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Emergence of SARS CoV-2 Variant B.1.1.7 in a Pandemic Hospital

Bir Pandemi Hastanesinde SARS CoV-2 B.1.1.7'nin Ortaya Çıkışı

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ABSTRACT

Introduction: *A clinically significant variant of SARS-CoV-2 was identified in the UK in December 2020 and was designated VOC-202012/01 (lineage B.1.1.7) on 14 December 2020. Our study aimed to evaluate the lineage B.1.1.7 prevalence over time and demographic, hematological, coagulation, inflammation characteristics in hospitalized patients with B.1.1.7 during February-March 2021.*

Materials and Methods: *Between 5 February and 20 March 2021, 182 inpatients with B.1.1.7 were included in this study. Bio-Speedy, SARS-CoV-2 Double Gene RT-qPCR (Bioeksen, İstanbul, Türkiye) kit was used to diagnose COVID-19. Cycle threshold< 27 samples were taken into mutation study with Bio-Speedy SARS-CoV-2 Variant Plus kit.*

Results: *Of the 5187 SARS-CoV-2 positive cases, 2288 (69.65%) were evaluated as variant B.1.1.7 positive. Throughout the study, the case number's daily increase rate was 8.78% in SARS CoV-2, 13.16% in B.1.1.7; the case number's doubling time was calculated as 7.9 days in SARS CoV-2 and 5.27 days in B.1.1.7. In ICU patients, hemoglobin (p< 0.001), platelet (p= 0.034) and lymphocyte (p< 0.001) levels were lower but neutrophil (p= 0.025), monocyte/lymphocyte ratio (MLR) (p= 0.002), neutrophil/lymphocyte (NLR) (p< 0.001) ratio and D-dimer (p= 0.008) levels were dedected higher than non-ICU patients.*

Conclusion: *Our study demonstrated that the infectiousness of B.1.1.7 was higher than previous variants and became the dominant SARS-CoV-2 in six weeks in our region. Therefore, urgent and decisive measures should be taken to minimize morbidity and mortality associated with COVID-19. In addition, our findings indicate that first hematologic markers of the patients can be an important biomarker for the prognosis of COVID-19 disease.*

Key Words: *SARS-CoV-2; Variant B.1.1.7; Growth rate; NLR*

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ÖZ

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Giriş: *Aralık 2020'de Birleşik Krallık'ta klinik olarak anlamlı bir SARS-CoV-2 varyantı tanımlandı ve 14 Aralık 2020'de VOC-202012/01 (soy B.1.1.7) olarak adlandırıldı. Çalışmamız; varyant B.1.1.7'nin zaman içindeki prevalansını ve Şubat-Mart 2021 döneminde hastanede yatan hastaların demografik, hematolojik, pıhtılaşma, inflamasyon parametrelerini değerlendirmeyi amaçladı.*

Materyal ve Metod: *5 Şubat-20 Mart 2021 tarihleri arasında B.1.1.7 tanısı ile hastanede yatan 182 hasta çalışmaya dahil edildi. COVID-19 teşhisi için Bio-Speedy, SARS-CoV-2 Double Gene RT-qPCR (Bioeksen, İstanbul, Türkiye) kiti kullanıldı. Cycle tershold (Ct)< 27 olan numuneler Bio-Speedy SARS-CoV-2 Variant Plus kiti ile mutasyon çalışmasına alındı.*

Bulgular: *Beş bin yüz seksen yedi SARS-CoV-2 pozitif vakanın 2288'i (%69.65) varyant B.1.1.7 pozitif olarak saptandı. Çalışma boyunca vaka sayısının günlük artış oranı SARS CoV-2'de %8.78, B.1.1.7'de %13.16; vaka sayısının iki katına çıkma süresi SARS CoV-2'de 7.9 gün, B.1.1.7'de 5.27 gün olarak hesaplanmıştır. Yoğun bakım hastalarında; hastaneye yatış sırasında hemoglobin (p< 0.001), trombosit (p= 0.034) ve lenfosit (p< 0.001) düzeyleri serviste yatan hastalara göre anlamlı derecede daha düşük; nötrofil (p= 0.025), monosit/lenfosit oranı (MLR) (p= 0.002), nötrofil/lenfosit oranı (NLR) (p< 0.001) ve D-dimer (p= 0.008) düzeyleri ise daha yüksek saptandı.*

Sonuç: *Çalışmamız, B.1.1.7'nin bulaşıcılığının önceki varyantlardan daha yüksek olduğunu ve altı hafta içinde bölgemizde baskın SARS-CoV-2 haline geldiğini göstermiştir; bu nedenle, B.1.1.7 ile ilişkili morbidite ve mortaliteyi en aza indirmek için acil ve kararlı önlemler alınmalıdır. Ayrıca bulgularımız, hastaların ilk hematolojik belirteçlerinin COVID-19 hastalığının prognozu için önemli bir biyobelirteç olabileceğini göstermektedir.*

Anahtar Kelimeler: *SARS-CoV-2; Varyant B.1.1.7; Büyüme hızı; NLR*

INTRODUCTION

As the COVID-19 outbreak continues, new clinically important variants of SARS-CoV-2 will emerge. A clinically significant variant of SARS-CoV-2 was identified in the UK in December 2020 and named as SARS-CoV-2 variant VOC 202012/01 or 20I/501Y.V1 on 18 December 2020[1-3]. Later in South Africa, another variant of SARS-CoV-2 (20H/501Y.V2 or B.1.351) appeared[4,5]. Finally, on 10 January 2021, four cases of COVID-19 associated with a new SARS-CoV-2 variant were reported in Japan in travelers returning from Brazil, designated as SARS-CoV-2 variant P.1[6]. All three variants identified so far are considered to pose a risk due to increased transmission rates and changes in the current epidemiological situation and rapidly spread around the world[7].

As of 8 March 2021, variant B.1.1.7 has been detected in 113 countries, mainly in Europe, Asia, Africa, and the USA[8]. On 3 February 2021, Turkish Ministry of Health announced that the UK mutation was detected in 196 people in our country, the South African variant in two people, and the Brazilian variant in one person[9]. Since the last week of February, in the risk assessment made according to the number of weekly cases (per 100 thousand people), Samsun ranked first among the provinces with very high risk and continued to rank first in the statement made on 3 April[9].

Hematological parameters are important to support the diagnosis of COVID-19. There are studies that have evaluated if these markers could be used as predictive parameters in the COVID-19 disease. This study aimed to evaluate the emergence of SARS-CoV-2 variant B.1.1.7 in a pandemic hospital and the detection and increase rates between February and March 2021 in our region. In addition, it was aimed to examine Hb, platelets, lymphocytes, neutrophils, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio

D-dimer and Cycle threshold values in hospitalized patients with B.1.1.7. and determine their prognostic value for COVID-19.

MATERIALS and METHODS

Ethics approval for the study was obtained from the Ethics Committee of Samsun Training and Research Hospital (Date: 24.03.2021, approval number: GOKA/2021/6/13). Furthermore, the study was approved by the Turkish Ministry of Health, General Directorate of Health Services, Scientific Study Platform (Date: 19.03.2021 and Decision No: Melek Bilgin-2021-03-19T14-17-19).

This study was conducted at the Microbiology-PCR laboratory due to COVID-19, and the patients were evaluated retrospectively. A total of 182 patients, positive for SARS-CoV-2 Variant B.1.1.7, aged 1-90 years, followed up in the ward and intensive care units of Samsun Training and Research Hospital between 1 February 2021 and 20 March 2021, were included in the study.

Bio-Speedy, SARS-CoV-2 Double Gene RT-qPCR (Bioeksen, İstanbul, Türkiye) kit was used to diagnose COVID-19 and studied with the BioRad CFX96 RT-PCR device. A diagnosis of COVID-19 was made with the SARS CoV-2 nucleoprotein and the oligo primers of the ORF1ab conserved gene region. RNase P human mRNA gene region was used as an internal control. Cyclethreshold (Ct)≤ 38 sigmoidal values were considered positive for SARS-CoV-2 by the manufacturer's recommendations. As stated in the studies of Washington NL et al.[10] when N gene detecting kits were used, samples with Ct≥ 27 could not produce strong amplification, so positive samples with Ct< 27 were included in the mutation study with the Bio-Speedy SARS-CoV-2 Variant Plus (Bioeksen, İstanbul, Türkiye) kit to detect SARS-CoV-2 variant B.1.1.7. Orf1ab and N gene region for SARS-CoV-2, variant-specific regions for B.1.1.7, B.1.351, P.1, B.1.525, and B.1.526 were targeted with this kit in a single multiplex reaction. The human RNase-P site targeting exome-exome splicing in mRNA was included in the multiplex reaction to control RNA stability, extraction, and amplification inhibition. Samples with a Ct≥ 27 were considered SARS-CoV-2 positive. Only one positive result of each patient was included in the study, and positive results in retests of the same patient were excluded from the study.

Statistical Analysis

Epi Info 7 program was used to calculate the sample size (population size= 147.560, expected frequency= 18.53%, standard error=0.01, confidence level= 99.99%) and Microsoft Excel 2010 program for graph drawing and calculations. Statistical analysis was performed using SPSS Statistics for Windows, version 22.0 (IBM, USA). P-value< 0.05 was considered statistically significant. Categorical variables were expressed as frequency and percentage and compared using the Chi-square test while continuous variables were expressed as mean ± standard deviation.

RESULTS

Between 5 February and 20 March, 147.560 COVID-19 PCR tests were performed in Samsun province, and 27.348 (18.53%) of these tests were positive. The sample size was found to be 19.793 according to these data (standart error= 0.01, confidence level= 99.99%). On the exact dates, 21.434 nasopharyngeal swabs were studied in our laboratory, and 5187 (24.20%) of these samples were detected as SARS-CoV-2 positive by the SARS-CoV-2 (2019-nCoV) RT-qPCR test. Three thousand two hundred eighty-five (63.33%) samples with Ct< 27 in PCR were included in the mutation study, and 2288 (69.65%) of them were found as variant B.1.1.7 positive.

Weekly evaluation of the total 5187 PCR positive and 2288 B.1.1.7 positive cases during the study period is demonstrated in Figure 1. While 23.23% of the total PCR positive cases were B.1.1.7 positive in the first week, this rate increased to 53.86% in the last week. Logistic curve of the SARS CoV-2 and variant B 1.1.7 case numbers done by evaluating each day and the six days before and taking the average of seven days is shown in Figure 2. On the first day of the study, 61 (89.71%) of 68 PCR (+) cases were found to be SARS CoV-2 and seven (10.29%) as variant B.1.1.7. On the last day, 2899 (55.89%) of 5187 PCR (+) cases were dedected as SARS CoV-2 and 2288 (44.11%) as variant B.1.1.7.

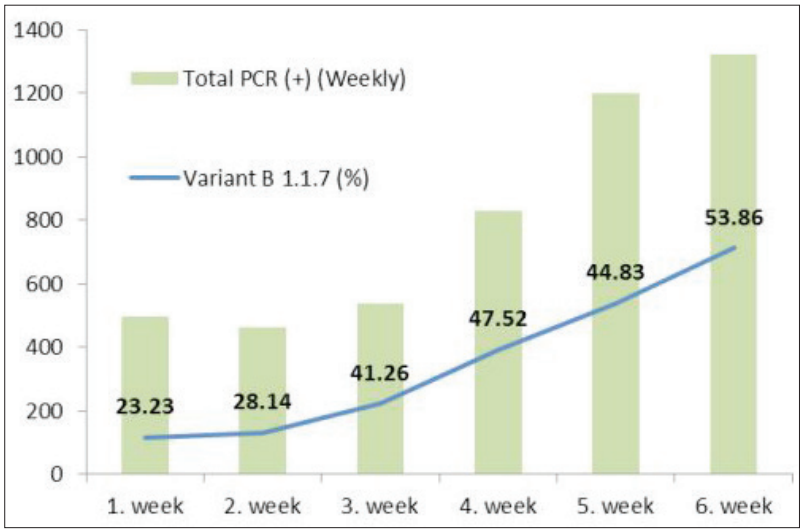

Figure 1. Number of weekly PCR (+) cases and variant B.1.1.7 rates (%).

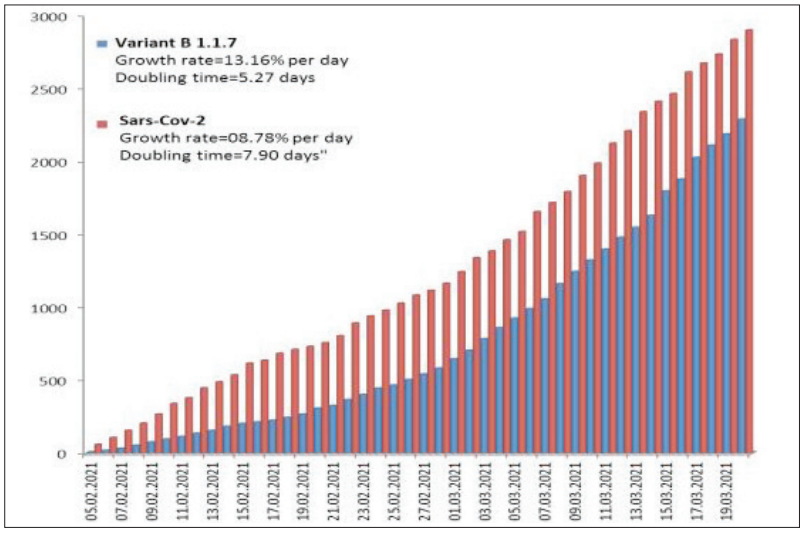

Figure 2. SARS-CoV-2 and variant B 1.1.7 growth curve.

Daily growth rate and doubling time of the case number were calculated by using logistic curve. Daily growth rate of the case number in SARS CoV-2 was 8.78% and 13.16% in variant B.1.1.7 and doubling time was calculated as 7.90 days in SARS CoV-2 and 5.27 days in B.1.1.7.

Of the 2288 cases identified as B.1.1.7 in the study, 1148 were females, and 1140 were males. The distribution of B.1.1.7 cases by sex is given in Table 1. Out of 2288 B.1.1.7 positive patients, 182 (7.95%) were hospitalized. Of the 182 hospitalized patients, 101 (55.49%) were females, 81 (44.51%) were males, with a mean age of 54.46 (0-94) years. There was no difference in terms of sex in hospitalized patients ($p> 0.05$). Sixteen of 182 hospitalized patients died, (12 were males and four were females). Mortality rate was statistically significant in males compared to females ($p= 0.001$).

The distribution of B.1.1.7 cases according to age groups in men and women is shown in Table 2. The highest case number for both men and women was observed in the 25-49 age group. The lowest case number in women was found in the group under two years old and

Table 1. Distribution of Variant B.1.1.7 cases by sex

B 1.1.7	Female	Male	Total
Case (%)	1148 (50.17)	1140 (49.83)	2288
Mean age	39.70 ± 18.84	38.00 ± 18.64	38.85 ± 18.75
p> 0.05			
Inpatient (%)	101 (55.49)	81 (44.51)	182
Mean age	54.03 ± 20.83	56.35 ± 18.56	55.06 ± 19.83
p> 0.05			
Ex (%)	4 (25.00)	12 (75.00)	16
Mean age	58.75 ± 37.81	70.75 ± 12.57	67.75 ± 20.75
p= 0.001			

Tablo 2. Number of B.1.1.7 cases by age groups

	<2	2-4	05-14	15-24	25-49	50-64	65-79	80
Case								
Female	12	16	68	178	525	236	88	26
Male	19	23	88	162	524	232	79	14
Total	31	40	156	340	1048	468	167	40
Inpatient								
Female (%)	1 (8.10)	1 (6.23)	1 (1.47)	6 (3.37)	29 (5.53)	34 (14.42)	14 (15.97)	15 (57.85)
Male (%)	2 (10.80)	1 (4.26)	0 (0.00)	1 (0.62)	22 (4.20)	23 (9.91)	25 (31.64)	7 (51.54)
Total (%)	3 (9.72)	2 (5.06)	1 (0.64)	7 (2.06)	51 (4.86)	57 (12.18)	39 (23.40)	22 (55.68)
Ex								
Female (%)	0 (0.00)	0 (0.00)	1 (1.47)	0 (0.00)	0 (0.00)	1 (0.42)	0 (0.00)	2 (7.71)
Male (%)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.19)	2 (0.86)	5 (6.33)	4 (29.45)
Total (%)	0 (0.00)	0 (0.00)	1 (0.64)	0 (0.00)	1 (0.10)	3 (0.64)	5 (3.00)	6 (15.19)

over 80 years old in men. The highest inpatient rate and death rate were detected in the group aged 80 and over. However, the case number under the age of 18 was 341 (15%), and seven (2%) of them were hospitalized. The only death case seen in the 5-14 age group was a six-year-old girl with cerebral palsy.

Of 182 patients, 48 (26.3%) were treated in the intensive care unit (ICU) and 134 (73.7%) were treated in the wards. Hematological, coagulation, inflammation parameters and Ct values in the PCR mutation study at the hospitalization of these patients are given in Table 3. According to these results, in ICU patients, hemoglobin ($p< 0.001$), platelet ($p= 0.034$) and lymphocyte ($p< 0.001$) levels were lower and neutrophil ($p= 0.025$), MLR ($p= 0.002$), NLR ($p< 0.001$) ratio and D-dimer ($p= 0.008$) levels were found to be higher than non-ICU patients. There was no significant difference between the Ct values of ICU and non-ICU patients.

Table 3. Hematological, coagulation, inflammation and PCR Ct values of ICU and non-ICU patients

Parameter	Ward median (25%-75%)	ICU median (25%-75%)	p
Hematological parameters			
WBC (*10^9/L)	8.05 (5.42-11.93)	9.30 (6.20-14.15)	0.241
Hemoglobin (g/dL)	12.40 (11.30-13.88)	10.10 (9.38-11.93)	<0.001
Platelet(*109/L)	226.00 (165.50-303.75)	173.50 (130.00-241.75)	0.034
Lymphocyte (*10^9/L)	1.05 (0.60-1.60)	0.55 (0.30-0.80)	<0.001
Monocyte(*10^9/L)	0.50 (0.30-0.70)	0.50 (0.30-0.70)	0.793
Neutrophil (*10^9/L)	6.15 (3.85-9.73)	8.50 (5.78-13.18)	0.025
MLR	0.44 (0.29-0.66)	0.86 (0.46-1.47)	0.002
NLR	5.46 (2.96-11.76)	15.27 (9.42-36.51)	<0.001
Coagulation parameters			
PT (sn)	11.80 (11.13-12.30)	11.80 (11.35-12.58)	0.659
APTT (sn)	26.75 (23.85-29.40)	25.05 (22.30-29.60)	0.471
INR	1.02 (0.97-1.06)	1.03 (0.99-1.10)	0.234
D-DİMER (µg/mL)	0,84 (0.51-1.60)	1.99 (0.63-2.97)	0.008
Inflammation parameters			
Ferritin (ng/mL)	409.00 (150.50-826.50)	560.00 (361.25-1062.70)	0.077
CRP (mg/L)	46.21 (18.48-89.88)	115.00 (54.82- 136.00)	0.004
Ct			
Ct	17.65 (15.80-21.00)	18.55 (16.45-21.70)	0.488

NLR: Neutrophil/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, Ct: Cycle threshold.

DISCUSSION

B.1.1.7 variant has been recognized as the dominant SARS-CoV-2 strain a few months after its detection in the UK[11,12]. VOC 202012/01 has been found 56% more contagious than previously defined SARS-CoV-2 variants in Davies et al.'s study and 36% more in Danish modeling studies[13]. Washington, NL et al. have reported that the increase rate of B.1.1.7 raised at least 35-45%, and the doubling time was 9.8 days in the USA, 12.2 days in California, and 9.1 days in Florida[10]. Similar to these reports, the B.1.1.7 variant became dominant in many regions, according to the Ministry of Health data in the last week of March in Türkiye[9].

From Germany, van Loon W et al. reported that while the first B.1.1.7 case in Germany was recorded in late December 2020, at their testing site, B.1.1.7 was observed three weeks later and replaced wild-type virus as the dominant strain within just five weeks. In addition, the proportion of B.1.1.7 increased from 2% to >90% in two months[14,15]. In our study, the daily increase rate of the case number in SARS CoV-2 between 5 February and 20 March was 8.78%, while 13.16% in variant B.1.1.7%; the doubling time was 7.90 days in SARS CoV-2 and 5.27 days in B.1.1.7. Despite the short study interval, we determined that B.1.1.7 was more contagious, increased faster than SARS-CoV-2, and became the dominant strain within just six weeks in our region.

In the study conducted by Günal et al. in XXX Training and Research Hospital in March-May 2020, mean age of COVID-19 positive patients was 54.42 years, and hospitalization rate in the intensive care unit was 15%[16]. In our study, mean age of 182 B.1.1.7 positive patients was similar, 54.46 years, whereas admission rate to the intensive care unit was higher (26.3%). There was no statistical difference between the patients followed up in the intensive care unit and hospitalized in the ward in terms of mean age and sex (p> 0.05). However, the mortality

rate in males was statistically significant compared to females (p= 0.001) in deceased patients (p= 0.001). First studies have reported that the more contagious nature of B.1.1.7 than other SARS-CoV-2 variants might cause more cases and hospitalizations and an approximately 30% higher death rate; however, they have also stated that more studies are needed on this subject[17-19]. However, in the studies of Grint et al., similar to our data, the risk of death in male cases has been found higher than in females; and the risk increases even more in the presence of age and comorbidity[18].

In our study, according to the distribution of B.1.1.7 cases by age groups, the highest case number was found in the 25-49 (45.76%) age group. However, the number of cases aged under 18 years was 341 (15%), and the hospitalization rate was 2%. In a meta-analysis conducted by Brookman S et al., the clinical features of 20 pediatric patients infected with SARS-CoV-2 and 60 infected with B.1.1.7 have been compared, and although the number of cases infected with B.1.1.7 has been detected high, no significant change in the clinical course has been reported[20]. Similarly, in our study, the group aged 18 years and under constituted 15% of B.1.1.7 positive cases, but their hospitalization rate was low. We considered that the increase in pediatric cases might be due to the very high incidence of B.1.1.7 in our region. The only mortality determined in the 5-14 age group was a six-year-old girl with cerebral palsy (CP). This case showed that COVID-19 infection in a child or adult with CP, as stated in the literature, might lead to severe respiratory symptoms, and caution is required[21]. More studies are needed regarding the clinic of variant B.1.1.7 in children and adolescents.

Laboratory medicine has a very important role in the diagnosis and management of variable diseases, and therefore, there are studies investigating the diagnostic values of hematological markers and their correlation with disease severity in COVID-19 patients[22-25]. Peng J. et al. have reported that the diagnostic value of MLR is very high in COVID-19 patients and have presented a significant decrease in lymphocyte and platelet counts in COVID-19 patients who developed ARDS compared to those who did not develop ARDS; and they have reported significant increases in NLR, MLR, and CRP values in the ARDS group[26]. Numerous studies have highlighted the importance of NLR in the diagnosis and prognosis of virus infection. For example, Qin et al. have shown that NLR is increased in severe COVID-19 cases, and it will be useful as an early indicator of exacerbation of the disease[27]. In the study conducted by Asan et al., higher NLR (p< 0.001) and MLR levels have been detected in ICU patients[28].

Viral infection causes dynamic changes in peripheral blood leukocyte counts and subgroups. Leukocytosis, high leukocyte counts ($\geq 9.5 \times 10^9$/L), has been associated with the disease course of COVID-19 and the increase may be an indicator of inflammation in severe and critical patients[29]. According to a meta-analysis, it has been shown that COVID-19 patients in the severe group tended to have higher leukocyte counts compared to the mild group[30]. A meta-analysis including 5872 COVID-19 patients has also found higher D-dimer concentrations associated with severity and mortality in these patients[31]. In our study, in ICU patients, hemoglobin (p< 0.001), platelet (p= 0.034) and lymphocyte (p< 0.001) levels were lower, and neutrophil (p= 0.025), MLR (p= 0.002), NLR (p< 0.001) ratio and D-dimer (p= 0.008) levels were found to be higher than non-ICU patients at hospital admission. According to these results, it was shown that first hematologic markers of the patients could be an important biomarker in the prognosis of the disease.

The results of SARS-CoV-2 RT-PCR diagnostic tests are interpreted based on cycle threshold an indicator of viral load. The utility of Ct values in patient management is still unclear, and the researchers are interested in the correlation of SARS-CoV-2 Ct values with clinical biomarkers and disease severity. Therefore, we also assessed whether there was a difference in Ct values between ICU and non-ICU patients infected with B.1.1.7. Lower Ct values have been seen in other studies on population and inpatient levels[32,33]. In a similar study, Bakir A et al. have found that mean Ct values in outpatients and inpatients were not statistically significant[34]. In our study, we observed no difference in Ct

values between ICU patients and non-ICU patients (median 18.55 vs. 17.65).

CONCLUSION

Although the data was collected from only one hospital, the study was statistically representative of Samsun province according to sample size calculation. Our study demonstrated that the transmissibility of B.1.1.7 was higher than previous variants and became the dominant lineage in six weeks in our region. Therefore, urgent and more decisive measures should be taken to fight COVID-19 infection, and vaccination should be accelerated as much as possible. In addition, our findings indicate that first hematologic markers of the patients can be an important biomarker in the prognosis of COVID-19 disease.

ETHICS COMMITTEE APPROVAL

Ethics approval for the study was obtained from the Ethics Committee of Samsun Training and Research Hospital (Date: 24.03.2021, approval number: GOKA/2021/6/13).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: MB, DY, MHT

Analysis/Interpretation: MB, MHT

Data Collection or Processing: DY, EÖ, MB

Writing: MB

Review and Correction: All of authors

Final Approval: All of authors

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