the neutrophil count in cases with severe disease. It was also stated that an increase in WBC values of patients with COVID-19 (14). In our study, the values of WBC, neutrophil of the inpatients in the intensive care was found to be higher than the values of the inpatients in the ward and the control group.

In a study of 1141 patients with COVID-19, severe patients had a higher NLR than non-severe patients. NLR has been described as a prognostic value biomarker for inpatients with sepsis (15). Our study, the values of NLR of the inpatients in the intensive care was found to be higher than the values of the inpatients in the ward and the control group.

Table 1. Whole blood and inflammatory parameter mean ± standard deviations of the groups

Parameters	Intensive care (n=130)	Service (n=147)	Control (n=47)	The reference range
Whole blood parameters				
WBC (*10^9/L)	9.29±5.14	6.17±2.26	6.97±3.19	4.5-10.5
Lymphocyte (*10^9/L)	1.06±0.71	1.36±0.73	1.45±0.55	0.6-3.4
Neutrophil (*10^9/L)	7.62±5.59	4.27±2.2	4.5±2.27	2-6.9
Platelet (*10^9/L)	229.61±101.08	235.84±97.28	256.77±113.76	142-424
Monocyte (*10^9/L)	0.58±0.43	1.6±13.07	0.58±0.28	0-0.82
NLR	11.79±15.36	4.07±3.42	3.3±1.69	
MLR	0.74±0.91	0.66±2.46	0.43±0.23	
Inflammatory parameters				
Ferritin (ng/mL)	817.56±500.01	212.4±181.67	162±108.33	13-150 female 30-400 male
Procalcitonin (ng/mL)	2.34±9.26	0.13±0.2	0.09±0.1	0-0.046
CRP (mg/L)	101.04±81.16	44.72±50	21.26±25.76	0-5
Albumin (g/dL)	3.07±0.51	3.68±0.47	3.76±0.45	3.5-5.2
ESR (mm/h)	50.28±24.79	33.86±23.2	22.11±16.13	0-20

WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation ratio

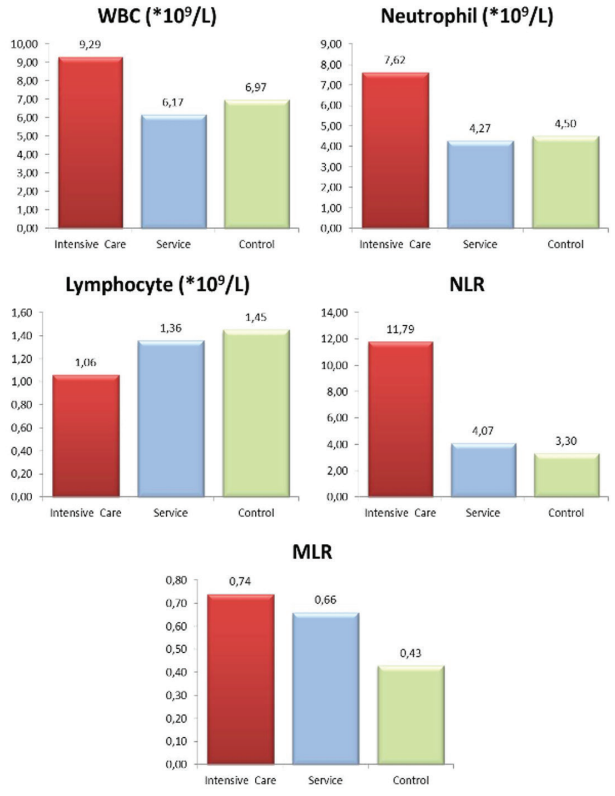

Figure 1. Whole blood parameter mean bar graph of groups WBC: White blood cell, NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio

In a study on coagulation and platelet parameters of patients with suspected COVID-19, platelet values of polymerase chain reaction (PCR)-negative participants were found to be higher than those of PCR-positive patients (16). In our study, there was no significant difference between the mean platelet levels of the groups.

Increase in CRP alone or with another marker can cause infections. CRP values are increased in patients with COVID-19 before compudet tomography findings and in the early stages of infection. More importantly, CRP has been associated with disease development (17). In a study including 663 patients, CRP value was found to be higher in patients with COVID-19 positive when compared with patients with COVID-19 negative (18). In our study, the values of CRP of the inpatients in the intensive care was found to be higher than the values of the inpatients in the ward and the control group. In addition, the values of CRP of the inpatients in the ward were found to be significantly higher than the control group.

Procalcitonin, a glycoprotein, is calcitonin precursor. Procalcitonin levels can be used to distinguish between viral and bacterial infections (19). In a study conducted in Wuhan with the inclusion of 191 positive patients, it was found that procalcitonin

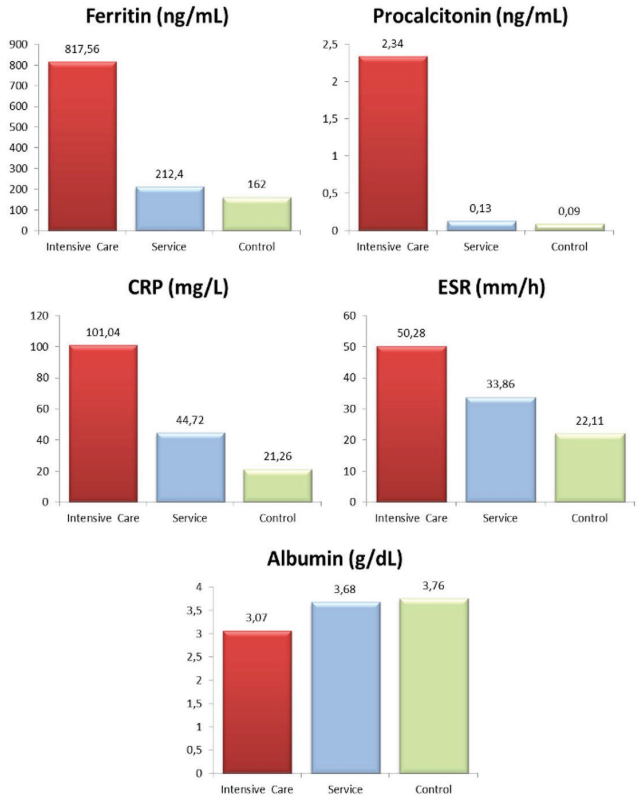

Figure 2. Inflammatory parameter mean bar graph of groups
CRP: C-reactive protein, ESR: Erythrocyte sedimentation ratio

level increased in association with the severity of the disease (7). In another meta-analysis including 1099 patients, almost four times higher procalcitonin value was found in the severe group (20). It has been found that procalcitonin can make a significant distinction between severe cases and non-severe and fatal cases and thus can function as a possible predictic biomarker in individual studies (21). In our study, the values of procalcitonin of the inpatients in the intensive care was found to be higher than the values of the inpatients in the ward and the control group.

Serum ferritin levels can increase significantly as a response to inflammation and various diseases. ferritin synthesis regulation is under the control of cytokine (22). Due to the cytokine storm observed in fatal and critical COVID-19 cases, an increase occurs in serum ferritin levels in these cases. It has been reported that ferritin levels ranging from 400 µg/L to >2000 µg/L are seen in COVID-19 patients and that the highest ferritin levels are seen in serious cases and in those who did not survive (7,13). In a previous study including 653 COVID-19 positive patients, it was found that mean ferritin level was 408.28 ng/mL and this value was correlated with disease severity and the increase in ferritin level could be used as prognostic marker of imminent death (23). In our study, the values of ferritin of the inpatients in the intensive care was found to be higher than the mean values of the inpatients in the ward and the control group.

There are very few data on ESR in patients with COVID-19. In a study conducted on 113 patients, it was reported that fatal cases had higher ESR tendency than the cases that recovered, without reporting the significance of the difference observed between positive and negative patients (13). In another study with 80 patients, it was found that ESR was associated with CRP and haemoglobin and patients with severe disease had higher ESR levels (24). In a study conducted with patients with COVID-19 with diabetes comorbidity, inflammatory parameters (ESR, procalcitonin, ferritin and CRP) were found to be higher (25). In our study, the values of ESR of the inpatients in the intensive care was found to be higher than the values of the inpatients in the ward and the control group. In addition, the values of ESR of the inpatients in the ward were found to be higher than the control group.

Conclusion

In summary, it has been concluded that haematological findings such as lymphocyte, WBC, MLR, NLR and inflammatory findings such as procalcitonin, CRP, ferritin, ESR are associated with the disease severity and that they could be used as very important risk factors for the progress of the disease. In addition, increased NLR levels reflecting an increased inflammatory process can show possibility of hospitalization in intensive care. For this reason, the surveillance of inflammatory findings, and NLR, can help in the diagnosis, early screening of COVID-19 and in the treatment of severe diseases.

Ethics

Ethics Committee Approval: Our study was carried out after obtaining 2020/13 session numbered and 2020.13.6 decision numbered Health Sciences University of Health Sciences Turkey, Samsun Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (date: 09.09.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.A., G.Ü.Ü., A.K., Concept: M.E., U.D., Design: M.E., G.Ü.Ü., U.D., Data Collection or Processing: R.A., U.D., A.K., M.B., Analysis or Interpretation: R.A., G.Ü.Ü., A.K., M.B., Literature Search: R.A., M.E., G.Ü.Ü., U.D., A.K., M.B., Writing: R.A., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics inWuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020; 382: 1199-207.
2. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020; 395: 470-3.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727-33.
4. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest 2013; 111: 1805-12.
5. Chen X, Yang Y, Huang M, Liu L, Zhang X, Xu J, et al. Differences between COVID-19 and suspected then confirmed SARS-CoV-2-negative pneumonia: a retrospective study from a single center. J Med Virol 2020; 92: 1572-9.
6. Tishkowski K, Gupta V. Erythrocyte Sedimentation Rate. In: StatPearls. StatPearls Publishing, Treasure Island (FL) USA, 2020.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, 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.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
9. Keskin A, Aci R, Taskin MH, Erdem M, Bilgin M, Ari M. Comparison of Laboratory Findings And Mortalıty Rates of Varıant ALPHA and SARS-COV-2 Infected Patients. International Anatolia Academic Online Journal Health Sciences 2021; 7: 79-88.
10. Keskin A, Ustun GU, Aci R, Duran U. Homocysteine as a marker for predicting disease severity in patients with COVID-19. Biomark Med 2022; 16: 559-68.
11. Guthrie GJK, Charles KA, Roxburgh CSD, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. Crit Rev Oncol Hematol 2013; 88: 218-30.
12. Zang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475-81.
13. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-13.
14. Yan Q, Li P, Ye X, Huang X, Mo X, Wang Q, et al. Longitudinal peripheral blood transcriptional analysis of COVID-19 patients captures disease progression and reveals potential biomarkers. medRxiv 2020.
15. Huang Z, Fu Z, Huang W, Wang G, Zheng Y, Zhong R, et al. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. Am J Emerg Med 2020; 38: 641-7.
16. Arslanbek Erdem M, Cubukcu M, Müderrisoğlu S, Aci R, Keskin A, Türe E. The Relationship between COVID-19 Suspected Patient's Coagulation and Platelet Parameters and Polymerase Chain Reaction Results. Konuralp Medical Journal 2022; 14: 92-98.
17. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed omographic findings and predicts severe COVID-19 early. J Med Virol 2020; 92: 856-62.
18. Zhang J, Wang X, Jia X, Li J, Hu K, Chen G, et al. Risk factors for disease severity, unimprovement, and mortality of COVID-19 patients in Wuhan, China. Clin Microbiol Infect 2020; 26: 767-72.
19. Rodriguez A, Reyes LF, Monclou J, Suberviola B, Bodi M. Sirgo G, et al. Relationship between acute kidney injury and serum procalcitonin concentration in critically ill patients with influenza infection. Med Intensiva (Engl Ed) 2018; 42: 399-408.
20. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J 2020; 55: 2000547.
21. Gulhar R, Ashraf MA, Jialal I. Physiology, Acute Phase Reagents. Treasure Island FL USA: StatPearls Publishing; 2020.
22. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol 2017; 29: 401-9.
23. Henry BM, Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020; 58: 1021-8.
24. Zhang W, Yuan Y, Zhang S, Jin C, Wu L, Mei H, et al. Erythrocyte Sedimentation Rate in COVID-19 Infections. medRxiv 2020.
25. Unluguzel Ustun G, Keskin A, Aci R, Arslanbek Erdem M, Ari M. Association Between Hb A1c and Severity of COVID-19 Patients. Hemoglobin 2021; 45: 124-8.