RESEARCH

Analysis of telomere length in patients with COVID-19 and investigation into its relationship with clinical- demographic data

COVID-19 hastalarında telomer uzunluğunun analizi ve klinik-demografik verilerle ilişkisinin araştırılması

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Abstract

Purpose: Novel coronavirus disease 2019 (COVID-19) is an infectious disease unknown before the 2019 outbreak in Wuhan. This study evaluated telomere length in COVID-19 (+) and (-) samples with clinical-demographic parameters.

Materials and Methods: DNA was isolated from COVID-19 (+) (n=70) and (-) (n=70) patients. Telomere length was determined by real-time-PCR (RT-PCR). The $2^{-\Delta\Delta Ct}$ method was used to analyze the telomere length of the samples.

Results: There were significant differences in creatinine, LDH, ferritin, WBC, NEU and CRP in COVID-19 (+) patients compared to COVID-19 (-) patients. The NEU/LYM (or N/L) ratio was found higher in the patients with COVID-19 (+), than in COVID-19 (-). On the other hand, our COVID-19 (+) patients (mean±std:0.93±0.58) had significantly shorter telomere lengths than the COVID-19 (-) (mean±std:1.26±0.76). Moreover, COVID-19 (+) male patients (mean±std:1.06±0.50) had longer telomere length than female patients (mean±std:0.76±0.54). Telomere length was significantly shorter in patients with COVID-19 (+) with high blood urea nitrogen (BUN), high creatinine, high hematocrit, high NEU levels, normal platelets (PLT), and low WBC levels.

Conclusion: Our findings suggest that telomere length and blood parameter levels influence the severity of COVID-19. Blood parameters differed in patients with COVID-19 (+) and COVID-19 (-). As a result, increasing the number of similar studies in the future can demonstrate the significance of our findings.

Keywords: COVID-19, Telomere length, RT-PCR, NEU/LYM, blood

Öz

Amaç: Yeni koronavirüs hastalığı 2019 (COVID-19), Wuhan'daki 2019 salgınından önce bilinmeyen bulaşıcı bir hastalıktır. Bu çalışma, klinik-demografik parametrelerle COVID-19 (+) ve (-) numunelerinde telomer uzunluğunu değerlendirdi.

Gereç ve Yöntem: DNA COVID-19 (+) (n=70) ve (-) (n=70) hastalarından izole edildi. Telomer uzunluğu gerçek zamanlı PCR (RT-PCR) ile belirlendi. $2^{-\Delta\Delta Ct}$ yöntemi, örneklerin telomer uzunluğunu analiz etmek için kullanıldı.

Bulgular: COVID-19 (+) hastalarında kreatinin, LDH, ferritin, WBC, NEU ve CRP'de COVID-19 (-) hastalara göre anlamlı fark vardı. NEU/LYM (veya N/L) oranı COVID-19 (+) hastalarında COVID-19 (-) hastalara göre daha yüksek bulundu. Öte yandan, COVID-19 (+) hastalarımızın telomer uzunluğu (ortalama ±standart sapma:0.93±0.58) COVID-19 (-) (ortalama ±standart sapma:1.26±0.76) olanlara göre anlamlı olarak daha kısaydı. Ayrıca COVID-19 (+) erkek hastaların telomer uzunluğu (ortalama±standart sapma:1.06±0.50) kadın hastalara (ortalama ±standart sapma:0.76±0.54) göre daha uzundu. Kan üre nitrojeni (BUN), yüksek kreatinin, yüksek hematokrit, yüksek NEU düzeyi, normal trombosit (PLT) ve düşük WBC düzeyi olan COVID-19 (+) hastalarda telomer uzunluğu anlamlı olarak daha kısaydı.

Sonuç: Bulgularımız, telomer uzunluğu ve kan parametre düzeylerinin COVID-19'un şiddetini etkilediğini göstermektedir. Kan parametrelerinin COVID-19 (+) ve COVID-19 (-) hastalarında farklılık gösterdiği tespit edildi. Sonuç olarak gelecekte benzer çalışmaların artması bulgularımızın önemini ortaya koyacaktır.

Anahtar kelimeler: COVID-19, telomer uzunluğu, RT-PCR, NEU/LYM, kan

INTRODUCTION

COVID-19 is an infectious disease, identified by the 2019 outbreak in Wuhan. COVID-19 pandemic has been considered a public health emergency that has influenced many countries worldwide[1]. The COVID-19 has affected not only physical health and mental health[2,3].

SARS-CoV-2 is the disease-causing agent in COVID-19[4]. Two fundamental varieties of checking out are used as useful resources for the prognosis of COVID-19 at some stage in a lively infection; molecular tests that discover the presence of the RNA genome and antigen tests that discover the presence of viral antigens, along with the viral protein coating[5]. Symptoms of the disease include pneumonia, fever, and dyspnea. Most infected patients are expected to recover without further treatment. Elderly and vulnerable individuals are at risk of severe and non-fatal complications with a mortality rate of approximately 2-3% [2].

COVID-19 virus spreads many systems, so it may be considered a systemic disease. Laboratory findings are not special to this disease, but they have been used to predict the prognosis of patients. COVID-19 virus leads to a cytokine storm that causes activation of immune cells including monocytes, mast cells, T cells, and endothelial cells[6]. When viruses enter the body, they will first see great defense from mast cells. The virus stimulates mast cells to release pro-inflammatory molecules, including Interleukins (ILs), Tumor necrosis factor-alpha (TNF-a), C-C Motif Chemokine Ligand 2 (CCL2), histamine, which exacerbate inflammation and so disease severity[6]. Cytokine storm and lymphopenia are utilized to estimate disease severity; furthermore, these are informative about patients with poor disease progression[7]. Laboratory findings like higher white blood cells (WBCs), lymphopenia, high neutrophil count, thrombocytopenia, increased liver enzymes, coagulation derangements and increased inflammatory agents have been related to disease severity[8]. In the patients with COVID 19 (+), the levels of creatinine, ferritin, and C-reactive protein (CRP) were higher[9]. Fibrinogen, prothrombin time, D-dimer have been used as laboratory measurements during hospitalization to estimate COVID-19 related pulmonary embolism[10], beside that plasma levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) that have been linked with disease severity have been utilized to monitor the liver function[11].

Telomeres are non-coding DNA sequences that protect the ends of chromosomes and shorten with age. Telomeres have long been suggested as one of the aging indicators[12]. telomere length is affected by genetic and environmental factors[13,14]. Despite the telomerase activity, telomere shortening continues with repeated cell divisions, which leads to impairment of cell function and ultimately to cell aging[15]. The "end replication problem" causes telomeres to shorten as cells divide and DNA needs to be copied[16,17]. Chronic disease and immunosenescence lead to shorter telomere, disrupting homeostasis at critical limit[18]. Telomere shortening is stimulated by inflammation, exposure to infectious agents, and oxidative stress parts of COVID-19 infection. These factors destroy the telomere and impair its' repair mechanisms and so cause telomere attribution[18-20]. When people are exposed to viral infections coronaviruses and the common cold virus, telomere length is altered[21,22]. Shorter telomere length has been linked to various indicators of COVID-19 severity in various groups, according to earlier studies[23,24]. Wang et al. (2021) shorter leucocyte telomere length is related to a higher risk of adverse COVID-19 outcomes[24]. Shorter telomere length was associated with the severity of COVID-19 infection, which can be helpful as a biomarker or understanding the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathophysiology[25]. There are various studies on the investigation into telomere length in COVID-19 (+). Confounding variables may have distorted the apparent link between COVID-19 and leukocyte telomere length in observational studies[26,27]. However, more studies are needed to investigate the factors that trigger the severity of the disease to reveal the causes that change the telomere length and demonstrate their effects on hematological and biochemical parameters.

Telomere length may change in line with physiologic conditions in the human body. Relation of diseases and telomere length was studied before many times but not in COVID-19 infection. The aim of this study is to reveal whether there is any link between telomere length and laboratory findings used in COVID-19 infection. Alteration of laboratory findings may influence telomere length in patients. We think that the effect of telomere length can

provide us with various clues regarding disease severity. Thus, telomere length analysis will guide the choice of treatment to be given to the patient.

MATERIALS AND METHODS

Sample

All patients suspected of COVID-19 and referred for further investigation were included in this study. Patients above 18 years of age diagnosed with SARS-CoV-2 RNA using the Polymerase Chain Reaction (PCR) test were included in this study, regardless of their symptom status, according to WHO (World Health Organization) guidelines. Individuals with had a PCR test showing signs of COVID-19 were randomly included in this study. None of our patients were vaccinated. This study was conducted by the Declaration of Helsinki. The Medical Research Ethics Committee approved the present study of Ordu University (Decision number: 2021/27).

Inclusion criteria were patients aged 18 and over who applied to the emergency department and having positive and negative SARS-CoV-2 PCR analysis. Pregnant patients, patients with immunosuppression and patients with discordant SARS-CoV-2 PCR analyzes and not diagnosed with COVID-19 were excluded. COVID-19 (+) (n=70) and COVID-19 (-) blood samples (n=70) were collected prospectively in Emergency Department at Ordu University Hospital's. A total of 140 samples were collected. Negative samples consist of individuals with negative PCR tests who applied to our outpatient clinic.

Procedure

Demographic data of the COVID-19 (+) patients enrolled in the research, other diseases, and laboratory data routinely queried in the emergency department, pulmonary tomography, clinical outcomes, and discharge from the hospital or death were collected by scanning the system data. The data were reviewed and verified by clinicians.

DNA extraction stage

DNA was isolated from all COVID-19 positive and negative whole blood samples using the Eco-Tech kit (Turkey). DNA isolation stage was carried out by Dr. Ebubekir Dirican at Bayburt University Medical Biology and Genetics Laboratory.

Each sample's DNA was successfully isolated using 200 μl of blood. 200 μl of lysis buffer was added to

each 200 μl of whole blood sample and the lysate was prepared. 20 μl of RNase was added and mixed well. It was left to incubate for 3 minutes. 20 μl of Proteinase K was added and mixed well. It was allowed to incubate for 10 minutes. 400 μl of binding buffer was added and mixed well. The mixture was transferred to the column Collection tube. Washing has begun. DNA was collected in 30-50 μl elution buffer at the last step. Take3 Plate was used to quantitatively determine the concentration of the DNA samples (BioTek, USA) and were stored at -20°C until used for PCR.

Telomere length analysis

The BioRad -CFX96 Real-Time PCR System was used to measure relative telomere length. Telomere length stage was carried out by Dr. Ebubekir Dirican and at Atatürk University Experimental Research Center Laboratory. Ten ng of genomic DNA was amplified in 10 μl with iTaq™ Universal SYBR® Green Supermix (2×) (BioRad) and 10 nmol of each primer. Primers (TELO and 36B4) were taken from a previous study [28]. Each reaction was performed in duplicate. In addition, the DNA sample was not added to the negative sample. Instead, the same amount of water in the other DNA samples was added. PCR reaction conditions were performed according to our previous study [29].

The telomere length analyses were carried out with cycling conditions: 95° C for 3 min, 95° C for 5 sec, and an annealing temperature of 60° C for 1 min. The T/S ratio represents the average telomere length per genome. Telomere length measurement analyses are determined according to the difference between the cycle thresholds (CTs) of the telomere reaction (T) and single-copy gene (S). Therefore, the delta-delta Ct method ($2^{-\Delta\Delta Ct}$ method) is a formula used to analyze the relative telomere length of samples when performing RT PCR [30]. We calculated ΔCt for 36B4 and TELO genes. ΔCt is the difference between the two genomic DNA samples (36B4 or TELO) quantification cycle numbers [31].

For single copy reference (36B4)

ΔCt (36B4) = Ct (36B4, sample 2) - Ct (36B4, sample 1)

For telomere (TELO);

ΔCt (TELO) = Ct (TELO, sample 2) - Ct (TELO, sample 1)

ΔΔCt = ΔCt (TELO) - ΔCt (36B4)

Relative telomere length of sample 2 to sample 1 (fold) = $2^{-\Delta\Delta Ct}$

Laboratory findings

Hemogram parameters (WBCs, mean corpuscular volume (MCV), hematocrit (HCT), platelet (PLT), hemoglobin (HGB), neutrophil (NEU), biochemical parameters (glucose, creatinine, blood urea nitrogen (BUN), AST, ALT, lymphocyte (LYM); lactate dehydrogenase (LDH), ferritin, CRP) were studied among routine blood tests in the emergency department from the COVID-19 (+) and (-) samples. Routine laboratory test results of all patients with COVID -19 (+) and (-) were retrospectively obtained from the hospital database.

Statistical analysis

GraphPad Prism 7.04 was used to analyze all of the data. The normal distribution of the data was shown by the Kolmogorov-Smirnov normality test. The Mann-Whitney U test was used to compare the biochemical test results of COVID19 (+) and COVID19 (-) individuals. The association between relative telomere length and clinical parameters was examined using Student's t-test and Mann-Whitney U test to relate two or more independent groups. The Mann-Whitney U test was used to compare the telomere lengths of COVID 19 (+) and COVID-19 (-) individuals. Student's t test was also used to compare telomere lengths in patients with COVID-19 (+) according to low and high BUN, CRE, AST, LDH, HGB, HCT, MCV, NEU, CRP and WBC blood parameter results. The Mann-Whitney u test was also used to compare telomere lengths in patients with COVID19 (+) according to the low and high ALT, ferritin, PLT and LYM blood parameters results of individuals. A One-way ANOVA test was used to assess distribution of telomere length and comorbid diseases of patients with COVID 19. Statistics were considered significant for values with a p-value of 0.05.

RESULTS

In this study, the blood tests taken at the time of the first admission to the hospital were evaluated (Table 1). From blood tests, hemogram and biochemistry parameters were examined. The distribution of WBCs, HGB, PLT, NEU, LYM, NEU/LYM ratio (or N/L), creatinine, liver function tests (ALT-AST), LDH, CRP, and ferritin values according to patient groups were examined.

The levels of WBC, NEU, CRP, LDH, creatinine, and ferritin were statistically different between COVID-19 positive and (-) individuals ($p < 0.0001$; $p < 0.0001$; $p < 0.0001$; $p = 0.024$; $p < 0.0001$; $p < 0.0001$, respectively) (Table 1). WBC, NEU, CRP, LDH, creatinine and ferritin values with COVID-19 (+) had higher than COVID-19 (-). When AST, ALT, PLT and LYM values were compared, there was no a statistical difference between those with COVID-19 (+) and (-) ($p = 0.326$; $p = 0.810$; $p = 0.101$; $p = 0.308$, respectively). However, AST, ALT, PLT and LYM values with COVID-19 (+) had higher than those of the patients with COVID-19 (-). HGB values with COVID-19 (+) had lower than those of the patients with COVID-19 (-) ($p = 0.055$).

In our research, the N/L ratio was found higher in the patients with COVID-19 (+) than in COVID-19 (-) ($p < 0.0001$) (Figure 1). These results can be attributed to the fact that the high N/L ratio is specific to patients with COVID-19 (+) and may increase in other inflammatory conditions. Thus, the N/L ratio is used in the early-stage prognosis follow-up of the disease rather than in the diagnosis of the disease.
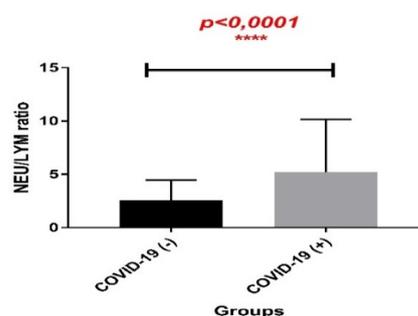

Figure 1. NEU/LYM ratio in patients with COVID-19 (+) and COVID-19 (-)

According to the results of our telomere length analysis, patients with COVID-19 (+) (mean±std:0.93±0.58) had shorter telomeres and a statistically significant difference compared to COVID-19 (-) individuals(mean±std:1.26±0.76) (p=0.0463) **(**Figure 2A). It might be that patients with COVID-19 (+) show accelerated telomere shortening rather than COVID-19 (-) patients show increased telomerase activity. Furthermore, female patients with COVID-19 (+) (mean±std:0.76±0.54) had shorter telomere lengths than male patients

(mean±std:1.06±0.50) ($p = 0.0282$) (Figure 2B). However, no significant difference was found in telomere length according to gender in COVID-19 (-) individuals ($p = 0.3616$) (Figure 2C). We also evaluated the distribution of telomere length by age in both patients with COVID-19 (+) and COVID-19 (-). However, we could not show a significant

relationship with the age of patients ($p > 0.05$). It has been shown that patients over 50 years of age who are positive for COVID-19 have a short telomere length (mean±SD=0.8913±0.07925) ($p = 0.467$). Mortality and malignancy had no statistically significant correlation with short telomere length ($p= 0.567$ and $p = 0.158$, respectively).
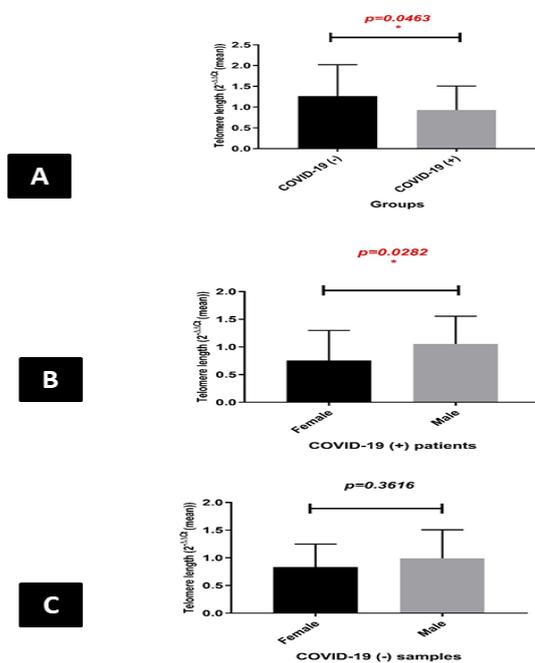

Figure 2. A. Telomere length in patients with COVID-19 (+) and COVID-19 (-), B. Telomere length in female and male patients with COVID-19 (+), C. Telomere length in female and male patients with COVID-19 (-).

Comparing telomere length with high and normal blood biochemical parameters of patients, it was found that those with high BUN, creatinine, HCT, and NEU levels had significantly shorter telomeres ($p=0.037$; $p=0.034$; $p=0.045$; $p=0.037$, respectively) (Figure 3A-D). In addition, patients with normal PLT

and low WBC levels were significantly shorter telomere length ($p=0.043$; $p= 0.019$, respectively) (Figure 4A-B). Although patients with high AST, high ALT, high ferritin, high CRP, low LYM and low MCV values had shorter telomeres. No statistically significant relationship was found ($p=0.288$; $p=0.295$; $p=0.575$; $p=0.266$; $p=0.188$, respectively).

Table 1. Distribution of biochemistry analysis results of patients with COVID-19 (+) and COVID-19 (-)

Parameters (Reference range)	COVID-19 (+) patients (n=70) Median (IQR)	COVID-19 (-) samples (n=70) Median (IQR)	* p value for U test
CRP(0-0.5 mg/dL)	3.69(7.97)	0.65(1.71)	****<0.0001
NEU(1.8-6.98 10*3/ UL)	4.95(4.195)	3.4(2.2)	****<0.0001
LDH(135-214 U/L)	214(117)	197(66)	*0.024
Creatinine(0.50-0.90 mg/dl)	0.9(0.435)	0.72(0.29)	****<0.0001
Ferritin(30-400 µg/l	173(360.65)	69.9(100.2)	****<0.0001
WBC(4.49-12.6 10*3/ UL)	7.58 (5.415)	5.615 (2.48)	****<0.0001
LYM(1.26-3.35 (0*3/ UL))	1.35(1.065)	1.505(0.81)	0.308
HGB(12.3-15.3 g/dL	12.6(2.7)	13.15(2.7)	0.055
PLT(150-450 10*3/ UL)	221(107.5)	203.5(88)	0.101
AST(0-32 U/L	21(16)	20(8)	0.326
ALT(0-33 U/L)	19(18)	18(17)	0.810

* $p<0.05$ was considered significant.
-IQR: Interquartile range; AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, LDH; Lactate dehydrogenase, WBC; White blood cell, HGB; hemoglobin, PLT; Platelet, NEU; Neutrophil, LYM; Lymphocyte, CRP; C-reactive protein.
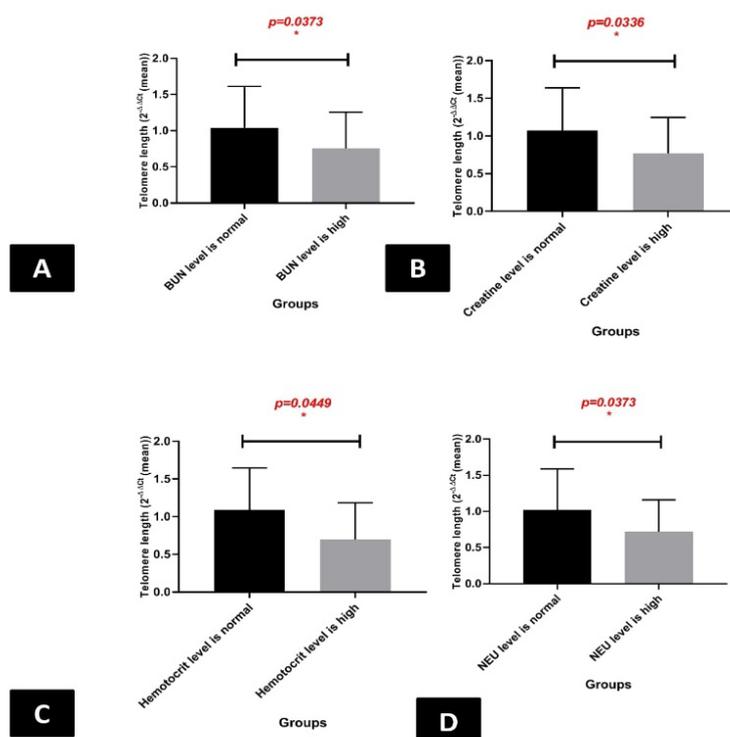

Figure 3A-D. The relationship between telomere length and BUN, creatine, hematocrit and NEU blood parameters of patients with COVID-19 (+)
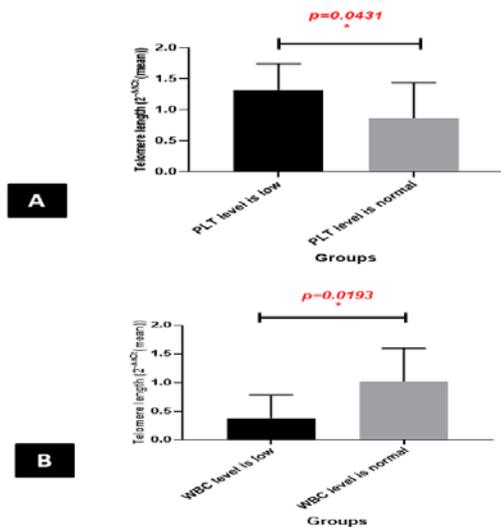
Figure 4A-B. The relationship between telomere length and PLT and WBC blood parameters of patients with COVID-19 (+).

When we evaluated the distribution of telomere length and comorbid diseases of patients with COVID-19 (+), we could not detect a significant difference ($p > 0.05$). Patients with COPD, hypertension and chronic kidney disease were shorter telomere length ($p = 0.4855$, (mean=0.7841); $p = 0.444$, (mean=0.8175); $p = 0.905$ (mean=0.8320) respectively). On the other hand, patients with cardiovascular disease, diabetes, neurological disease and hepatitis B had longer telomeres, no statistically significant relationship was found ($p = 0.663$, (mean=0.932057); $p = 0.236$, (mean=1.055); $p = 0.859$, (mean=0.9165); $p = 0.349$ (mean=0.9432), respectively)

DISCUSSION

This research focused on the Turkish COVID-19 population and examined the correlation between telomere length changes and clinical parameters. Telomeres are non-coding DNA sequences that protect the ends of chromosomes and shorten with age. Adults with shorter telomeres are more vulnerable to respiratory viral infections, have a higher risk of severe acute respiratory distress syndrome and have a lower chance of survival from sepsis[32].

COVID-19 severity increases with age, with elderly patients having the highest mortality rate, suggesting that age-related molecular changes play a role in COVID-19 severity [18]. There are few studies in the literature analyzing telomere length in COVID-19 patients. However, there are no conclusive data yet. Tsilingiris et al. (2020) highlighted the significance of establishing a potential pathogenic link between telomere shortening and severe SARS-CoV-2 infection [33]. Given COVID-19, the shorter telomeres of hematopoietic cells in older people, in those with cardiometabolic disease, and male individuals may impede lymphopoiesis, CD4/CD8 lymphopoiesis, in particular, increasing the risk for severe illness and death[34]. The shortening of telomeres negatively affects immune cell function and development[35].

In this research, patients with COVID-19 (+) had significantly higher WBC, NEU, CRP, LDH, creatinine and ferritin levels than (-) patients. Patients with COVID-19 (+) who develop new-onset renal disease should be followed up after discharge to assess renal recovery, especially if they are elderly or have high discharge creatinine [36]. Keski (2021) reported that WBCs and neutrophil count were significantly higher, while lymphocyte counts were significantly lower. The researcher indicated that the deceased patients had significantly higher values of CRP, procalcitonin, D-dimer, and ferritin [37]. Banchini

et al. (2021) found a considerably higher ferritin median level in COVID-19 (+) than patients with COVID-19(-)[38].

Disease severity is dependent on clinical and laboratory findings. Laboratory findings, including CRP, ferritin, and procalcitonin, etc., are not specific to COVID-19 infection; however, they are considered as a biomarker of acute COVID-19 infection. This study, found no significant correlation between AST, ALT, HGB, PLT, and LYM levels between patients with COVID-19 (+) and COVID-19 (-). Many recent studies have highlighted the relationship between laboratory findings and disease severity. Fu et al. (2020) reported that the AST/ALT ratio, urea nitrogen, total bilirubin (TBIL), and LDH were positively correlated with mortality risk in patients with COVID-19 at admission[39]. According to Demir (2020), the AST level of patients with COVID-19 in the intensive care unit (ICU) was significantly higher than that of those in the ward [40]. Patients with COVID-19 appear to have a higher rate of liver dysfunction. In a study conducted in China with a large population, AST/ALT levels were high in 18.2/19.8% of patients with mild disease and 39.4/28.1% of patients with severe disease[41]. Lei et al. reported that AST is strongly associated with to mortality risk in patients with COVID-19[42].

According to studies in the literature, the N/L ratio has been used as one of the indicators of inflammation in the diagnosis and follow-up phase of diseases in recent years[43]. In the meta-analysis conducted with 660 people, the N/L ratio was found to be high in 40% of the participants[44]. A high N/L ratio was found in 35.1% of patients with acute respiratory syndrome (ARDS)[45]. In the current study, the N/L ratio was found higher in the patients with COVID-19 (+) than in COVID-19 (-). These results can be attributed to the fact that the high N/L ratio is specific to patients with COVID-19 (+) and may increase in other inflammatory conditions. Hence, the N/L ratio is used in the early-stage prognosis follow-up of the disease rather than in the diagnosis of the disease.

Telomere length decreases with age and is considered a cellular marker of biological aging[12,46,47]. In addition, telomere shortening or attrition is a natural part of cell division that can be accelerated by inflammation[48], oxidative stress[49] and decreases by telomerase activity[50]. People with critically short telomeres due to telomerase mutations have a reduced regenerative capacity. They are more likely to develop degenerative diseases in low- proliferative and high -proliferative tissues[51].

Patients with COVID-19 (+) had significantly shorter telomere length than COVID-19 (-), according to our result. This situation demonstrates that patients with COVID-19 (-) may have higher telomerase activity than positive patients. The distribution of telomere length and comorbid diseases of patients with COVID 19 (+), could not detect a significant difference. Patients with COPD, hypertension and chronic kidney disease were shorter telomere length. However, patients with cardiovascular disease, diabetes, neurological disease and hepatitis B had longer telomere length. This situation does not provide us with sufficient data to explain that the additional disease state of patients with COVID-19 (+) causes shortening or longer telomere length. In addition, telomere length was shorter in our female patients than in male patients. Similarly, when compared to the reference cohort, a significantly higher proportion of patients with COVID-19 with short telomeres (10th percentile) was discovered by Froidure et al. (2020)[19]. Many subtypes of fibrotic interstitial lung disease, including idiopathic pulmonary fibrosis (IPF), have been linked to short telomere length in blood leucocytes[52]. Shorter telomere length is related to with the severity of COVID-19 infection, suggesting that it could be used as a biomarker or to understand the pathogenesis of SARS-CoV-2[25].

The present study, also investigated the relationship between telomere length and blood parameters of patients with COVID-19 (+). We discovered that telomere length differed significantly according to BUN, creatinine, HCT, PLT, NEU, and WBCs biochemical blood parameters. Patients with high BUN, creatinine, HCT, and NEU levels, in particular, had short telomere length. Patients with low WBC count, on the other hand, had short telomere length. The relationship between serum creatinine and a cellular senescence marker reveals an underlying mechanism that influences both decreasing serum creatinine and cellular senescence[53]. In addition, telomere length in subcutaneous adipose tissue cells was linked to serum creatinine. Accordingly, increased oxidative stress is a common mechanism linking telomere length and serum creatinine concentration[53]. In a study, telomere length was found to be negatively related to HGB and positively associated with WBCs. A small but significant positive relationship was between telomere length

and reticulocyte percentage[54]. Telomere length in WBCs could be a biomarker for accumulating systemic oxidative stress[55]. According to Colella et al. (2017), telomere length and hemoglobin level positively correlate, while telomere length and lymphocyte count have a negative correlation[56]. As a result, we understand that some blood parameters, whether high or low, may be affected by telomere length.

This study has some limitations that should be noted. We investigated the telomere length and clinical parameters of patients with COVID-19 (+). First of all, we did not measure telomerase activity. Thus, it would be much better if we could compare telomere length to telomerase activity. Second, we did not have the budget to look at telomere length in many patients.

In conclusion, impairment homeostasis at COVID-19 infection alteration physiologic conditions may influence telomere length in patients. Increased oxidative stress, expanding cytokine levels, and decreased ventilation capacity of the lung that has been shown in COVID-19 also may contribute to the shortening of telomere length. Telomere attrition was demonstrated due to oxidative stress and inflammation[20, 22, 57]. Impairment of plasma level of laboratory findings may lead to shorter telomere length in patients with COVID-19 infection due to decreasing telomerase activity. Alterations of laboratory findings increased oxidative stress, and changed telomere length have a relation and so if laboratory findings show disease severity, telomere length also may reflect this severity. Furthermore, a higher neutrophil/lymphocyte ratio considered an inflammation indicator in patients with COVID-19 may also affect the telomere length. Future telomere studies with an expanded patient population may make telomere a marker of COVID-19 disease severity.

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