DOI: 10.37990/medr.1192730 Med Records 2023;5(1):170-5

MEDICAL RECORDS-International Medical Journal

Research Article

CRP and LDH Levels Can Be Used for Support the COVID-19 Diagnose in Intensive Care Unit Patients

Onder Otlu[1], Zeynep Kurt[1], Feyza Inceoglu[2], Ulku Karaman[3], Tugba Raika Kiran[1]

[1]Malatya Turgut Özal University Faculty of Medicine, Department of Biochemistry, Malatya, Türkiye
[2]Malatya Turgut Özal University Faculty of Medicine, Department of Biostatistic, Malatya, Türkiye
[3]Ordu University Faculty of Medicine, Department of Parasitology, Ordu, Türkiye

Abstract

Aim: The coronavirus disease (COVID-19) has been a public health problem that causes severe acute respiratory syndrome affected all over the word since 2019. The most commonly used parameters as inflammatory response in the clinic are leukocytes, neutrophils, erythrocyte amount and serum C-reactive protein (CRP). In recent years, it has been reported that serum PCT (procalcitonin) level may be useful in the diagnosis of bacterial and viral infections. The aim of our study is to compare blood parameters that may play a supportive role to diagnose of COVID-19 in healthy control and critically COVID-19 patient groups.
Material and Methods: This retrospective research was carried out in Malatya Turgut Ozal University Training and Research Hospital, Malatya, Türkiye. Total 88 critically ill patients and 90 healthy people accepted to the study and electronic medical records of patients and control group has been collected from hospital information system (HIS). COVID-19 diagnose has been confirmed by real-time polymerase chain reaction (RT-PCR) results.
Results: No statistically significant difference was found between the patient and control groups according to gender in the participants included in the study. A statistically significant increase was observed in CRP, LDH, PCT, D-dimer, urea, sediment, lympocyte and neutrophil levels in COVID-19 patients. According to logistic regression analysis CRP, LDH and sediment values were found to be statistically effective in estimating the COVID-19 infection. These results also supported by ROC analysis, CRP, neutrophil, LDH, PCT and D-dimer results were determined to be distinguishing parameters for COVID-19 patients.
Conclusion: We found that CRP, PCT and LDH levels higher in the COVID-19 patients and these parameters can be used to diagnose and estimate the prognose of COVID-19 infection in intensive care patients.

Keywords: COVID-19, CRP, LDH, Intensive care

INTRODUCTION

The coronavirus disease (COVID-19) has been a public health problem that causes severe acute respiratory syndrome affected all over the word since 2019 and it is originated in Wuhan, China (1). The disease spread from the Asian Continent to Europe and America in a short period of two months, and the World Health Organization (WHO) declared the COVID-19 disease as a “Pandemic” on March 11, 2020. Coronaviruses are single-stranded, positively charged viruses; have extensions on their surface. For this reason, these viruses are named as Coronavirus (crowned virus) (2). As a result of the examination of the samples taken from COVID-19 patients, it was understood that the virus causing the disease was from the coronavirus family as well as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (3,4). There is no treatment yet whose efficacy and safety have been proven by scientific studies. COVID-19 is transmitted mainly through droplets. Respiratory symptoms, fever, cough, and dyspnea are the most prevalent symptoms of the disease (5). Efforts are being carried out intensively for effective treatment to control the pandemic (6). COVID-19 disease is a potent disease that leads to multi-organ failure. Studies have shown that oxidative damage, coagulation problems and some metabolic changes occur due to hyperinflammation in COVID-19 disease. These events lead to pathological conditions, especially in critically ill patients (1). Inflammatory cytokines can manifest themselves for a long time in acute kidney injury (7). COVID-19 diagnostic tests are an important part of the epidemic (8). In addition to the evaluation of inflammatory

CITATION
Otlu O, Kurt Z, Inceoglu F, et al. CRP and LDH Levels Can Be Used for Support the COVID-19 Diagnose in Intensive Care Unit Patients. Med Records. 2023;5(1):170-5. DOI: 10.37990/medr.1192730

Received: 21.10.2022 **Accepted:** 21.11.2022 **Published:** 13.01.2023
Corresponding Author: Onder Otlu, Malatya Turgut Özal University, Faculty of Medicine, Department of Biochemistry, Malatya, Türkiye **E-mail**: onder.otlu@ozal.edu.tr

markers, it is critical to closely monitor potential indicators of organ failure in intensive care units. The most used parameters in clinical acute phase response are leukocytes, absolute neutrophils, erythrocyte amount, serum C-reactive protein (CRP). In recent years, it has been reported that serum procalsitonin (PCT) levels may be useful in the diagnosis of bacterial and viral infections (2). Procalcitonin and ferritin tests are other parameters used in the evaluation of the inflammatory process and "cytokine storm". Liver and kidney function tests, creatine kinase (CK) and D-dimer test, which is a fibrin breakdown product, are widely used in the evaluation of complications of the disease (9).

In the light of these information, the aim of our study is to compare blood parameters that may play a supportive role to diagnose of COVID-19 in healthy control and critically COVID-19 patient groups.

MATERIAL AND METHOD

Selecting participants and Data Collecting

This retrospective research was carried out in Malatya Turgut Ozal University Training and Research Hospital, Malatya, Turkey. Intensive care specialists were in charge for all the patients in the intensive care unit. Electronic medical records of patients and control group has been collected from hospital information system (HIS) and screening period was between 09.04.2020 and 09.04.2022. COVID-19 diagnose has been confirmed by real-time polymerase chain reaction (RT-PCR) results in the HIS. Participants forming control group have been selected from the same health center and attention was paid to have a parallel characteristic with the critically ill group in terms of age and gender. Total 88 critically ill patients and 90 healthy people accepted to the study as COVID-19 and Control group respectively. Seconder comorbidities such as diabetes mellitus, cardiovascular disease, hypertension, chronic obstructive pulmonary disease, cerebrovascular disease, and chronic kidney disease were determined as exclusion criteria.

Biochemistry, hemogram and coagulation analysis were performed by Abbott Architect c16000, Sysmex Corporation XN-10 and Diagon Coag XL medical devices respectively.

Statistical Analysis

The analysis of the data was carried out with the SPSS (Statistical Program in Social Sciences) 25 program. In order to check whether the data show the normal distribution, Shapiro Wilk Test was used (10). The significance level (p) for comparison tests was taken as 0,05. Since the variables did not have a normal distribution (p>0.05), the analysis was continued with non-parametric test methods. Mann Whitney U test was used to comparisons in independent pairs. ROC analysis was performed to determine the cut-off point (11).

RESULTS

Comparison of the Demographic Characteristics

The mean age of 88 COVID-19 patients was 72.63 (IQR, 22-98). The number of women was 41 (46.6%) and the number of men was 47 (53.4%). The mean age of 90 healthy controls was 69.97 (IQR, 24-95) and the number of women and men were equal and 45.

No statistically significant difference was found between the patient and control groups according to gender in the participants included in the study (p>0.05, Table 1). The groups show a homogeneous distribution according to the gender and age variable.

Table 1. Comparison of groups by gender and age

Parameter	Group		Group Covid-19 (n/%)	Control	Total	Test Value[a]	p Value
Gender	Male		47 (53.4%)	45 (50.0%)	92 (51.7%)	0.207	0.649
	Female		41(46.6%)	45 (50.0%)	86 (43.7%)		
	Total		88 (100.0%)	90 (100.0%)	178 (100.0%)		
Parameter	Group	n	Mean ± SD	Min-Max		Test Value[b]	p Value
Age	Covid-19	88	72.63±14.92	(22-98)		1.212	0.227
	Control	90	69.97±14.34	(24-95)			

Test value[a]; Ki-square test value (X^2), p value; statistical significance, SD; standart deviation, Min; minimum value, Max; maximum value, Test Value[b]; Mann Whitney U Test value

Laboratory Parameters of Participants

Measurements of serum biochemical parameters are given in Table 2. A statistically significant increase was observed in blood sediment, CRP, PCT, LDH, D-dimer, urea, lympocyte and neutrophil levels in COVID-19 patients compared to the healthy control group (p=0.001). On the contrary, significant decrease was found between the patient and control groups according to the calcium (Ca) and magnesium (Mg) levels (p<0.05, Table 2). Apart from that there was no statistically significant difference between the patient and control groups according to the variables of sodium (Na), potassium (K), chlorine (Cl), phosphorus (P) and creatinine in the participants included in the study.

Table 2. Comparations of the COVID positive and control groups blood parameters

Parameter	GROUPS		Test Value	p Value
	Covid-19 (Mean±SD)	Control (Mean±SD)		
CRP (mg/dL)	8.91±8.5	2.7±2.88	1864.500	0.001*
Neutrophil (10^3/µL)	10.46±5.9	7.83±5.65	2640.000	0.001*
LDH (U/L)	532.94±672.13	261.7±117.08	1572.500	0.001*
Lymphocyte (10^3/µL)	1.71±8	1.84±1.01	1397.000	0.001*
PCT (ng/mL)	2.5±7.26	0.47±0.89	2743.500	0.001*
D-dimer (µgr FEU/mL)	2.63±2.69	1.68±2.01	2703.000	0.001*
Urea (mg/dL)	88.23±60.05	63.91±44.03	2785.000	0.001*
Creatinine (mg/dL)	1.47±1.61	1.17±1.03	3327.000	0.066
Ca (mg/dL)	7.96±0.94	8.49±0.86	2458.000	0.001*
Mg (mg/dL)	2.24±0.76	6.16±29.49	3225.500	0.033*
Na (mmol/L)	139.55±5.74	139.11±5.37	3859.500	0.769
K (mmol/L)	4.17±0.96	4.17±0.63	3725.000	0.494
Cl (mmol/L)	103.44±7.19	104.18±5.56	3505.500	0.185
P (mg/dL)	3.57±1.78	3.6±1.37	3592.000	0.284
Blood sediment (mm/hour)	45.3±27.92	23.83±18.31	660.000	0.001*

SD; Standart deviation, Test Value; Mann Whitney Test value; *Shows the statistically significant difference between the groups ($p<0.05$)

Logistic Regression Analysis for Groups

Logistic regression analysis of the variables are given in Table 3. CRP, LDH and sediment values were found to be statistically effective in estimating the groups (patient – control) ($p<0.05$). Neutrophil, lymphocyte, procalcitonin, Ca, D-dimer, Mg values were not found to be statistically effective in estimating the groups (patient – control) ($p>0.05$).

Regression analyzes for CRP, LDH and sediment values are given below.

CRP value is 0.849 times more effective in estimating groups correctly (OR=0.849, 95% CI 0.730-0.988). 1 unit increase in CRP value, increases the risk of COVID-19 infection 0.849 times.

LDH value is 0.985 times more effective in estimating groups correctly (OR=0.849, 95% CI 0.976-0.993). 1 unit increase in LDH value, increases the risk of COVID-19 infection 0.985 times.

Sediment value is 0.961 times more effective in estimating groups correctly (OR=0.961, 95% CI 0.935-0.988). 1 unit increase in sediment value increases the risk of COVID-19 infection 0.961 times.

Table 3. Estimated values of the parameters in the model

Parameters	β	S.E.	W	sd	p Value (sig)	Exp(β)	95% CI for EXP(β)	
							Lower Limit	Upper Limit
CRP	**-0.163**	**0.077**	**4.489**	**1**	**0.034***	**0.849**	**0.730**	**0.988**
Neutrophil	0.014	0.057	0.062	1	0.803	1.014	0.908	1.134
LDH	**-0.015**	**0.004**	**12.078**	**1**	**0.001***	**0.985**	**0.976**	**0.993**
Lymphoside	0.011	0.046	0.062	1	0.803	1.012	0.924	1.107
PCT	-0.016	0.145	0.012	1	0.913	0.984	0.740	1.309
Ca	0.378	0.326	1.344	1	0.246	1.460	0.770	2.767
D-dimer	0.067	0.201	0.112	1	0.738	1.070	0.721	1.587
Mg	-0.851	1.251	0.463	1	0.496	0.427	0.037	4.962
Blood sediment	**-0.040**	**0.014**	**7.958**	**1**	**0.005***	**0.961**	**0.935**	**0.988**
Constant	4.569	4.097	1.244	1	0.265	96.410		

β; parameter estimates, S.E.; standard error, W; Wald statistics, sd; degrees of freedom, EXP (β); odds ratio, 95% CI; confidence intervals

ROC Analysis

ROC analysis results are given in Table 4. According to ROC analysis results, CRP, neutrophil, LDH, PCT and D-dimer results were determined to be distinguishing parameters for COVID-19 patients. It was observed that the parameter with the highest AUC value among these parameters was LDH and the lowest AUC value belonged to the D-dimer parameter. As a result of the ROC analysis for LDH, 274.5 points, which corresponds to the point with the highest sensitivity and the lowest specificity, were determined as the cut-off point, at this point the sensitivity of the scale was found to be 0.778 and the specificity as 0.762. The highest AUC value after LDH belongs to the CRP parameter and as a result of the ROC analysis, it was determined as the cut-off point of 3.45 points, which corresponds to the point with the highest sensitivity and the lowest specificity. At this point, the sensitivity of the scale was found to be 0.698 and the specificity to be 0.810. ROC curves of all analyzed parameters are given in Figure 1.

Table 4. Result of ROC analysis

Parameters	Cutting Point	Sensitivity	Specificity	p	AUC	95% C.I.	
						Lower Limit	Upper Limit
CRP	**3.455**	**0.698**	**0.810**	**0.001***	**0.804**	**0.722**	**0.886**
Neutrophil	**7.205**	**0.730**	**0.714**	**0.001***	**0.734**	**0.635**	**0.833**
LDH	**274.500**	**0.778**	**0.762**	**0.001***	**0.843**	**0.770**	**0.916**
Lymphocyte	0.165	0.968	0.001	0.053	0.186	0.099	0.272
PCT	**0.134**	**0.762**	**0.690**	**0.001***	**0.773**	**0.680**	**0.866**
Ca	6.950	0.905	0.024	0.051	0.246	0.153	0.338
Na	138.500	0.651	0.524	0.113	0.592	0.483	0.701
K	3.675	0.762	0.190	0.291	0.439	0.329	0.549
Cl	104.500	0.460	0.571	0.419	0.453	0.343	0.564
P	5.200	0.127	0.929	0.353	0.446	0.332	0.560
D-dimer	**1.315**	**0.635**	**0.619**	**0.004***	**0.666**	**0.560**	**0.772**
Mg	1.715	0.905	0.095	0.095	0.596	0.488	0.704
Blood sediment	**26.500**	**0.698**	**0.786**	**0.001***	**0.751**	**0.654**	**0.847**

*Shows statistical significant difference (p<0,05), AUC; area under the curve, %95 CI; confidence interval

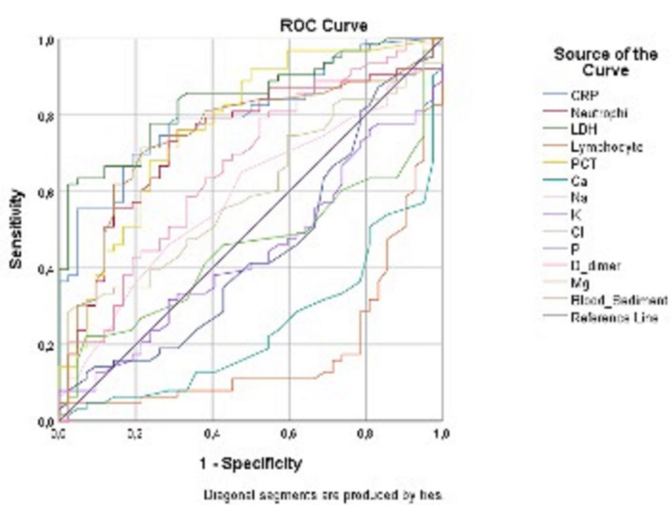

Figure 1. Cutting points according to ROC analysis

DISCUSSION

COVID-19 disease is a severe disease that leads to multi-organ failure. Virus infections can affect various organs, including kidney damage. Studies have shown that oxidative damage, coagulation problems and some metabolic changes occur due to hyperinflammation in COVID-19 disease. These events lead to pathological conditions, especially in critically ill patients (1). Inflammatory cytokines can manifest themselves for a long time in acute kidney injury (7). PCT levels is associated with hyper-inflammation seen in COVID-19 infection. In our research, we analysed the level of procalcitonin in intensive care patients and found a significant association between disturbances in PCT and COVID-19 disease. Serum PCT levels increase not only in severe and life-threatening systemic inflammatory conditions, but also return to normal soon after the septic state has resolved (12). During infection, this value rises above 0.5ng/mL. (3). PCT levels have been investigated during the COVID-19 process in many studies due to inflammation in COVID-19 disease, and high PCT levels in kidney patients lead to pathology (13,14).

CRP is used to distinguish between viral and bacterial infections and to identify developing complications (15).

CRP levels increases significantly after surgery, infections, tumors, autoimmune diseases, and chronic inflammatory diseases (12). Elevated CRP is considered as a risk factor. The normal limit values of CRP are 0-5 mg/L. CRP is slightly higher in women than in men (16). CRP value increases in patients with COVID-19 (17). Studies show that the amount of CRP in plasma increases due to inflammation in COVID-19 patients (18). We observed that CRP were significantly different between the two groups. CRP value groups (patient-control) are 0.849 times more effective in estimating correctly (OR=0.849, 95% CI 0.730-0.988). 1 unit increase in CRP value increases the risk of COVID-19 infection 0.849 times.

Lactate dehydrogenase, a hydrogen transfer enzyme, catalyzes the oxidation of L-lactate to pyruvate. The enzyme enters the circulation in case of inflammation and tissue damage and there is a marked increase in serum levels (19). It is thought that high LDH levels in severe COVID-19 patients may be a potential marker of lung injury and tissue destruction (20). We found a significant difference between the COVID-19 infected and healthy control group in terms of LDH levels.

D-dimer; It is a fibrin degradation product formed by the breakdown of thrombus by the endogenous fibrinolytic system. D-dimer levels increase with inflammation in COVID-19 patients (21). In a study, it was found that some of the COVID-19 patients with high D-dimer (>5000 µg/L) levels had an elevation associated with sepsis (22). In our study, we found that D-dimer levels increased in patients with critical COVID-19 compared with healthy people.

Careful control of kidney functions during COVID-19 infection is vital (23). Various studies have examined the relationship between COVID-19 infection and acute kidney injury, and the risk of death increases with kidney damage in COVID-19 patients (24-26). In COVID-19 disease; fluid and electrolyte imbalance causes many complications. Studies have reported that the risk of death due to kidney damage increases in COVID-19 patients due to pH and electrolyte imbalances in biological fluids. Electrolyte imbalance leads to conditions such as hyponatremia, hypernatremia, hypokalemia, hypocalcemia, and hypochloremia in patients. Hypokalemia (decreased potassium level) in COVID-19 infection is important in various pathophysiological mechanisms (27). According to another study; sodium decreased significantly in COVID-19 patients, similarly, there was a decrease in potassium and calcium levels, but no statistically significant difference was observed for chlorine level (28,29). In our study, no significant difference was observed between the patient and control groups for chlorine levels. There was no statistically significant difference between the patient and control groups according to the variables of sodium, potassium, chlorine, phosphorus and Ca in the participants included in the study.

Structural analysis of COVID-19 is important in terms of activation of calcium-dependent mechanisms and interaction of this ion with the target cell membrane (29). Calcium ions; It is one of the substances involved in signal transmission in every cell. Regulation of the activity of nuclear transcription factors, intracellular and extracellular enzymes, transmembrane channels, ion channels, membrane receptors, various calcium sensitive components; it depends on Ca signals in the cell. Ca is involved in many steps such as the post-translation process of viral proteins, viral gene expression, entry of the virus into the cell, and the viral life cycle. In addition, very rapidly rising creatinine values can be detected, serum calcium levels are decreased in COVID-19 patients (21). In our study, we found that calcium and magnesium levels decreased significantly in COVID-19 infected people.

Serum creatinine and urea levels are the most commonly used tests to evaluate kidney functions. Acute kidney injury (AKI) is one of the major complications of COVID-19 infection and is also associated with increased morbidity and mortality. It is vital to carefully control kidney functions, especially during COVID-19 infection (23). A statistically significant difference was found between the patient and control groups according to the variables of urea in the participants included in the study ($p<0.05$, Table 2).

It is a group of peripheral blood cells consisting of neutrophils, monocytes, eosinophils, basophils and lymphocytes. Their main function is to clear pathogens, dead or aged cells and foreign materials from the body (30). Approximately 75% of leukocytes consist of neutrophils. They play a role in body immunity in inflammation with phagocytosis and degranulation (31). Platelets play a role in the realization of primary hemostasis by initiating coagulation and wound healing at the injury site. In addition, they may exert a direct antimicrobial activity, similar to neutrophils and monocytes, and have a significant effect on the acute inflammatory response (32). In healthy individuals, the total lymphocyte count is over 1500/mm^3. There are also publications that conclude that lymphopenia can indicate the severity of COVID-19 disease (33).

CONCLUSION

Significant differences were found in some routine biomarkers between patients diagnosed with COVID-19 and control group. We found that CRP, PCT and LDH levels higher in the COVID-19 patients and these parameters can be use to diagnose and estimate the prognose of COVID-19 infection in intensive care patients. We also believe that the elevated procalcitonin values, low calcium and magnesium levels of COVID-19 patients may show the risk of multiple organ damage but new researches are needed to test this idea.

Financial disclosures: *The authors received no support from any financial institution or organization for this study.*

Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *Ethical approval was obtained from Malatya Turgut Özal University Clinical Research Ethics Committee (Approval no: 2022/144).*

REFERENCES

1. Otlu Ö, Erdem M, Korkmaz K, et al. Effect of altered iron metabolism on hyperinflammation and coagulopathy in patients with critical COVID-19: A Retrospective Study. Int J Acad Med Pharm. 2022;4:60-4.
2. Chorba T. The Concept of the Crown and Its Potential Role in the Downfall of Coronavirus. Emerging Infectious Diseases, 2022;26:2302.
3. European Centre for Disease Prevention and Control. Rapid Risk Assessment: Outbreak of acute respiratory syndrome associated with a novel coronavirus, Wuhan, China; first update – 22 January 2020. ECDC: Stockholm; 2020.
4. Coronavirus disease (COVID-19). https://www.who.int/health-topics/coronavirus#tab=tab_1 access date 13.09.2022
5. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmunity, 2020;109:102433.
6. Batırel A. Specific treatment of COVID-19. Southern Clinics of Istanbul Eurasia. 2020;31(Suppl):31-41.
7. Carriazo S, Kanbay M, Ortiz A. Kidney disease and electrolytes in COVID-19: more than meets the eye. Clin Kidney J. 2020 Jul 16;13:274-80.
8. Bozkurt İ, Keleş GT. Laboratory Tests Used in the Diagnosis and Treatment of COVID-19 Disease. CBU-SBED. 2021;8: 380-7.
9. Doruk ÖG, Örmen M, Tuncel P. Bıochemıcal And Hematologıcal Parameters In Covıd-19, Deu Tıp Derg. 2021;35:71-80.
10. Alpar R. Kuramsal Dağılımlar. In: Spor Sağlık ve Eğitim Bilimlerinden Örneklerle Uygulamalı İstatistik ve Geçerlik-Güvenilirlik. 6. Baskı. Detay Yayıncılık, Ankara, 2020;165-218.
11. Dirican A. Evaluation of the diagnostic test's performance and their comparisons. Cerrahpaşa J Med. 2001;32:25-30.
12. Ertuğrul Ö, Ertuğrul MB. Prokalsitonin ve Enfeksiyon, Klimik Dergisi. 2005;18:59-62.
13. Sitter T, Schmidt M, Schneider S, Schiffl H. Differential diagnosis of bacterial infection and inflammatory response in kidney diseases using procalcitonin. J of Nephrol 2001;15:297-301.
14. Gianotti L, D'Agnano S, Pettiti G, et al. Persistence of elevated procalcitonin in a patient with coronavirus disease 2019 uncovered a diagnosis of medullary thyroid carcinoma. AACE Clinical Case Rep. 2021;7:288-92.
15. Meier-Ewert HK, Ridker PM, Rifai N, et al. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. Clin Chem. 2001;47:426-30.
16. Hutchinson WL, Koenig W, Frohlich M. Immunoradiometric assay of circulating C-reactive protein: Age-related values in the adult general population. Clin Chem. 2000;46:934-8.
17. Dubey DB, Mishra S, Reddy HD, et al. Hematological and serum biochemistry parameters as a prognostic indicator of severally ill versus mild Covid-19 patients: A study from tertiary hospital in North India. Clin Epidemiol Glob Health. 2021;12:100806.
18. Stenvinkel P, Chung SH, Heimbürger O, Lindholm B. Malnutrition, inflammation, anda therosclerosis in peritoneal dialysis patients. Perit Dial Int. 2001;21:157–62.
19. Alba-Patiño A, Vaquer A, Barón E, et al. Micro-and nanosensors for detecting blood pathogens and biomarkers at different points of sepsis care. Microchimica Acta. 2022; 189:1-26.
20. Doğan Ö, Devrim E. Tanı ve İzlemde Laboratuvar Testleri. In: COVID-19. Ankara Üniversitesi Basımevi, Ankara, 2020;29-33.
21. Liu J, Han P, Wu J, et al. Prevalence and predictive value of hypocalcemia in severe COVID-19 patients, J Infect Public Health. 2020;13:1224–8.
22. Schutte T., Thijs A., Smulders Y.M. Never ignore extremely elevated D-dimer levels: they are specific for serious illness. Neth J Med. 2016;74:443-8.
23. Şit D, Kayabaşı H. Acute kidney injury associated with SARS-CoV-2 Dicle Med J. 2020;47:498-507.
24. Li Z, Wu M, Yao J, et al. Caution on kidney dysfunctions of COVID-19 patients. MedRxiv. 2020;27.
25. Lotfi B, Farshid S, Dadashzadeh N, et al. Is Coronavirus Disease 2019 (COVID-19) Associated with Renal Involvement? A Review of Century Infection, Jundishapur J Microbiol. 2020;13:e102899.
26. Mohamed MM, Lukitsch I, Torres-Ortiz AE, et al. Acute kidney injury associated with coronavirus disease 2019 in urban New Orleans. Kidney360. 2020;1:614-22.
27. Nahkuri S, Becker T, Schueller V, et al. Prior fluidand electrolyte imbalance is associated with COVID-19 mortality. Commun Med. 2021;1:51.
28. Lippi G, South AM, Henry BM. Electrolyte Imbalances in Patients with Severe Coronavirus Disease 2019 (COVID-19). Ann Clin Biochem. 2020;57:262–5.
29. Filippo L, Doga M, Frara S, Giustina A. Hypocalcemia in COVID 19: Prevalence, clinical significance and therapeutic implications. Rev Endocr Metab Disord. 2022;23:299–308.
30. Carrick JB, Begg AP. Peripheral blood leukocytes. Veterinary Clinics of North America: Equine Practice. 2008;24:239-59.
31. Witko-Sarsat V, Rieu P, Descamps-Latscha B, et al. Neutrophils: molecules, functions and pathophysiological aspects. Lab Invest. 2000;80:617-53.
32. Flad HD, Brandt E. Platelet-derived chemokines: Pathophysiology and therapeutic aspects. Cell Mol Life Sci. 2010;67:2363-86.
33. Tan L, Wang Q, Zhang D, et al. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther. 2020;5:33.