**Araştırma Makalesi / Research Article**

# Is Capillary Refill Time an Early Prognostic Factor in COVID-19 Patients?

## *Kapiller Dolum Süresi, COVID-19 Hastalarında Erken Prognostik Faktör mü?*

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### Öz

**Amaç:** Hipoksemi, koronavirüs hastalığında (COVID-19) prognozu belirlemek için kullanılan hayati bir kriterdir. Bu çalışmada, COVID-19 hastalarında hipoksiye bağlı hastalık şiddetini tanımlamada kapiller dolum zamanının (KDZ) etkinliği değerlendirilmiştir.
**Hastalar ve Yöntem:** Bu prospektif çalışma, COVID-19 hastaları ve yaşça eşleştirilmiş bir sağlıklı grubu ile gerçekleştirilmiştir. Ölçüm için optimum test ortamı sağlandı ve yöntemimizi standartlaştırmak ve ölçümleri (milisaniye cinsinden) kaydetmek için sabit bir akıllı telefon platformu kullanıldı. Kaydedilen videolar daha sonra bir video işleme programı kullanılarak değerlendirildi.
**Bulgular:** Çalışmaya toplamda 39 COVID-19 hastası ve 40 kontrol grubu katıldı. Hastalar hastalık şiddetlerine göre orta (n= 25) veya ağır (n= 14) gruplara ayrıldı. Her iki orta / şiddetli grubun ortalama oksijen satürasyonu %94'ün üzerindeydi. Hastalık şiddetine göre KDZ ölçümleri şiddetli grupta orta gruba göre daha yüksekti (p= 0.009). Lenfopeni olmayan hastalarda (n= 18), KDZ değerlerinin şiddetli grupta arttığı saptandı (p= 0.008). Covid-19'lu hastaların takibinde KDZ kullanımı uygulanabilirdi (AUC: 0.91; %95 SH 0.848-0.978; P= 0.001).
**Sonuç:** Sonuçlarımız, COVID-19'lu hastalarda KDZ süresinin uzayabileceğini göstermektedir. Lenfopenisi olmayan ve O2 seviyesi normal olan hastalarda, KDZ uzamasının saptanması yoğun bakıma erken kabul için bir kriter olabilir.

**Anahtar Kelimeler:** Absolüt lenfosit sayısı, COVID-19, hastalık şiddeti, hipoksi, kapiller dolum zamanı

### Abstract

**Aim:** Hypoxemia is a vital criterion used to determine prognosis in coronavirus disease (COVID-19) cases. This study thus examined the effectiveness of capillary refill time (CRT) in defining hypoxia-dependent disease severity in COVID-19 patients.
**Patients and Methods:** This prospective study was conducted with COVID-19 patients and an age-matched healthy group. The optimum test ambiance was provided, and a stable smartphone platform was used to record the measurements (in ms) to standardize our method. The captured videos were then evaluated using a video processing program.
**Results:** In total, 39 patients with COVID-19 and 40 control groups participated in this study. The patients were further divided into the moderate (n = 25) or severe group (n = 14) according to disease severity. The mean oxygen saturation of both moderate/severe groups was above 94%. Per disease severity, the CRT measurements were higher in the severe group than in the moderate group (p = 0.009). In patients without lymphopenia (n = 18), CRT values were found to be increased in the severe group (p = 0.008). The use of CRT in patients with Covid-19 was practicable (AUC: 0.91; 95% CI 0.848-0.978; P = 0.001).
**Conclusions:** Our results show that CRT prolongation can occur in patients with COVID-19. In patients without lymphopenia and with normal O2 levels, detecting CRT prolongation may be a criterion for early admission to ICU.

**Key words:** Absolute lymphocyte count, COVID-19, disease severity, hypoxemia, capillary refill time
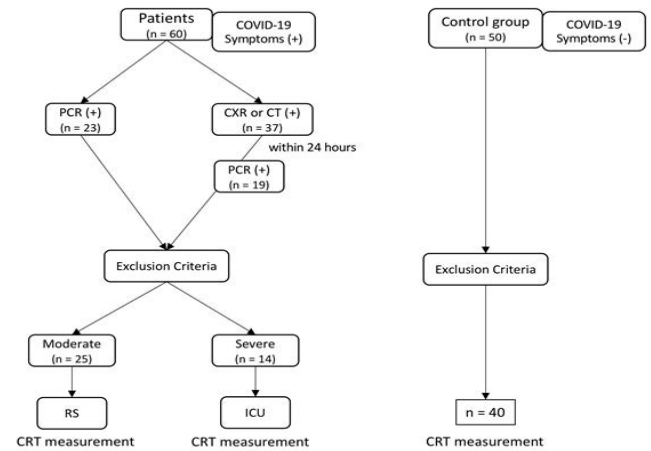
## INTRODUCTION

The COVID-19 outbreak is a pandemic disease in which we frequently see different presentations and complications. Although the disease seems to mostly affect the respiratory tract, it has caused fibrosis in various organs (1,2). COVID-19 has a high mortality rate of up to 12% (3). As cases continue to be reviewed, essential parameters in COVID-19's prognosis (dyspnea, tachypnea, sPO2 level, comorbidity, immunosuppressive therapy, laboratory abnormalities) must be further determined. Patients with severe COVID-19 disease complain about dyspnea according to the degree of pulmonary involvement. Hypoxemia caused by dyspnea will affect the peripheral tissues of the human body. Many tools can measure peripheral blood supply and oxygenation. Capillary refill time (CRT) can also be included in this class as a practical, non-invasive, reliable, and inexpensive physical examination performed at the bedside.

CRT effectively evaluates the peripheral vascular bed's fullness in favorable conditions, especially in the intensive care unit (ICU) (4) . Fundamentally, it is the observation of the filling rate of the arteriole and capillary system. CRT can give accurate objective information in case of septic shock (5). In addition, it can quickly and safely show severe dehydration in pediatric patients (6,7). CRT's examination time of < 2 s is considered one means of proving circulatory disorder (8,9). However, though CRT is considered such an important method, it is influenced by many factors, such as age, ambient or skin temperature, ambient light, pressure application, and observer reliability; therefore, CRT is not a daily measurement tool (4,10).

The year 2020 has been a period in which medicine must make several evaluations regarding COVID-19. A test such as CRT, which can predict multiple organ failure (MOF) and evaluate tissue perfusion, has not yet been applied in patients with COVID-19. The evaluations and results of our study thus contribute to determining CRT's role in COVID-19 prognosis.

## PATIENTS AND METHODS

Our research consisted of a prospective study conducted with patients diagnosed with COVID-19 via polymerase chain reaction (PCR) and computed tomography (CT), and an age-matched control group. A PCR test was definitely requested from patients with a CT diagnosis (Figure 1). Study approval numbered 2020/296 was obtained from the university ethics



PCR, Polymerase Chain Reaction; CT, Computed tomography; CXR, Chest X-ray; RS, Respiratory Service; CRT, Capillary refill time; ICU, Intensive care unit

**Figure 1.** Study design

committee. Informed consent forms were received from all participating patients prior to the study. The patients' laboratory parameters were recorded simultaneously. Those over 18 years of age who did not have decongestant, caffeine, or tea intake within the preceding 24 h were included in the study, while those with nail bed pathology (onychomycosis, cosmetic application, manicure) were excluded. Then, the patients were categorized into two groups based on COVID-19 disease severity (11). Accordingly, patients with clinical complaints (fever, cough, anosmia, headache, sour throat), pneumonic infiltrations in Chest X-Ray (CXR) or CT, and an $O_2$ saturation >94% were rated as moderate; and those with serious clinics (tachypnea and $O_2$ saturation < 94%) and bilateral CXR or CT pneumonic infiltrations were rated as severe (11). Cases with absolute lymphocyte count < 1000 x106/L were considered lymphopenic (12). The control group consisted of age-matched healty individuals who had no disease symptoms and had no comorbities.

We began taking measurements after obtaining optimum CRT conditions. Firstly, body temperature measurements were taken from all patients before evaluation, and between 36.5 - 38 Celcius was considered normal (13). Secondly, age-matching was provided in the control group for the CRT-caused age deflection effect. Thirdly, in order not to be affected by the light, the measurement was made at the same time of the day (between 09-10 am), and

the amount of light of the measurement area has been set for a brightness level to 300-500 lux, via a photometric freeware software (Lux-Meter) installed on the smartphone used in the measurement. Finally, measurements were made by the same healthcare personnel to prevent measurement technique variations.

To standardize each evaluation, we designed a 3D platform via Solidworks 2019 (Dassault Systèmes HQ) and a manufacturing procedure with Ultimaker Cura (ver. 4.6.2). Images were recorded with a smartphone placed on a mobile, focused tray that can observe the finger placement area from above. After the patient's finger was placed in the appropriate position, adequate pressure was applied to the finger pulp or nail root with a transparent, flat, and hardened tool until whitening occurred, and the examination was completed by immediately pulling the tool from the camera frame after 5 s. The pressure applied was documented by a physical open code programming platform (Arduino). Accordingly, the minimum pressure required for the evaluation was 4 Newtons. All these stages were recorded in video format via the smartphone placed on the tray platform. The images taken were evaluated using the color threshold filter available through VLC media player (ver. 3.0.5, Vetinari clang-902.0.39.2) software to show the visual blood flow in the images. We then made evaluations by observing the images from the moment the blood flow disappeared until the refill began and the skin color completely regulated. The time between these moments was recorded on the screen in ms.

### Statistical Analysis
Statistical analyses were performed using SPSS ver. 21 (SPSS Inc., Chicago, IL, USA). We used a Pearson correlation to correlate normally distributed data, whereas in non-normal data, we used a Spearman correlation. We also used independent t-tests to compare the CRT results between the COVID-19 patients and control group. In continuous data pinpointing comparisons with CRT and in comparisons according to disease severity, an independent t-test was used in normal distributions and the Mann–Whitney U-test in non-normal distributions. The area under the receiver-operating characteristics curve (AUC) and 95% confidence intervals (CI) were used to assess the ability of each CRT of the patient and control groups to predict the severity. In all calculations, a p-value of 0.05 was accepted as significant.

## RESULTS
Thirty-nine patients with COVID-19 diagnosed via PCR and 40 age-matched healthy control group were included in this study. The male and female populations were 69%:31% in the patient group and 50%:50% in the control group (p = 0.110). The mean age of the patients and control group was 70.4±13.7 and 69.3±13, respectively (p = 0.124). In the patient group, 51.3% of the patients with positive CT had a positive PCR, and the overall PCR positivity rate was 65%. Among the patients grouped according to disease severity, the moderate patients (n = 25, 64%) were followed up in the respiratory service (RS), and severe ones (n = 14, 36%) were treated at ICU. During treatment, none of the patients from moderate and severe groups were transferred to each other.

There were no vital abnormalities such as fever, pulse irregularity, low saturation, tachypnea in the control group. In the control group, mean body temperature was 36.8±0.6, mean saturation percentage was 96±2, and mean heart rate was 77.1±17.2. In the vital evaluations of the patient group, we did not note high-fever and dyspnea in any of the patients in the moderate group. Two of the patients had a non-persistent tachycardic period, one of them used montelukast for asthma treatment which needs no further medications, and the mean oxygen saturation percentage was 95.56±1.3 in the moderate patient group. Similarly, 2 of the patients had asthma in the severe group, but their oxygen saturations were above 90%. The severe group had no high-fever and tachycardia, unlike low oxygen saturation percentage (mean 92.85±1.3) and moderate dyspnea were noted. The demographic data and laboratory values of the patients are given below in Table 1.

CRT was measured above normal in 29 patients (74.3%) in the patient group. The longest CRT was 6.568 s, and it was in the patient group. The mean CRT for the patients with COVID-19 was prolonged (3.18±1.57), whereas, in the control group, the mean CRT was at normal range (1.32 ± 0.4 s). The CRT results comparison between the patient and control groups was statistically significant as well (p= 0.001,±= 0.404) (Figure 2/a). Age was positively correlated with CRT values in both patient (r= 0.248) and control group (r= 0.302). While the patient CRT values positively correlated with C-Reactive Protein (CRP) (r= 0.503) and International Normalized Ratio (INR) (r= 0.479), conversely, they negatively correlated with $PO_2$ (r= -0.339), and platelet count (r= -0.349). In addition, there was a statistical significance between

**Table 1.** Demographics and Laboratory findings of patients with COVID-19

| | All Patients (n= 39) | Respiratory Service (n= 25) | ICU (n = 14) | P value |
|---|---|---|---|---|
| **Characteristics** | | | | |
| Males, n (%) | 25 (64.1%) | 12 (48%) | 13 (92%) | 0.005 |
| Age | 64.4±16.3 | 66.3±17.2 | 75±13.2 | 0.112 |
| Comorbidities | | | | |
| DM | 12 (30.8%) | 7 (28 %) | 5 (35.7 %) | 0.616 |
| HT | 18 (46.2%) | 9 (36 %) | 9 (64.3 %) | 0.089 |
| CAD | 7 (17.9%) | 5 (20 %) | 2 (14.3 %) | 0.655 |
| COPD or/and Asthma | 3 (7.7%) | 1 (4 %) | 2 (14.3 %) | 0.247 |
| **Laboratory tests** | | | | |
| WBC, x$10^9$/L | 7.8 (4.8-10.9) | 7.3 (4.7-10) | 9.5 (6.2-12.9) | 0.228 |
| ANC, x$10^9$/L | 5.3 (3.1-8.8) | 4.1 (3.1-6.8) | 7.8 (3.5-11.1) | 0.149 |
| ALC, x$10^9$/L | 0.9 (0.7-1.66) | 1.2 (0.6-2.2) | 0.9 (0.7-1) | 0.251 |
| N/L r | 4.83 (2.67-8.71) | 3.39 (2.59-5.61) | 7.73 (5.1-14.45) | 0.026 |
| AMC, x$10^9$/L | 0.7 (0.5-0.9) | 0.7 (0.5-0.9) | 0.7 (0.4-0.9) | 0.874 |
| Hb, gr/dL | 11.78±2.18 | 11.94±2.44 | 11.52±1.67 | 0.573 |
| Plt count, x$10^9$/L | 180 (159-276) | 202 (163-301) | 164.5 (137-191) | 0.087 |
| CRP, mg/L | 21.8 (6.5-69.5) | 9.9 (4.5-23.5) | 74.9 (41.7-104.1) | 0.001 |
| Procalcitonin, µg/L | 0.07 (0.05-0.16) | 0.06 (0.05-0.1) | 0.12 (0.06-0.44) | 0.017 |
| Ferritine, ng/mL | 227 (102.7-418.8) | 151.2 (76-408) | 284 (213-502) | 0.044 |
| D-Dimer, ng/mL | 661 (470-1120) | 661 (411-1105) | 773 (571-1892) | 0.460 |
| INR | 1.04 (1– 1.1) | 1.02 (1-1.1) | 1.05 (1-29.8) | 0.017 |
| APTT, sec | 21.62±11.1 | 23.05±7.9 | 19.05±15.2 | 0.373 |
| pH -log[H$^+$] | 7.37±0.05 | 7.37±0.05 | 7.37±0.06 | 0.802 |
| PCO$_2$, (%) | 45.71±10.26 | 47.41±12.26 | 42.66±3.87 | 0.084 |
| Met Hb, (%) | 0.5 (0.2–1) | 0.7 (0.35-0.95) | 0.35 (0.2-1.1) | 0.331 |
| Lactat (%) | 2.5 (1.7–3.8) | 2 (1.7-3) | 2.85 (1.6-5) | 0.361 |
| HCO$_3^{-1}$, (%) | 25.1 (22.2-27.4) | 25.6 (23.1-28.1) | 23.8 (21.8-26.3) | 0.361 |
| sPO$_2$, (%) Hypoxemia | 94.58±1.87 | 95.56±1.35 | 92.85±1.35 | 0.001 |
| (sPO$_2$<94%), n (%) | 17 (44%) | 4 (16%) | 13 (93%) | 0.477 |
| Lymphopenia at sPO$_2$<94%, n (%) | 10 (59%)) | 2 (8%) | 8 (57%) | 0.044 |
| CRT, sec | 3.18±1.57 | 2.71±1.45 | 4.01±1.47 | 0.011 |

P values are the comparison of severe and moderate groups. (Chi-square test, Mann-Whitney U test, or Independent Samples t-test); Data are the median, n (%), or n/N (%); ALC, absolute lymphocyte count; ANC, absolute neutrophil count; AMC, absolute monocyte count; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT, capillary refill time; DM, Diabetes Mellitus; Hb, Hemoglobin; HT, Hypertension; INR, international normalized ratio; N/L r: Neutrophil-lymphocyte ratio; Plt, Platelet; PTT, partial thromboplastin time; sPO2, blood oxygen saturation; WBC, White blood cell.

prolonged CRT measurements and PO2 (p = 0.018, η=0.143), and D-dimer values (p= 0.016, η= 0.149). However, there was no statistical relation between CRT and Complete Blood Count abnormalities such as anemia, lymphopenia, monocytopenia, infection indicators (CRP, procalcitonin, ferritin), and local acidemia influencers such as lactate, bicarbonate, PCO$_2$, pH (p > 0.05). In addition, no correlation or statistical significance was found between chronic diseases in the study and CRT measurements.

In comparing the moderate and severe groups in terms of CRT, as shown in figure 2/b, a Mann-Whitney U test revealed a significant difference (p= 0.009, η= 0.175). We also noted another significance between the patient groups in terms of gender, CRP,

procalcitonin, ferritin, and blood oxygen saturation (p< 0.05). The percentage of lymphopenia (< 1000 x 106 per L) in the moderate patient group with a normal oxygen saturation (sPO$_2$ ≥ 94%) was 44% (n= 11). Prolonged CRT (3.85 ± 1.39 s) was measured in 63.6% (n= 7) of these lymphopenic, non-hypoxic patients in the moderate group. Similarly, lymphopenia was detected in 80% (n = 8) of the severe patients with an oxygen saturation < 94%. The mean CRT was prolonged (3.48 ± 1.14 s) in 90% (n= 9) of lymphopenic severe patients. However, in patients without lymphopenia there was a difference between the groups' CRT results in terms of treatment location (p = 0.008) (Figure 2/c). And the neutrophil to lymphocyte ratio results were statistically significant
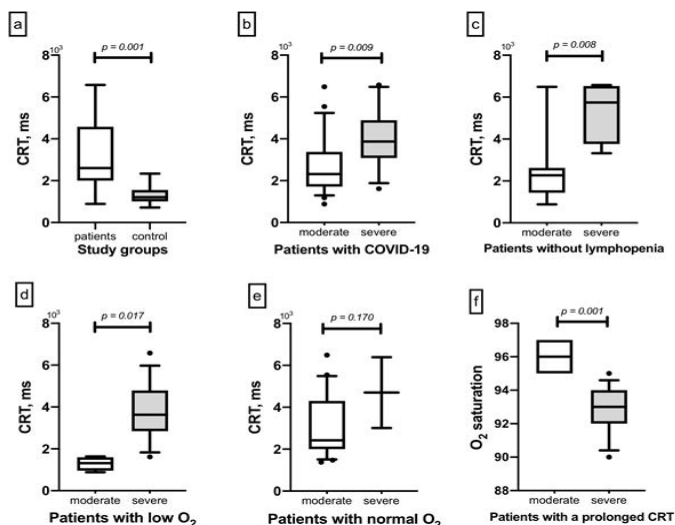
**Figure 2. a)** CRT comparison between patients and control group; **b)** CRT comparison among the patient subgroups; **c)** CRT comparison among the patient subgroups without lymphopenia; **d)** CRT comparison among the patient subgroups at low $O_2$ saturation; **e)** CRT comparison among the patient subgroups at normal $O_2$ saturation; **f)** Saturation comparison among the patient subgroups with prolonged CRT; CRT, Capillary refill time (ms).



**Figure 3.** The ROC analysis of the CRT results.

in the severe group (p = 0.026).

When CRT measurements were evaluated according to the patients' saturations, there was a difference between the moderate and the severe groups at low saturations (p= 0.002, η= 0.50) (Figure 2/d), whereas a Mann–Whitney U-test showed that the inter-groups CRT differences were not statistically significant at normal saturations (p= 0.182) (Figure 2/e). A similar CRT differences were not detected in other prognostic markers such as CRP, lactate, d-dimer, procalcitonin, and ferritin. And finally, we found a statistically significant difference in the $O_2$ saturation comparison of 29 patients with prolonged CRT results (p= 0.001) (Figure 2/f). The evaluation for the prognostic significance of CRT measurement was given in figure 3 (AUC: 0.91; 95% CI 0.848-0.978; S.E.: 0.03; P = 0.001).

## DISCUSSION

Our study evaluated the CRT in COVID-19 cases. There was an increase in CRT for the patients with COVID-19 compared to the control group. CR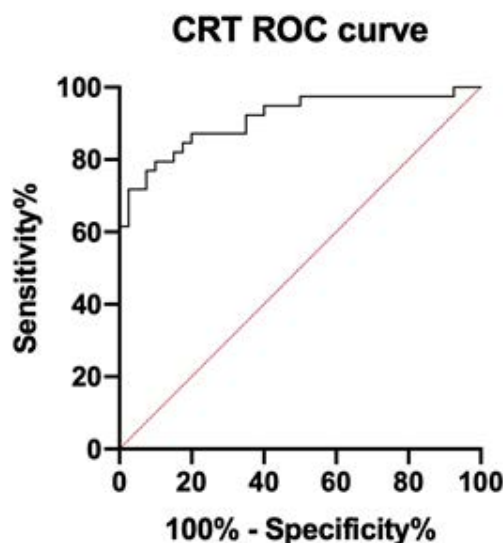T prolongation was also more frequent among the ICU patients than the RS patients. In lymphopenic patients, the mean ICU CRT values were greater than the RS CRT values. And, all patients with normal oxygen saturation were a tendency to have a prolonged CRT. There are many CRT studies that predict sepsis per sepsis criteria. These studies have generally been carried out in critical locations, such as ICUs and emergency services. A recent research found CRT to correlate with lactate levels in the ICU (14). Similarly, when the patient lactate level was > 2 mmol, CRT prolongations noted significant regardless of oxygen saturation (15). Although other reasons may have increased lactate levels in these studies, the results were found to be associated with CRT. Likewise, lactate is also among COVID-19's prognostic factors. We took our study's lactate samples from the arterial blood gas test. The mean lactate levels were 2.7±1.5 in the moderate group and 3.23±1.6 in the severe group. There was no correlation between CRT and lactate levels, however, when the lactate level >2 mmol, we found a relationship in CRT results between the RS and ICU patients.

In a study investigating the impact of cold conditions on CRT, periodic measurements were taken from the central and peripheral regions of the human body (10). A similar study stated that the different results are more pronounced in shock cases (4). In our study, 14 of the patients were monitored in the ICU. Additionally, fever confirmations were performed from the forehead in both the RS and ICU.

Hypothermic measurements were not available in any of the patients. Nevertheless, we expected the CRT measurements in the ICU to be prolonged. In our study, the local factors affecting the CRT did not differ statistically from the CRT results, thus, this indicates that the CRT measurements were made under optimal conditions. Due to physiological aging, CRT also changes with age. Anderson et al. studied CRT's environmental factors with 1,000 participants, finding an increase of 3.3% in CRT per each decade of life (16). Another issue evaluated in the study was ambient temperature. The researchers found that CRT was affected more by patient temperature than ambient temperature. Therefore, they still considered CRT to be clinically significant. The minimum age in our study was forty-eight, however we matched ages in the control group in order to minimize the age-dependent CRT prolongation impact. Consequently, age was positively correlated with CRT values in both patient and control group. None of the patients had a recorded high or low temperature. Although we compared the temperature values of the two different conditions, the CRT change level was trivial since no personal fever elevations occurred. In this way, our CRT measurements were affected by external factors as little as possible. In the evaluation of chronic diseases, we did not find any statistical difference between the two patient groups.

When we evaluated other laboratory results that may affect CRT, such as age, we found that CRT was highly positively correlated with CRP and moderately positively correlated with INR. Conversely, it was moderately negatively correlated with sPO2 level and platelet count. Thus, both negative and positive correlations seem to be compatible with physiopathology and the clinical stage. CRT will be prolonged because the increase in the platelet count will decrease blood fluidity, inflammation will cause tissue hypoxia, and hypoxia will increase arteriole constriction (17). Violi et al. (18) (2020) further examined hypercoagulation and antithrombotic therapy in patients with COVID-19. They found that pneumonia, coagulation disorders, platelet activation, and artery dysfunction can lead to MOF. CRT, which can rapidly evaluate peripheral circulation in the process leading to MOF after macrophage activation syndrome (MAS), can prove useful in this regard. None of our patients progressed toward MOF or MAS. However, CRT was significant in evaluating microcirculation of ICU patients as these patients are more prone to MAS. In our study, CRT prolongation was higher in patients without lymphopenia in ICU compared to the service. Detection of CRT prolongation in patients without lymphopenia may predict the predisposition to MAS before lymphopenia occurs.

In a study evaluating subjective CRT measurements, 12 experts commented on 34 different CRT videos (19). There were even 9 s among the results with a median value of 1.5. In a similar study, the CRT measurements of 63 healthy people were taken by direct view or video analysis methods (20). In the study with two different observers, a time difference of at least 1 s was detected in the results. Due to this observer-induced problem, only one person evaluated the video recordings in our study. Furthermore, the videos were interpreted with a video processing program that showed the pulp's blood flow from the pulp turning white with pressure to complete restoration. Since the results were recorded in ms, the error level, if any, was 1/1000. Finally, we found that CRT measurements increased in patients with normal saturation but lymphopenia. This may be clinically important because prolonging CRT before low O2 saturation happens may mean predicting peripheral circulatory disorders in COVID-19. This study's scope was limited in terms of evaluating the videos with the human eye instead of a digital software. The small sample size did not allow us to use machine-learning software either.

In conclusion, this study evaluated the CRT measurements in patients with COVID-19. This study's findings may provide new prognostic value in the disease's survey. Our study also revealed that CRT was more prolonged in the COVID-19 group: as COVID-19's severity increases, so does CRT. Moreover, in patients without lymphopenia, CRT prolongation may more valuable for the prognosis. Further studies need to be carried out to develop new prognosis strategies for COVID-19.

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