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Distribution of Hepatitis C Virus Genotypes in Patients Diagnosed with Hepatitis C in Our Hospital: 2015-2018

Hastanemizde Hepatit C Tanısı Alan Hastalarda Hepatit C Virüs Genotiplerinin Dağılımı: 2015-2018

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Abstract

Introduction: This study aimed to investigate the distribution of hepatitis C virus (HCV) genotype and its variability in certain sociodemographics in patients with chronic hepatitis.

Materials and Methods: Anti-HCV was performed by chemiluminescent micro-particle immune assay (Abbott Architect i2000SR, Germany), and HCV-RNA viral load detection was applied with real-time reverse transcriptase polymerase chain reaction (RT-PCR) in the system (Cobas AmpliPrep-Cobas TaqMan, Roche, Germany). Genotype detection was performed with RT-PCR upon with RT-PCR method in the system of Abbott RT-HCV Genotype 2 (Abbott Laboratories, USA) and with Bosphore-HCV Genotyping KitV3 in the Montania 4896 device (Anatolia Diagnostics and Biotechnology Products, Turkey). Frequency and percentage dispersions of all data obtained from patient files and laboratory information system were evaluated through the Statistical Package for the Social Sciences statistics software program.

Results: HCV-RNA was positive in 628 of 2,381 patients with anti-HCV positivity (26.4%), and genotypes of 319 of which were evaluated. Mean age of 319 patients was 51.6 (standard deviation: 16.1). The most frequent genotypes were 1b (61%), 3 (19%), and 1a (10%). Incidences of genotype 1b among all genotypes between the dates of 2015–2018, were found 34.7%, 29%, 15.5% and 20.7% respectively ($p=0.001$). Contagion sources were medical interventions, and 1b was the most frequent genotype. Genotype 3 was most common in patients with intravenous drug addiction. A total of 168 of 238 patients who were Turkish citizens were detected to have genotype 1b, whereas 28 of them had genotype 3 and 25 had genotype 1a. Seventy-eight (24.7%) of the 316 patients, whose genotypes were tested, were foreigners coming mostly from Georgia, Turkmenistan, and Syria respectively. The most frequent genotype of Georgian and Turkmenistanian was 1b and Syrian was both 1a and 4.

Conclusion: This study shows the most frequent genotype to be 1b and its prevalence is statistically decreased over the years, whereas other genotypes (1a, 3, 4, 3a, 1a/3, 1b/3, c-k, 2/3, 1/4, 3/4, and 5) increased.

Keywords: Hepatitis C virus, epidemiology, genotype, intravenous drug addiction

Öz

Giriş: Hepatit C virüs (HCV) genotip tayini; tedavi protokolüne karar verilmesi ve tedaviye yanıtın izlenmesinde önemlidir. Bu çalışmada hastanemize başvuran ve kronik hepatit C tanısı alan hastaların HCV genotip dağılımı ve dağılımın bazı sosyo-demografik özelliklere göre değişiminin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Ocak 2015–Aralık 2018 yıllarında hastanemize başvuran anti-HCV pozitif hastalar retrospektif olarak incelendi. Anti-HCV kemiluminesan mikropartikül immünoassay yöntemiyle (Abbott Architect i2000SR, Almanya) ve HCV-RNA viral yük tayini tam otomatize gerçek-zamanlı ters transkriptaz polimeraz zincir reaksiyonu (RT-PCR) yöntemiyle (Cobas AmpliPrep-Cobas Taqman, Roche, Almanya) sisteminde çalışıldı.

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Öz

Genotip tayini gerçek zamanlı PCR yöntemi ile Abbott RT-HCV Genotip 2 sisteminde (Abbott Laboratories, ABD) ve Bosphore HCV Genotyping Kiti V3 ile Montania 4896 cihazında (Anatolia Tanı ve Biyoteknoloji ürünleri, Türkiye) çalışıldı. Laboratuvar bilgi sistemi ve hasta dosyalarından elde edilen tüm verilerin frekans ve yüzde dağılımları Statistical Package for the Social Sciences istatistik programı ile değerlendirildi.

Bulgular: Anti-HCV pozitif 2.381 hastanın 628'inde (%26,4) HCV-RNA pozitif ve bunların 319'unun genotipi değerlendirildi. Üç yüz on dokuz hastanın yaş ortalaması 51,6 (standart deviasyon: 16,1) olarak hesaplandı. En sık saptanan genotipler sırası ile; 1b (%61), 3 (%19) ve 1a (%10) idi. Tüm genotiplerin içerisinde genotip 1b görülme oranı 2015-2018 yıllarında sırasıyla; %34,7, %29, %15,5, %20,7) bulundu ($p=0,001$). Türkiye Cumhuriyeti (T.C.) vatandaşı olan 238 hastanın 168'inde genotip 1b, 28'inde genotip 3 ve 25'inde genotip 1a saptandı. Olası bulaş yolu sorulan 80 T.C. vatandaşı hastaların çoğunda tıbbi bir müdahale vardı ve bu kişilerde de en sık görülen genotipin, 1b olduğu bulundu. İntravenöz ilaç bağımlılığı olan 11 hastada (%14) en sık genotip 3 tespit edildi. Genotipleri değerlendirilen 316 hastanın 78'i (%24,7) yabancı uyruklu olup ilk üç sırayı Gürcistan, Türkmenistan ve Suriye almaktaydı. Gürcistan ve Türkmenistan'da en sık genotip 1b (sırasıyla %48 ve %60), Suriye'de ise eşit oranda genotip 1a ve 4 (%42) görülmekteydi.

Sonuç: Bu çalışmada en sık saptanan genotipin 1b olduğu, yıllar içinde 1b oranının istatistiksel olarak anlamlı şekilde düştüğü ve diğer genotiplerden 1a, 3, 4, 3a, 1a/3, 1b/3, c-k, 2/3, 1/4, 3/4'ün oranlarının arttığı gösterilmiştir.

Anahtar Kelimeler: Hepatit C virüs, epidemiyoloji, genotip, intravenöz ilaç bağımlılığı

Introduction

Chronic hepatitis C is a liver infection caused by bloodborne transmission of hepatitis C virus (HCV). Most people are infected by sharing needles or other materials used in injection of drugs, and 70% (55-80%) of these people developed long-term chronic infection^[1].

HCV has a single-stranded RNA genome with positive polarity, which is responsible for genetic diversity. The fact that the RNA-dependent RNA polymerase enzyme of the virus does not have backtracking (error correction) capability leads to mutations in glycoprotein and other genes, and consequently genetic diversity^[2,3]. In terms of genetic diversity, at least seven genotypes and 67 subtypes have been demonstrated^[4]. This genetic diversity, caused by three N-terminal HCV proteins (C, E1, and E2/NS2) and four C-terminal proteins (NS2, NS3, NS4, and NS5) involved in viral replication and an "Open reading frame" with different number of nucleotides in each genotype enabling the virus to escape from immune response, affecting the course and treatment of disease^[3]. Viral load, alcohol consumption, and duration of exposure to HCV infection also play a role in the progression of liver damage^[5]. In patients infected with genotype 1b, the severity of liver disease is higher compared to other genotypes, and the disease has a more aggressive course^[3]. Hepatocellular carcinoma due to HCV most often develops with genotype 1b. Best long-term remission rates after treatment with a 48-week therapy with interferon and ribavirin are obtained in patients infected with genotype 1^[6].

Treatment objective for patients without cirrhosis is to decrease HCV-RNA below detectable limit in the 12th and 24th weeks after treatment (<15 IU/ml). Different genotypes may respond differently to drugs, thus, determining the quantity of HCV-RNA (in IU/ml) at the beginning of treatment with a sensitive method,

deciding on drugs to be used in treatment, and identifying the genotype recommended^[7].

HCV genotyping is important in terms of determining treatment protocol and monitoring response, thus, this study aimed to evaluate the genotype distribution in patients admitted to our hospital between 2015 and 2018 and diagnosed with chronic hepatitis C.

Materials and Methods

Data of 2,381 patients who applied to the Infectious Diseases Outpatient Clinic of Kartal Dr. Lütfi Kırdar Training and Research Hospital in İstanbul between January 1, 2015 and December 31, 2018, and whose anti-HCV antibody titers were positive, were obtained from the hospital automation system. Among these patients, 319 patients who were diagnosed with hepatitis C and whose HCV-RNA viral load and genotype were determined were included in the study. HCV-RNA levels and genotypes were evaluated from initial blood samples of patients. Possible transmission routes for HCV were evaluated by examining patient records.

Detection of Anti-HCV

Anti-HCV detection in serum samples taken from patients was performed by chemiluminescent micro-particle immune assay method (Architect Anti-HCV, Abbott Laboratories, USA), and the index value of results (cut-off index) was recorded. Samples with anti-HCV reactivity were analyzed two more times with the same method, and cases with reactivity in two out of three analyses were recorded as recurrent reactivity.

Determination of HCV-RNA Viral Load

The presence of HCV-RNA in plasma samples was studied with nucleic acid extraction and quantitative real-time reverse transcriptase polymerase chain reaction (RT-PCR) method (Cobas

AmpliPrep-Cobas TaqMan HCV Test, v2.0, Roche Diagnostics Germany). The lower limit for detecting HCV-RNA was 15 IU/ml."

Testing for HCV Genotype Determination

Until October 2017, genotyping was performed in an Abbott RT-HCV Genotype 2 system (Abbott Laboratories, USA) by RT-PCR method, and samples were scanned for genotypes 1, 2, 3, 4, 5, 6, 1a, and 1b. In this method, the HCV-RNA level required for successful genotyping was >500 IU/ml.

After October 2017, genotyping was performed by RT-PCR in a Montania 4,896 device with Bosphore-HCV Genotyping V3 kit (Anatolia Diagnostic and Biotechnology Products, Turkey), and samples were scanned for genotypes 1a, 1b, 2, 3, 4, 5a, and 6. In this method, the HCV-RNA level required for successful genotyping was >100 IU/ml.

All tests were performed according to manufacturers' recommendations.

Demographic Data of Patients

Personal information and laboratory results of patients were obtained from the laboratory information system of our hospital and inspection of records in clinical files.

Statistical Analysis

Statistical analyses were performed using International Business Machines Statistical Package for the Social Sciences version 21 software. Suitability of variables to normal distribution was examined by histogram analysis and Kolmogorov-Smirnov test. For non-normally distributed variables, descriptive statistics were presented by median and interquartile ranges. For two or more intergroup comparisons, Student's t-test and Mann-Whitney U test were used for numerical variables, and chi-square and Fisher's exact tests were used for categorical variables. P value of <0.05 was evaluated as statistically significant in all analyses.

Results

HCV-RNA was found to be positive in 628 (26.4%) of 2,381 patients who were found as anti-HCV positive by enzyme-linked immunosorbent assay method. Median HCV viral load values of patients were calculated in log values as 5.8 (interquartile range 1.2) for 2015, 5.8 (interquartile range 1.3) for 2016, 5.8 (interquartile range 1.5) for 2017, and 5.7 (interquartile range 1.3) for 2018. The distribution of HCV-RNA results by years is shown in Table 1.

Genotyping was performed in 319 of 628 patients with HCV-RNA positivity. When the retrospective records of other patients were examined, genotyping was impossible to perform because their treatment was not done at our hospital.

The mean age of 319 patients was 51.6 (standard deviation: 16.1). Female/male ratio was found as 131/188.

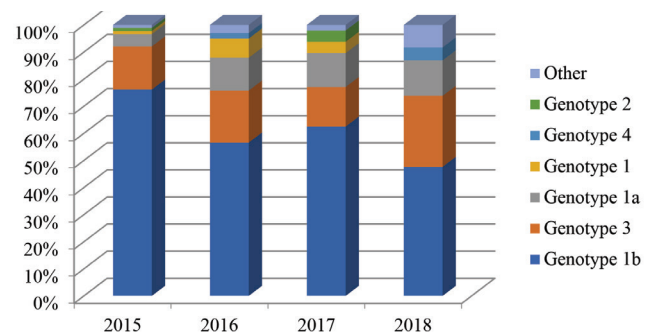
The most common genotypes were 1b (61%), 3 (19%), and 1a (10%). Genotypes 1a and 3 were concomitant in two patients, genotypes 1b and 3 in one patient, genotypes 2 and 3 in one patient, and genotypes 1 and 4 were concomitant in one patient.

Among all genotypes, the incidence of genotype 1b was found to be 34.7%, 29%, 15.5%, and 20.7%, between 2015-2018 ($p=0.001$), respectively. Genotype distribution by years is shown in Table 2 and in the Graphic 1.

Among 319 patients who were genotyped, 316 were evaluated in terms of nationality since nationality information was unavailable for three patients. Of these 316 patients, 238 (75.3%) were citizens of the Republic of Turkey and 78 (24.7%) were foreign nationals. Among foreign patients, top three nationalities were Georgian, Turkmen, and Syrian. Genotype distribution according to the nationality of patients is shown in Table 3.

Of the 238 Turkish Republic citizens who were genotyped, 168 (71%) were found to be genotype 1b, 28 (12%) were genotype 3, and 25 (11%) were genotype 1a.

Mean age of Turkish patients with genotype 1b [61.0, standard error (SE)=12.1] was significantly higher compared to mean age of patients with other genotypes (44.8, SE=16.5) ($p=0.001$) (Mann-Whitney U test).



Graphic 1. Hepatitis C virus genotype distribution by years

Table 1. The distribution of hepatitis C virus-RNA results by years

Year	HCV-RNA negative		HCV-RNA positive		Total
	n	%	n	%	
2015	432	69.1	193	30.9	625
2016	425	70.8	175	29.2	600
2017	391	77.4	114	22	505
2018	505	77.6	146	22.4	651
Total	1,753	73.6	628	26.4	2,381

HCV: Hepatitis C virus

Mean age of Turkish patients with genotype 3 (41.0, SE=2.4) was significantly lower compared to mean age of patients with other genotypes (58.3, SE=14.6) ($p=0.001$) (Mann-Whitney U test).

The prevalence of genotype 1b among all genotypes was significantly higher in women (56.5%) compared to that of men (43.5%) ($p=0.001$) (Fisher's exact test).

The prevalence of genotype 3 among all genotypes was significantly lower in women (10.7%) compared to that of men (89.3%) ($p=0.001$) (Fisher's exact test).

When patient files were examined for transmission routes of HCV, it was found that of the 80 Turkish patients, 51 patients had history of tooth extraction, 35 had history of previous operation, 17 had history of transfusion, 13 had history of transmission within household, and 11 had history of intravenous drug use. The most common genotype in these patients was found to be genotype 1b. The most frequent genotype detected was 3 (45%) among 11 patients (14%) who had addictions to intravenous drugs (Table 4).

Discussion

Chronic HCV infection is responsible for the majority of liver-related mortality such as cirrhosis and hepatocellular carcinoma. Rapid recovery is observed when the treatment is applied quickly. Direct-acting antiviral drugs used in recent years provide over 90% virological response. HCV eradication is possible with new treatment options that are effective, well tolerated, and allow shorter treatment regimens^[5].

When HCV genotype distribution in the world is examined, it is seen that genotypes 1a and 1b are most common in the USA and Europe, genotype 1b is dominant in Japan, genotypes 2a and 2b are seen in North America, Europe, and Japan, and genotype 2c is seen in Northern Italy. Genotype 3a is common in Europe and the USA among people using intravenous drugs. Genotype 4 is common in North Africa and the Middle East,

genotype 5 in South Africa, and genotype 6 is common in Hong Kong. Genotypes 7, 8, and 9 are only seen in Vietnam, whereas genotypes 10 and 11 are common in India^[8].

In the present study, the most common genotypes in all patients including both Turkish citizens and other nationalities were genotype 1b (61%), genotype 3 (19%), and genotype 1a (10%). A total of 78 (24.7%) genotyped patients were foreign nationals. Georgian (25 patients), Syrian (12 patients), and Turkmen (10 patients) were the top three nationalities. The most common genotype in Georgian and Turkmen nationals was genotype 1b, whereas genotype 1a was the most common in Syrian nationals. Literature studies reported genotype 1b to be the most common genotype in Turkmenistan and Georgia^[9,10]. As Turkey and Georgia are neighboring countries, molecular and epidemiological similarities between genotype maps of these countries are expected since travel between Georgia and Turkey has increased recently. This may also be the case with Turkmenistan.

A Syrian study reported that the most common genotype was genotype 4 followed by genotype 1^[11]. In a publication in Kahramanmaraş, genotype 1 (54.5%) was reported to be the most common genotype among Syrians^[12]. In our present study, genotype 1a and genotype 4 were found to be equally common in Syrian citizens. In environments with increased cohabitation due to migration, molecular and epidemiological changes in genotypes may be expected.

Studies conducted in Turkey reported the most common genotype as 1b, but the prevalence rates vary depending on the region. The prevalence of genotype 1b is reported in high ratios as 98% in Gaziantep, 88% in İzmir, 87.5% in the Eastern Black Sea Region, 88.6% in the Western Black Sea Region, 86.7% in Antakya, 84.7% in Mersin, and 72% in Aydın^[13-18], whereas lower rates have been reported in Antalya as 63.3%^[19], in Adana as 58.8% and 55.2% in two separate studies^[20,21], and in Kayseri as 52.8%^[22]. In a multicenter study conducted in Turkey, the mean frequency of genotype 1b was 67.7% although rates varies

Table 2. Hepatitis C virus genotype distribution by years

Genotypes	Year				p value
	2015 (n=88)	2016 (n=99)	2017 (n=48)	2018 (n=84)	
Genotype 1b (n=193)	67 (34.7%)	56 (29%)	30 (15.5%)	40 (20.7%)	0.001
Other genotypes (n=126)	21 (16.7%)	43 (34.1%)	18 (14.3%)	44 (34.9%)	
Genotype 3 (n=62)	14 (22.6%)	19 (30.6%)	7 (11.3%)	22 (35.5%)	
Genotype 1a (n=33)	4 (12.1%)	12 (36.4%)	6 (18.2%)	11 (33.3%)	
Genotype 1 (n=10)	1 (10%)	7 (70%)	2 (20%)	0	
Genotype 4 (n=6)	0	2 (33.3%)	0	4 (66.7%)	
Genotype 2 (n=3)	1 (33.3%)	0	2 (66.7%)	0	
Other genotypes* (n=12)	1 (8.3%)	3 (25%)	1 (8.3%)	7 (58.3%)	

*Other genotypes=Genotype 3a, 1a/3, 1b/3, c-k, 2/3, 1/4, 3/4, and 5

by region^[23]. In another study published at another hospital located on the Anatolian side of İstanbul close to our hospital, the most common genotype was reported to be 1b with a rate of 56.5%^[24]. Data of our study include patients followed by one of the big hospitals located at the Anatolian side of İstanbul, and the frequency of genotype 1b obtained as 61% is consistent with the data of the other hospital in İstanbul.

Other genotypes observed also vary from region to region. Second most common genotype has been reported as genotype 1a^[16,19,20], 2^[17], and 4^[22] in different cities, whereas other studies reported genotype 3 as the second most common genotype^[14,18,21]. Genotype 3 (19%) was the second most common genotype in our study. In another study conducted in İstanbul, the second most common genotype was genotype 1a (22.9%)^[24].

Geographical proximity and neighboring relations of countries or regions affect genotype distribution. It is reported that in regions of Thailand neighboring Myanmar and Vietnam, the most common genotype is genotype 6 similar to Myanmar and Vietnam, whereas in the southern regions neighboring Malaysia, the most common genotype is genotype 3a^[25]. The

above-mentioned data and data in the present study suggest that the geographical proximity of provinces where the study is conducted to other regions and countries, demographic characteristics of the population, socioeconomic status, and exposure to migration lead to differences in genotype distribution.

Our study has also revealed the existence of genotypes 1, 2, 4, and others (genotypes 3a, 1a/3, 1b/3, c-k, 2/3, 1/4, 3/4, and 5). Genotypes identified by RT-PCR method and classified as "other" include 3a, 1a/3, 1b/3, c-k, 2/3, 1/4, 3/4, and 5. It is reported that samples with mixed type detected by RT-PCR method should be verified by reference methods such as Restriction Fragment Length Polymorphism and sequence analysis^[26]. It is reported that the dominant genotype responds to treatment, and mixed genotypes appear after treatment^[27]. However, this present study is a retrospective study, thus, mixed genotypes were re-analyzed but could not be verified by reference methods. The limitation of this study includes the usage of two kits with different sensitivity and specificity arising from the procurement system over a four-year period and retrospectively analyzed patients with such results.

Table 3. Hepatitis C virus genotype distribution according to the nationality of patients

Nationality	Genotype 1b n (%)	Genotype 3 n (%)	Genotype 1a n (%)	Genotype 1 n (%)	Genotype 4 n (%)	Genotype 2 n (%)	Other genotypes n (%)	Total n (%)
Turkish	168 (71)	28 (12)	25 (11)	8 (3)	1 (0)	1 (0)	7 (3)	238
Georgian	12 (48)	11 (44)	1 (4)	0	0	1 (4)	0	25
Turkmen	6 (60)	3 (30)	0	0	0	0	1 (10)	10
Syrian	0	1 (8)	5 (42)	0	5 (42)	0	1 (8)	12
Afghanistan	2 (25)	4 (50)	0	0	0	1 (13)	1 (13)	8
Russian	2 (40)	0	2 (40)	0	0	0	1 (20)	5
Ukrainian	0	5 (100)	0	0	0	0	0	5
Moldovan	1 (100)	0	0	0	0	0	0	1
Iranian	0	1 (100)	0	0	0	0	0	1
German	0	2 (67)	0	1 (33)	0	0	0	3
Armenian	1 (50)	1 (50)	0	0	0	0	0	2
Uzbek	0	3 (100)	0	0	0	0	0	3
Azerbaijani	1 (50)	0	0	1 (50)	0	0	0	2
Pakistani	0	1 (100)	0	0	0	0	0	1
Total	193 (61)	60 (19)	33 (10)	10 (3)	6 (2)	3 (1)	11 (3)	316

Table 4. Hepatitis C virus genotype distribution of Turkish citizens according to the possibility of transmission routes (n=80)

Medical history	Genotype 1 n (%)	Genotype 1b n (%)	Genotype 1a n (%)	Genotype 2 n (%)	Genotype 2 and 3 n (%)	Genotype 3 n (%)	Total n (%)
Tooth extraction	3 (6)	41 (80)	4 (8)	0	1 (2)	2 (4)	51 (64)
Operation	2 (6)	28 (80)	3 (9)	1 (1)	0	1 (3)	35 (44)
Transfusion	1 (6)	13 (76)	2 (12)	0	1 (6)	0	17 (21)
Transmission within household	1 (8)	6 (46)	2 (15)	0	0	4 (31)	13 (16)
Intravenous drug abuse	0	3 (27)	3 (27)	0	0	5 (45)	11 (14)

HCV prevalence in the world is higher in men due to greater exposure to risk factors such as intravenous drugs use, whereas in Turkey prevalence is higher in women, which can be explained by the fact that HCV infection in Turkey is generally nosocomial and hospitalization is more common in women compared to men^[28]. A study conducted in İstanbul reported that genotype prevalence distribution varied according to age and gender. Genotypes 1 and 2 were more common in women and genotypes 3 and 4 were more common in men, whereas genotype 1 was more common in the elderly and genotype 3 in young population^[29].

In the present study, the prevalence of genotype 1b was higher in women compared to men and genotype 3 was lower. The higher prevalence of 1b in women may be due to greater exposure to bloodborne infection routes (the ratio of women/men with a history of transfusion, operation, and tooth extraction was 62/55). The low prevalence of genotype 3 in the present study may be attributed to the very low use of intravenous drugs in women (1 woman/16 men). Genotype 1b is the most prevalent genotype in neighboring countries; however, HCV genotype 3 is increasing with intravenous drug abuse^[30,31]. Our study shows that genotype 3 is the most prevalent genotype among patients using intravenous drug (45%).

Conclusion

Findings of this study show that the most common genotype is 1b, with a prevalence that has statistically decreased over the years, whereas the prevalence of other genotypes increased. The rate of 1b was lower than that of other regions in our country. Variability in findings and difference between regions may be due to population mobility, caused by various factors such as tourism and migration. Characteristics of each province or region differ from others, thus, it will be beneficial for centers to track and keep their own data. An observation in İstanbul, one of the cities in Turkey where population mobility is intense, revealed more than half of patients with chronic hepatitis C having genotype 1b, which means that almost one out of two patients admitted to the outpatient clinic may be infected with different genotypes, suggesting the necessity of genotyping for treatment decisions.

Ethics

Ethics Committee Approval: Approval for the study was obtained from Kartal Dr. Lutfi Kırdar Training and Research Hospital Clinical Research Ethics Committee (approval date: 12.06.2019, no: 2019/514/167/26).

Informed Consent: This study was designed retrospectively.

Peer-review: Externally peer-reviewed.

Concept: D.H., **Design:** D.H., A.G., R.C.S., G.S., **Data Collection or Processing:** D.H., A.G., A.B., **Analysis or Interpretation:** A.G., D.H.,

R.C.S., A.B., G.S., **Literature Search:** D.H., A.G., R.C.S., **Writing:** D.H., R.C.S., A.G.

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