Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2021;46(4):1711-1718
DOI: 10.17826/cumj.989978

ARAŞTIRMA / RESEARCH

QTc interval is associated with increased inflammatory markers (neutrophil-to-lymphocyte ratio and LDH level) in COVID-19 patients

QTc aralığı, COVID-19 hastalarında artan inflamatuar belirteçlerle (nötrofil-lenfosit oranı ve LDH seviyesi) ilişkilidir

Şerife Torun[1], İrem Karaman[2], Nurtaç Özer[3], Olgun Çelik[3], M. Şule Akçay[4]

[1]Baskent University Research and Training Hospital, Department of Pulmonary Diseases, Konya, Turkey
[2]Bahcesehir University School of Medicine, Istanbul, Turkey
[3]Baskent University Research and Training Hospital, Department of Cardiology, Konya, Turkey
[4]Baskent University Faculty of Medicine, Department of Pulmonary Diseases, Ankara, Turkey

Cukurova Medical Journal 2021;46(4):1711-1718

Abstract

Purpose: This study aimed to investigate the association between QTc interval and laboratory parameters in COVID-19 patients before and after the treatment.
Materials and Methods: Forty-three COVID-19 patients who had baseline and follow-up ECG findings and laboratory reports were evaluated and 40 patients were included in the study.
Results: Among 40 patients, 16 were women and 24 were men. The neutrophil-to-lymphocyte ratio (NLR) and corrected QT (QTc) interval were significantly higher in females than males. After the treatment, a significant fall in CRP and ferritin values, and significantly prolonged QTc interval were seen. A significant positive correlation was observed between QTc interval and age, LDH levels, neutrophil and leukocyte count, NLR, magnesium levels, and heart rate of the patients prior to treatment. A positive correlation was observed between increased QTc interval and decreased LDH levels and NLR after treatment.
Conclusion: QTc prolongation was associated with increased inflammatory markers, increased NLR and LDH levels before and after treatment in COVID-19 patients. The increase in the QTc interval was correlated with the reduction in LDH levels and NLR with treatment.
Keywords:. COVID-19, electrocardiogram, QTc interval, inflammation, neutrophil-to-lymphocyte ratio, LDH

Öz

Amaç: Bu çalışma, COVID-19 hastalarının tedavi öncesi ve sonrası QTc aralığı ile laboratuvar parametreleri arasındaki ilişkiyi araştırmayı amaçlamıştır.
Gereç ve Yöntem: Başlangıç ve takip EKG bulguları ve laboratuvar raporları olan 43 COVID-19 hastası değerlendirildi ve çalışmaya 40 hasta dahil edildi.
Bulgular: 40 hastanın 16'sı kadın, 24'ü erkekti. Nötrofil/lenfosit oranı (NLO) ve düzeltilmiş QT (QTc) aralığı kadınlarda erkeklere göre anlamlı olarak daha yüksekti. Tedavi sonrası CRP ve ferritin değerlerinde belirgin düşüş ve QTc intervalinde belirgin uzama görüldü. QTc aralığı ile hastaların yaşı, tedavi öncesi LDH düzeyleri, nötrofil ve lökosit sayıları, NLO, magnezyum düzeyleri ve kalp atım hızı arasında anlamlı pozitif korelasyon gözlendi. Tedavi sonrası artan QTc aralığı ile azalmış LDH seviyeleri ve NLO arasında pozitif bir korelasyon gözlendi.
Sonuç: QTc uzaması, COVID-19 hastalarında tedaviden önce ve sonra artan inflamatuar belirteçler, artan NLR ve LDH seviyeleri ile ilişkili olarak gözlemlenmiştir. QTc aralığındaki artış, tedavi ile LDH seviyelerindeki ve NLR'deki azalma ile korele idi.

Anahtar kelimeler: COVID-19, elektrokardiyogram, QTc aralığı, inflamasyon, nötrofil-lenfosit oranı, LDH

Yazışma Adresi/Address for Correspondence: Dr. Şerife Torun, Baskent University Research and Training Hospital, Department of Pulmonary Diseases, Konya, Turkey. E-mail: serifetor@hotmail.com
Geliş tarihi/Received: 02.09.2021 Kabul tarihi/Accepted: 19.11.2021 Çevrimiçi yayın/Published online: 23.11.2021

INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) has resulted in a dramatic pandemic, that has killed nearly 3 million people globally by causing mainly a respiratory disease that can rapidly progress to pneumonia and, in severe cases, to acute respiratory distress syndrome (ARDS)[1]. Although the respiratory system is the most frequently affected part in patients who develop clinical disease in response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), tissues harboring angiotensin-converting enzyme 2 receptors such as vascular endothelial cells, lungs, heart, brain, kidneys, intestine, and liver may also be affected SARS-CoV-2 infection can either directly cause injury in multiple organs, or it might disturb the homeostasis of the immune system and result in hyperinflammation, endothelial dysfunction, and hypercoagulability, which results in rapid deterioration[1]. The hyperinflammatory response and endothelial dysfunction together form a novel microvascular thromboinflammatory syndrome, which eventually leads to multiorgan failure and death[2]. Therefore, early identification of critical patients is critical to decrease the health care burden by the rational allocation of resources and the improvement of patients' prognosis.

Cardiac and renal dysfunction is among the most common adverse events that are reported in the COVID-19 deaths[3]. Multiple studies have described cardiac involvement in COVID-19, including multiple infarcts, myocarditis, myocardial injury, and non-obstructive coronary artery disease[4]. It has been reported that patients with signs of cardiac involvement have a worse prognosis and higher mortality rate[5]. Electrocardiographic (ECG) abnormalities caused by COVID-19 include wide QRS complex (>120 ms), prolonged QTc interval (>450 ms in males, >470 ms in females), lateral ST-T segment abnormalities, abnormal PR interval, as well as arrhythmias[5-8]. Besides the effect of SARS-CoV-2 infection, drugs such as hydroxychloroquine (HCQ) and azithromycin used in the treatment of COVID-19 at the beginning of the pandemic may increase the QTc interval (through the effects of cytokine-mediated potassium channel expression) and the risk of developing arrhythmias such as Torsades de pointes[4,9].

The effect of drugs to treat COVID-19 on the QTc interval has been well studied. While hydroxychloroquine (HCQ) and azithromycin are known to increase the QTC prolongation significantly, particularly when they are used simultaneously, the antiviral favipiravir seems to have no significant effect on the QTc interval [4]. However, the relationship between the change in QTc interval and laboratory parameters in COVID-19 patients after treatment has been partly known. Therefore, the current study aimed to investigate the association between change in QT interval and laboratory parameters of COVID-19 patients before and after treatment, to demonstrate if COVID-19 or its' treatment affects any of the parameters significantly at the same time.

MATERIALS AND METHODS

Study population

This is a retrospective study that evaluated 43 confirmed COVID-19 patients who had baseline ECG at the time of admission between April 1 and May 31, 2020. The patients were admitted to the cardiology and pulmonology COVID-19 inpatient clinic in Konya Baskent University Hospital. COVID-19 diagnosis was confirmed by a real-time reverse-transcription polymerase chain reaction (RT-PCR) assay. Patients aged >18 years with typical symptoms of COVID-19 and pulmonary ground-glass opacities on thoracic computed tomography (CT) were included in the study. Those with electrolyte abnormalities, a history of chronic inflammatory diseases, chronic kidney disease (glomerular filtration rate < 30 ml/ min), bundle branch block, atrial fibrillation, and pre-excitation syndromes were excluded from the study. Accordingly, total of forty-three patients were evaluated, and three patients were excluded from the study.

Descriptive characteristics (gender, age, smoking status) and information regarding the medical history of the patients were retrieved from medical records. Biochemical parameters that were received during the admission including hemoglobin (Hb), white blood cell (WBC) count, D-dimer, ferritin, and C-reactive protein (CRP), glucose, urea, creatinine, sodium, and potassium were measured from the blood samples.

All the patients read the patient information form about the study procedure and written informed consent was obtained from each patient. This study was performed in accordance with the ethical principles in the Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. Ethical

approval for this study procedure was obtained from the Baskent University Institutional Review Boards/ethical committees with the approval number: KA20/483 (19/01/2021) with respect to its scientific content. This study was supported by the Baskent University Research Fund.

Treatment protocol

The decision of treatment with chloroquine/hydroxychloroquine±azithromycin±favipiravir was made by pulmonologists according to the clinical, laboratory, and radiological findings of the patients and in accordance with Turkish Health Ministry COVID-19 treatment guideline. Supplemental oxygen therapy was administered based on oxygen saturation levels. Hydroxychloroquine was given orally at 400 mg BID for the first day (loading dose) followed by 200 mg BID for 4 days. Favipiravir was given orally at 1600 mg BID for the first day (loading dose) followed by 600 mg BID for 4 days. Serial assessments of the QT interval and laboratory parameters were performed during the treatment.

Electrocardiography analysis

A 12-lead ECG was obtained by cardiologists from all patients before treatment at the first admission and after 48 hours of treatment. Nihon Kohden's Cardiofax® M electrocardiogram was utilized to conduct electrocardiography. The QTc and PR intervals, as well as QRS duration were determined as following: PR interval; normal range 120–200 ms, QRS duration; lead V5 was selected and the QRS interval > 120 ms was determined as prolongation, corrected QT interval (QTc); the QT interval measured in either lead II or V5 and calculated by using Bazett's formula (QTc =QT / (√RR)[10].

Statistical analysis

The association between laboratory and ECG findings of the patients and their characteristics, and the relationship between the changes in those parameters after treatment were investigated. All analyses and calculations were performed with the statistical package program SPSS 15.0. Descriptive statistical methods (mean and standard deviation) were used when evaluating the study data. Student's t-test and Mann-Whitney U test were used to compare the quantitative variables. To compare the change in laboratory values and ECG findings before and after treatment, Paired Samples t-test and Wilcoxon Signed Ranks Test were used. Pearson correlation analysis was used to evaluate the relationships between the change in laboratory parameters and QTc interval after treatment. In all the analyses, a p-value of <0.05 was considered statistically significant.

Based on the Zhu et al (2020) study, an effect value of 0.5740741 was found for the NLR, with a 20% bias. With this effect value, the minimum number of people to be recruited for this study was found as 35 patients, according to the results of the power analysis performed in the GPower 3.1.9.2 program, with a margin of error of 0.05 and a confidence interval of 95% (Critical T=1.6909243)[11].

RESULTS

Forty patients who had baseline and follow-up ECG findings and laboratory reports were included in the study. Among the 40 patients, 16 were women (40%) and 24 (60%) were men. The mean age was 55.20 ± 16.90 (ranging from 27 to 87). No additional comorbid illness was present in 28 patients (70%). Among 12 patients (%30) with comorbid illnesses, 2 patients had diabetes mellitus, 2 patients had hypertension, 3 patients had hypertension and diabetes, 1 patient had hypertension and asthma, 1 patient had hypertension and COPD, 1 patient had cancer, 1 patient had a history of arrhythmia. The most common reported comorbidity was hypertension. No arrhythmic fatalities were documented, nor did sudden cardiac arrest occur. None of the patients died and none of them had QTc interval >500 msec.

The demographical and clinical characteristics of patients and comparison of characteristics between two genders were shown in Table 1. The mean corrected QT interval (QTc) at admission was 442±29 msec for female patients and 422±27 msec for male patients. None of the patients showed a significant QTc prolongation (>450 ms in men, >470 ms in women). NLR and QTc intervals were significantly higher in females than males, whereas ferritin and Hb levels were significantly higher in males at the time of clinical admission.

Table 1. The distribution of baseline characteristics, clinical, laboratory, and electrocardiographic findings of the patients at the time of admission and the comparison of findings according to the gender of the patients.

Variable	Woman (n=15)		Man (n=23)		p
	Mean	S.D.	Mean	S.D.	
Age	58.3125	19.84849	53.1250	14.70969	0.379[a]
Leukocyte (10^9/L)	7.0775	2.16300	6.5463	1.78379	0.402[a]
Neutrophil (10^9/L)	4.7763	2.02143	4.0300	1.35541	0.169[a]
NLO	4.6983	5.06878	2.5110	1.09117	**0.047**[a]
Lymphocyte (10^9/L)	1.6219	.91267	1.8183	.72920	0.455[a]
Monocyte (10^9/L)	.6806	.86310	.6953	.44684	0.944[b]
Eosinophil (10^9/L)	.0716	.09916	.2381	.60460	0.284[b]
Hemoglobin (g/dL)	13.3687	1.64305	14.8583	.95913	**0.001**[a]
Platelet (10^9/L)	238.1188	71.43537	240.6000	111.11324	0.938[a]
BUN (mg/dL)	19.1250	17.55325	17.1250	13.41742	0.686[b]
Creatinine(mg/dL)	1.6613	2.09156	.9121	.22002	0.088[b]
AST (U/L)	22.6250	10.76956	28.4167	11.50772	0.118[a]
ALT(U/L)	22.8750	10.64503	31.2500	16.43234	0.080[a]
Na (mmol/L)	130.3125	34.85727	126.7083	39.11908	0.767[b]
K (mmol/L)	3.9125	1.12894	3.8958	1.25091	0.966[a]
Ca (mmol/L)	2.7750	4.26059	2.5667	4.09853	0.878[a]
Mg (mEq/L)	.1456	.58250	.0742	.36334	0.635[a]
Ferritin (ng/mL)	276.6569	541.15395	447.4917	487.78271	**0.003**[b]
LDH (U/L)	304.2667	175.57842	263.3478	99.02277	0.364[a]
CRP (mg/L)	36.9333	29.89392	55.5261	39.14369	0.127[a]
D-dimer (mcg/mL)	1.0107	1.05657	.9965	1.10735	0.970[a]
Heart rate	84.4667	17.06654	79.2609	13.13987	0.296[b]
PR (ms)	160.4000	22.29926	153.3478	16.54912	0.271[b]
QRS interval (ms)	85.6000	9.03801	91.1304	10.25274	0.098[b]
QTc1 interval (ms)	442.5333	29.21073	422.6522	27.79079	**0.042**[a]

S.D.: Standard deviation ; *NLR: neutrophil-to-lymphocyte ratio; a. Student's t-test b. Mann-Whitney U test.
BUN: blood urea nitrogen, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein,

Table 2. The comparison of laboratory values and ECG findings before and after treatment.

Variable	Before		After		
	Mean	S.D.	Mean	S.D.	p
LDH (U/L)	290.735	137.077	247.529	114.056	0.077[a]
CRP (mg/L)	48.186	36.524	13.615	27.734	**<0.001**[a]
D-Dimer (mcg/mL)	.978	1.096	.870	1.859	0.777[a]
QTc (ms)	432.00	29.529	447.875	36.498	**<0.001**[a]
Ferritin (ng/mL)	401.589	550.084	264.548	364.817	**0.017**[b]

S.D.: Standard deviation, LDH: lactate dehydrogenase, CRP: C-reactive protein. ; a.Paired Samples t-test b.Wilcoxon Signed Ranks Test

The levels of inflammatory parameters and QT interval were compared before and after treatment and presented in Table 2. After the treatment, a statistically significant fall in CRP and ferritin values, and significantly prolonged QTc interval were seen ($p < 0.05$). The fall observed in D-dimer levels, LDH, and after treatment was not statistically significant. The relationship between QTc interval and age, clinical, and pre-treatment laboratory parameters was presented in Table 3. A significant positive correlation was observed between QTc interval and age ($r = 0.377$ $p = 0.020$), pre-treatment LDH levels ($r = 0.363$ $p = 0.025$), NLR ($r = 0.505$ $p = 0.001$), neutrophil count ($r = 0.412$ * $p = 0.010$), leukocyte count ($r = 0.360$ $p = 0.027$), magnesium levels ($r = 0.620$ $p < 0.001$) and heart rate ($r = 0366$ $p = 0.024$). The association between the change in QTc interval and changes in CRP, LDH, D-dimer, ferritin levels, and NLR that were obtained in the following days of treatment was investigated in Table 4.

Table 3. The relationship between QTc1 interval and patients' parameters before treatment.

Parameter	r	p
Heart rate	.366*	.024
PR interval	-.029	.865
NLR*	.505**	.001
D-dimer	.158	.350
LDH	.363*	.025
Ferritin	.144	.388
CRP	.122	.466
Age	.377*	.020
Leukocyte	.360*	.027
Neutrophil	.412*	.010
Lymphocyte	-.109	.514
Monocyte	.010	.951
Eosinophil	-.063	.706
Hemoglobin	-.023	.892
Platelet	.002	.989
BUN	.178	.285
Creatinine	.094	.574
AST	.282	.087
ALT	.011	.946
Na	-.097	.564
K	-.098	.556
Ca	.307	.061
Mg	.620**	.000

r: Pearson correlation test. p<0.05 accepted as statistically significant. LDH: lactate dehydrogenase, CRP: C-reactive protein, BUN: blood urea nitrogen, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, NLR: Neutrophil-to-lymphocyte ratio

Table 4. The relationship between the change in QTc interval and change in the LDH, D-dimer, ferritin, NLR after treatment

Change in the parameter	r	p
CRP	.009	0.955
LDH	.357*	0.038
D-dimer	.113	0.518
Ferritin	.190	0.298
NLR	.255*	0.001

r: Pearson correlation test*. p<0.05 is statistically significant.; CRP: C-reactive protein, LDH: lactate dehydrogenase, NLR: Neutrophil-to-lymphocyte ratio

Since LDH, CRP, D-Dimer and Ferritin have decreased and QTc interval increased after treatment, the association between the changes in those parameters was investigated. There was a significant positive correlation between the increase in QTc and the decrease in LDH (r = 0.357 p = 0.038) and NLR (r = 0.255 p = 0.001) with treatment.

DISCUSSION

The novel coronavirus SARS-CoV-2 caused a rapid pandemic with a significantly fatal course, particularly in the high-risk population. While evidence-based treatments have yet to emerge, identification of useful clinical parameters to assess patients who are at increased risk of complications and extra-pulmonary involvement remains crucial to decrease the global burden of the disease. In this study, the effect of COVID-19 and its treatment on QTc change and laboratory values, and the association between QTc prolongation and inflammatory parameters before and after treatment have been investigated. After the treatment, a significant fall in CRP and ferritin values, and significantly prolonged QTc interval were seen. A significant positive correlation was observed between QTc interval and age, LDH levels, neutrophil and leukocyte count, NLR, magnesium levels, and heart rate of the patients prior to treatment. After treatment, increased QTc was

positively correlated with decreased LDH level and NLR.

Although the most common reported symptoms of COVID-19 patients are fever, cough, and dyspnea, sinus tachycardia caused by hypoxia and fever is a common presentation during the course of the disease [8]. Besides the respiratory symptoms which are the main clinical presentation of COVID-19 patients, acute myocardial damage, as well as arrhythmias and cardiogenic shock have also been largely observed during the course of the disease. In some cases, ventricular arrhythmias might represent the first clinical manifestation of COVID-19 [9].

QTc prolongation is commonly seen among patients treated with antimalarial, antivirals, and antibiotics [5]. The prolonged QTc interval was reported in COVID-19 patients as the predominant side effects of hydroxychloroquine and azithromycin. Therefore, the present study aimed to investigate the association between QTc interval and changes in the laboratory parameters after treatment. In this study, no other pathological ECG findings were observed in COVID-19 patients. Santoro et al. described age, basal heart rate and dual antiviral therapy as the independent predictors of prolonged QTc[5]. Consistently, in our study, increased age and heart rate were associated with prolonged QTc. The patients' comorbidities as well as higher fragility in older ages can be the reason for prolonged QTc in this subset of patients. The study by Bernardini et al. also supported that the QT interval increases with lifetime and the drug therapy seemed to magnify this effect[12].

Elevated inflammatory markers such as C-reactive protein(CRP), lactate dehydrogenase (LDH), ferritin, and fibrinogen were observed in COVID-19 patients, which was mostly positively correlated with the extent of involvement and disease severity[13-15]. Increased levels of alanine aminotransferase (ALT)/aspartate aminotransferase (AST), creatinine, and D-dimer were also linked to the progression of COVID-19[16]. In this study, we also observed elevated CRP, LDH, ferritin, fibrinogen, and D-dimer levels in COVID-19 patients.

Systemic inflammation is a well-known risk factor for QTc prolongation [17]. Severe COVID-19 cases are reported to be presented with lymphopenia (lymphocyte count <1,000), higher leukocyte counts, higher neutrophil-to-lymphocyte ratio(NLR), as well as lower percentages of monocytes, eosinophils and basophils[2]. The utilization of cost-effective NLR as a prognostic marker has been described in multiple inflammatory diseases including cardiovascular diseases and oncological processes. Martínez-Urbistondo et al. reported that NLR can be utilized as an independent marker of systemic endothelial dysfunction in asymptomatic patients with high risks of cardiovascular events [18]. NLR was also described as an independent prognostic factor determining in-hospital mortality of COVID-19 patients[19-21].

A significant positive correlation was observed between QTc interval and neutrophil count, leukocyte count and NLR ratio in COVID-19 patients at the time of admission. Padilla et al. reported that COVID-19 patients with higher NLR demonstrated a moderate-to-severe QTc prolongation due to myocardial injury and required careful QTc interval monitoring[22]. Yu-Qing Cai et al. suggested that increased NLR and LDH levels suggest a poor prognosis and may be useful in the early identification of critical COVID-19 patients by reflecting an enhanced systemic inflammatory process[23]. In the present study, we found a significant positive correlation between the increase in QTc interval and the decrease in LDH and NLR with treatment. Since LDH is released as a result of tissue damage and involved in several pathophysiological processes, it serves as a non-specific indicator of cellular death. Decreased LDH levels were reported as indicators of radiologic improvement and treatment success in the COVID-19 patients[24]. However, increased levels of LDH and NLR may indicate myocardial injury, leading to QTc prolongation following SARS-CoV-2 infection.

In our study, a significant positive correlation was observed between the QTc interval and magnesium levels of COVID-19 patients. Generally, Mg deficiency and other electrolyte imbalances are among the known risk factors for QT prolongation[25]. Micke et al. reported that in COVID-19 patients treated with pro-arrhythmogenic drugs, keeping Mg levels above 1.23 mmol/L is effective in preventing QT prolongation[26]. They also suggested that Mg deficiency may be a risk factor for severe COVID-19, and that Mg deficiency is often associated with other comorbid conditions such as diabetes, advanced age, obesity, and cardiovascular disease. This may suggest that hypomagnesemia still contributes to QTc prolongation, even if Mg levels appear to be increasing below the reference range.

This study has some limitations that limit statistical power, including the small sample size due to the lack of baseline and follow-up ECG recordings from COVID-19 patients. Although a small number of patients were included in the current study, the strength of the study is the homogeneity of the procedures and treatment observed in all patients. Additionally, it is important to distinguish the effect of SARS-CoV-2 infection itself and the current treatment on QTc interval. Large-scale prospective studies are warranted to clarify the concerns about this issue. Since the cardiac complications of COVID-19 in previously healthy individuals, it is hard to determine which population to follow up closely. Therefore, identifying individuals who are at risk of potentially critical situations is required to prevent life-threatening conditions.

The result of this study supports that evidence of myocardial injury with strong inflammatory response indicated by higher LDH and NLR values should be of particular concern for QTc interval monitoring. An additional parameter that might contribute to QTc prolongation was serum magnesium levels, which should be taken into account in the management of electrolyte abnormalities of the patients to reduce the risk of serious complications, particularly in patients with enhanced inflammatory response. Taken together, our data suggest that besides drug toxicity, disease-related inflammatory myocardial injury, which provides a mechanism for cardiac conduction abnormalities in COVID-19 patients, requires close follow-up, especially in the later stages of the disease.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ST, IK, NO, OÇ, MSA; Veri toplama: ST, IK, NO, OC; Veri analizi ve yorumlama: ST, IK, NO, OÇ, SA; Yazı taslağı: ST, IK, NO, OC; İçeriğin eleştirel incelenmesi: ST, NO, OC, SA; Son onay ve sorumluluk: ST, IK, NO, OC, MŞA; Teknik ve malzeme desteği: ST, NO, OC, MSA; Süpervizyon: ST, NO, OC; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Başkent Üniversitesi Tıp ve Sağlık Bilimleri Araştırma kurulu tarafından 19.01.2021 tarih ve KA20/483 sayılı proje onay almiştir.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Author Contributions: Concept/Design : ST, IK, NO, OÇ, MSA; Data acquisition: ST, IK, NO, OC; Data analysis and interpretation: ST, IK, NO, OÇ, SA; Drafting manuscript: ST, IK, NO, OC; Critical revision of manuscript: ST, NO, OC, SA; Final approval and accountability: ST, IK, NO, OC, MŞA; Technical or material support: ST, NO, OC, MSA; Supervision: ST, NO, OC; Securing funding (if available): n/a.
Ethical Approval: For this study, the project dated 19.01.2021 and numbered KA20/483 was approved by the Başkent University Medical and Health Sciences Research Board.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

REFERENCES

1. Zheng HY, Zhang M, Yang CX, Zhang N, Wang XC, Yang XP et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. Cell Mol Immunol. 2020;17:541-3.
2. Jimeno S, Ventura PS, Castellano JM, García-Adasme SI, Miranda M, Touza P et al. Prognostic implications of neutrophil-lymphocyte ratio in COVID-19. Eur J Clin Invest. 2021;51:e13404.
3. Jain U. Effect of COVID-19 on the Organs. Cureus. 2020;12:e9540.
4. Çap M, Bilge Ö, Işık F, Burak C, Karagöz A, İnci Ü, et al. The effect of favipiravir on QTc interval in patients hospitalized with coronavirus disease 2019. J Electrocardiol. 2020;63:115-9.
5. Santoro F, Monitillo F, Raimondo P, Lopizzo A, Brindicci G, Gilio M et al. QTc interval prolongation and life-threatening arrhythmias during hospitalization in patients with COVID-19. Results from a multi-center prospective registry. Clin Infect Dis. 2020.
6. Sonsoz MR, Oncul A, Cevik E, Orta H, Yilmaz M, Ayduk Govdeli E et al. Wide QRS complex and lateral ST-T segment abnormality are associated with worse clinical outcomes in COVID-19 patients. Am J Med Sci. 2021;361:591-7.
7. Pavri BB, Kloo J, Farzad D, Riley JM. Behavior of the PR interval with increasing heart rate in patients with COVID-19. Heart Rhythm. 2020;17:1434-8.
8. Ece İ, Koçoğlu M, Kavurt AV, Bağrul D, Gül AEK, Koca S et al. Assessment of cardiac arrhythmic risk in children with Covid-19 infection. Pediatr Cardiol. 2021;42:264-8.
9. Rubin GA, Desai AD, Chai Z, Wang A, Chen Q, Wang AS, et al. Cardiac corrected QT interval changes among patients treated for COVID-19 infection during the early phase of the pandemic. JAMA Netw Open. 2021;4(4):e216842.
10. Das MK, El Masry H. Fragmented QRS and other depolarization abnormalities as a predictor of mortality and sudden cardiac death. Curr Opin Cardiol. 2010;25:59-64.
11. Zhu C, Yu S, Zhao H, Shen H, Yang J, Zhao L and Wu W. Neutrophil-to-lymphocyte ratio predicts the clearance of SARS-CoV-2 RNA in mild COVID-19 patients–a retrospective analysis from Dongxihu Fangcang Hospital in Wuhan, China. Clin Chem Lab Med. 2020;58:e167-e170.
12. Bernardini A, Ciconte G, Negro G, Rondine R, Mecarocci V, Viva T, et al. Assessing QT interval in COVID-19 patients:safety of hydroxychloroquine-azithromycin combination regimen. Int J Cardiol. 2021;324:242-8.
13. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50:332-4.

14. Li C, Ye J, Chen Q, Hu W, Wang L, Fan Y, et al. Elevated lactate dehydrogenase (LDH) level as an independent risk factor for the severity and mortality of COVID-19. Aging (Albany NY). 2020;12:15670-81.
15. Upadhyay J, Tiwari N, Ansari MN. Role of inflammatory markers in corona virus disease (COVID-19) patients: A review. Exp Biol Med (Maywood). 2020;245:1368-75.
16. Aydemir D, Ulusu NN. Correspondence: Importance of the validated serum biochemistry and hemogram parameters for rapid diagnosis and to prevent false negative results during COVID-19 pandemic. Biotechnol Appl Biochem. 2021;68:390-1.
17. Lazzerini PE, Laghi-Pasini F, Bertolozzi I, Morozzi G, Lorenzini S, Simpatico A et al. Systemic inflammation as a novel QT-prolonging risk factor in patients with torsades de pointes. Heart. 2017;103:1821-9.
18. Martínez-Urbistondo D, Beltrán A, Beloqui O, Huerta A. The neutrophil-to-lymphocyte ratio as a marker of systemic endothelial dysfunction in asymptomatic subjects. Nefrologia. 2016;36:397-403.
19. Liu Y, Du X, Chen J, Jin Y, Peng L, Wang HHX et al. Neutrophil-to-lymphocyte ratio as an independent risk factor for mortality in hospitalized patients with COVID-19. J Infect. 2020;81:e6-e12.
20. Lagunas-Rangel FA. Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): A meta-analysis. J Med Virol. 2020;92:1733-4.
21. Tatum D, Taghavi S, Houghton A, Stover J, Toraih E, Duchesne J. Neutrophil-to-lymphocyte ratio and outcomes in louisiana COVID-19 patients. Shock. 2020;54:652-8.
22. Padilla S, Telenti G, Guillén L, García JA, García-Abellán J, Ding C et al. Predictive factors for cardiac conduction abnormalities with hydroxychloroquine-containing combinations for COVID-19. Int J Antimicrob Agents. 2020;56:106142.
23. Cai Y-Q, Zeng H-Q, Zhang X-B, Wei X-J, Hu L, Zhang Z-Y et al. Prognostic value of neutrophil-to-lymphocyte ratio, lactate dehydrogenase, D-Dimer and CT score in patients with COVID-19. Aging (Albany NY). 2021;13:20896-905.
24. Wu M-y, Yao L, Wang Y, Zhu X-y, Wang X-f, Tang P-j et al. Clinical evaluation of potential usefulness of serum lactate dehydrogenase (LDH) in 2019 novel coronavirus (COVID-19) pneumonia. Respir Res. 2020;21:171.
25. Etheridge SP, Asaki SY. COVID-19 Infection and corrected QT interval prolongation—collateral damage from our newest enemy. JAMA Network Open. 2021;4:e217192.
26. Micke O, Vormann J, Kisters K. Magnesium deficiency and COVID-19–What are the links? Trace Elem Med. 2020;37:103-7.