



Distribution of Hepatitis C Virus Genotypes: 18-Year Experience in an Academic Center

Hepatit C Virüs Genotip Dağılımı: Akademik Bir Merkez, 18 Yıllık Deneyim

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ABSTRACT

Objectives: Hepatitis C virus (HCV) is an important public health problem worldwide. This study examined long-term changes in distribution of HCV genotypes in HCV-RNA-positive patients in a large population.

Materials and Methods: Following HCV genotype and subtype sequence analysis, the sequence and the reference sequences were compared with the "line probe assay" method or the multiplex amplification methods of 5'UTR and NS5B or only NS5B.

Results: In the study, HCV-RNA positive 670 patients undergoing genotyping were included. Genotype 1 was detected in 603 patients (90.0%), genotype 3 in 45 (6.7%), genotype 2 in 12 (1.8%), genotype 4 in 6 (0.9%), combined genotypes 1 and 2 in 2 (0.3%), and genotypes 1 and 4 in 2 (0.3%). Genotypes 5, 6, 7 and 8 were not observed in this study. The most dominant subtypes by years were genotype 1b (82.8%) and genotype 3a (4.5%). Genotype 1b was detected in 63.2% of patients under <50 years of age and in 89.7% of those ≥50 years of age ($p<0.001$), while genotype 3 was determined in 2.0% of patients aged ≥50 years of age and in 20.1% of those <50 years of age ($p<0.001$).

Conclusion: This study revealed that changes occurred in the general distribution of HCV genotype and subtypes by years, and that HCV genotype 1b was seen at the highest rate, especially in patients over 50 years old.

Keywords: Genotype, hepatitis C virus, subtype

ÖZ

Amaç: Hepatit C virüsü (HCV) kronik hepatit, siroz, hepatosellüler karsinom gibi hastalıklara yol açması nedeniyle önemli bir halk sağlığı sorunudur. Bu çalışmada, geniş bir popülasyondaki HCV-RNA pozitif hastalarda, HCV genotip dağılımında uzun bir dönemdeki değişimin incelenmesi amaçlandı.

Gereç ve Yöntemler: HCV genotip ve subtipleri dizi analizi sonrasında dizinin referans dizilerle karşılaştırılması; "line probe assay" yöntemiyle veya 5'UTR ve NS5B'nin veya sadece NS5B'nin multipleks amplifikasyonu yöntemlerinden biriyle gerçekleştirildi.

Bulgular: Çalışmada HCV-RNA pozitif olup genotiplendirme yapılan toplam 670 hasta yer aldı. Hastaların 603'ünde (%90,0) genotip 1, 45'inde (%6,7) genotip 3, 12'sinde (%1,8) genotip 2 ve 6'sında (%0,9) genotip 4, 2'sinde (%0,3) genotip 1 ve 3 ve yine 2'sinde (%0,3) genotip 1 ve 4 birlikteliği tespit edildi. Çalışmada genotip 5, 6, 7 ve 8'e rastlanmadı. Yıllara göre en baskın subtip genotip 1b (%82,8) idi. İkinci en sık saptanan subtip ise genotip 3a (%4,5) idi. Genotip 1b <50 yaş olan hastalarda %63,2 ve ≥50 yaş olan hastalarda %89,7 oranında ($p<0,001$) saptanırken, ≥50 yaş olan hastalarda genotip 3 %2,0 ve <50 yaş olan hastalarda ise %20,1 oranında saptandı ($p<0,001$).

Sonuç: Bu çalışmada HCV genotip 1b'nin en yüksek oranda, özellikle de 50 yaş üzerindeki hastalarda görüldüğü ortaya konmuştur.

Anahtar Kelimeler: Genotip, hepatit C virüs, subtip

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Introduction

The hepatitis C virus (HCV), a member of the genus hepacivirus from the family flaviviridae, infects an estimated 130-200 million individuals worldwide (1,2). According to World Health Organization figures for 2018, 71.1 million individuals worldwide are infected with HCV, and approximately 475,000 die from the infection every year (3). Since the prevalence of HCV varies among different regions, countries are grouped in terms of the incidence of HCV infection. Eighty percent of HCV infections are seen in 31 countries. Six countries in particular (China, Pakistan, Nigeria, Egypt, India, and Russia) are host to 50% of all cases (4). HCV is also an important public health problem with a high probability of chronicization and still with no effective vaccine, that leads to severe liver diseases such as hepatocellular carcinoma and cirrhosis (2,5).

There are eight confirmed HCV genotypes and 86 subtypes to date (4). The distribution of HCV genotypes and subtypes exhibits geographic variations. Genotype 1 is responsible for 44% of all HCV infections worldwide, and for 60% of infections in high and middle-income countries (4). Globally, the leading genotypes are 1a, 1b, 2a, 2b, and 3a. Approximately one in three genotype 1 infections are seen in East Asia. Genotype 3 infections are more widespread in lower-middle-income countries than in high-income, upper-middle-income, and lower-income countries and constitute 25% of all HCV infections (4). Approximately 75% of HCV genotype 3 infections are seen in South Asia. Genotype 4 has been detected more widely in Central Africa and the Middle East, and genotypes 2 and 6 in East Asia (1,4). Genotype 5, 7, and 8 represent less than 1% of all HCV infections, with several cases emerging from southern and central sub-Saharan Africa (1,4). HCV genotypes have been shown to vary in terms of disease severity, prognosis, and response to antiviral drugs (4,6). Therefore, HCV genotyping is an important component of pre-treatment diagnostic algorithms, especially as it guides the therapeutic regimen process (7). Knowing the genotypes is the most important factor determining the selection of an effective antiviral agent, the length of treatment, and the expected virological response (6,8). A knowledge of regional HCV genotype distributions is therefore essential for the development of international and domestic HCV infection management strategies.

The purpose of this study was to examine the HCV genotype distribution in the previous 18 years among HCV-RNA-positive patients in a broad population.

Material and Methods

Research Type and Study Group

HCV genotype results from HCV-RNA-positive blood specimens studied at the Karadeniz Technical University Clinical Microbiology

Laboratory, Turkey, between 2002 and 2019 were evaluated retrospectively. Patients' demographic data were retrieved from the hospital information system.

Specimens from the patients included in the study were investigated in the academic clinical microbiology laboratory of a 960-bed tertiary university hospital in the Eastern Black Sea region of Turkey. The study population consisted of patients infected with HCV, the great majority living in the region (approximate population 2.9 million individuals per year). Six hundred seventy patients were enrolled in the study, the first specimen being evaluated in case of repeated specimens.

The study was approved by Karadeniz Technical University Faculty of Medicine Clinical Research Ethical Committee (approval number: 2020/169).

HCV-RNA Quantitation

The HCV-RNA load in specimens was determined using bDNA (Branched DNA, HCV 3.0 bDNA assay, Bayer Diagnostics, USA) or one of various real time PCR applications (COBAS® AmpliPrep/COBAS®TaqMan® HCV test, Roche Diagnostics Corporation, USA, Abbott RealTime HCV Assay, Abbott Molecular Inc., USA, and Bosphore® HCV Quantification Kit, Anatolia Geneworks, Turkey).

HCV Genotyping Procedure

Following HCV genotype and subtype "5'untranslated region (5'UTR)" or "non-structural 5B" (NS5B) amplification and sequence analysis, the comparison of the sequence with reference sequences were studied with either using the "line probe assay" method (INNO-LiPA HCV II, Innogenetics, Belgium) or two different commercial Real-Time PCR kits, by the method of multiplex amplification of the 5'UTR and NS5B (Abbott RealTime HCV Genotype II Assay, Abbott Molecular Inc., USA) or only NS5B (HCV Genotyping Kit v1 Bosphore, Geneworks Anatolia, Turkey).

Statistical Analysis

Statistical analysis was performed on SPSS version 21 software (SPSS Inc., Chicago, IL, USA). Non-parametric data not conforming to normal distribution at the Kolmogorov-Smirnov test were compared using the Mann-Whitney U test. The chi-square test and Fisher's exact test were employed in the comparison of categorical variables. P-values <0.05 were regarded as statistically significant.

Results

Three hundred fifty-nine (59.6%) of the 670 patients in the study were men and 311 (46.4%) were women. The patients' mean age was 58.27±16.53 years (minimum-maximum: 4-112). Genotype distributions by gender are shown in Table 1. No significant difference in genotype distribution was observed between the genders (p=0.461).

	HCV genotypes n (%)								4*	Mixed	Total n (%)
	1			2		3					
Gender	1*	1a	1b	2*	2b	3*	3a				
Female	13 (4.2)	9 (2.9)	261 (83.9)	6 (1.9)	-	6 (1.9)	11 (3.5)	3 (1.0)	2 (0.6)	311 (46.4)	
Male	10 (2.8)	16 (4.5)	294 (81.9)	5 (1.4)	1 (0.3)	9 (2.5)	19 (5.3)	3 (0.8)	2 (0.6)	359 (53.6)	

*Subtyping could not be performed. HCV: Hepatitis C virus

Table 2. Distribution of HCV genotypes by years

Year	HCV Genotypes n (%)									Total (n)
	1			2		3		4*	Mixed	
	1*	1a	1b	2*	2b	3*	3a			
2002	-	-	5 (100.0)	-	-	-	-	-	-	5
2004	-	-	10 (90.9)	-	-	-	1 (9.1)	-	-	11
2005	-	1 (16.7)	4 (66.7)	-	-	-	1 (16.7)	-	-	6
2006	-	-	4 (100.0)	-	-	-	-	-	-	4
2007	-	1 (50.0)	1 (50.0)	-	-	-	-	-	-	2
2008	-	-	5 (100.0)	-	-	-	-	-	-	5
2009	-	2 (3.9)	49 (96.1)	-	-	-	-	-	-	51
2010	5 (5.8)	1 (1.2)	72 (82.8)	1 (1.2)	-	3 (3.5)	4 (4.6)	-	1 (1.2) (genotip 1b+3a)	87
2011	3 (4.9)	1 (1.6)	55 (90.2)	2 (3.3)	-	-	-	-	-	61
2012	2 (3.2)	2 (3.2)	50 (79.4)	2 (3.2)	-	2 (3.2)	2 (3.2)	2 (3.2)	1 (1.6) (genotip 1b+4)	63
2013	-	4 (5.4)	63 (85.1)	1 (1.4)	-	2 (2.7)	2 (2.7)	1 (1.4)	1 (1.4) (genotip 1b+4)	74
2014	2 (4.4)	2 (4.4)	38 (84.4)	-	-	1 (2.2)	1 (2.2)	1 (2.2)	-	45
2015	-	3 (11.1)	23 (85.2)	-	-	1 (3.7)	-	-	-	27
2016	8 (11.9)	2 (3.0)	52 (77.6)	1 (1.5)	-	4 (6.0)	-	-	-	67
2017	1 (1.9)	-	48 (90.6)	1 (1.9)	-	-	2 (3.8)	-	1 (1.9) (genotip 1b+3a)	53
2018	1 (1.8)	3 (5.3)	43 (75.4)	1 (1.8)	-	-	7 (12.3)	2 (3.5)	-	57
2019	1 (1.9)	3 (5.8)	33 (63.5)	2 (3.9)	1 (1.9)	2 (3.9)	10 (1.9)	-	-	52
Total	23 (3.4)	25 (3.7)	555 (82.8)	11 (1.6)	1 (0.2)	15 (2.2)	30 (4.5)	6 (0.9)	4 (0.6)	670

*Subtyping could not be performed. HCV: Hepatitis C virus

Genotype 1 was determined in 603 patients (90.0%), genotype 3 in 45 (6.7%), genotype 2 in 12 (1.8%), genotype 4 in six (0.9%), combined genotypes 1 and 3 in two (0.3%), and genotypes 1 and 4 in two (0.3%). Genotypes 5, 6, 7, and 8 were not encountered. The most frequently identified subtypes were genotype 1b (82.8%) and genotype 3a (4.5%). Detailed distributions by years of genotypes and subtypes are shown in Table 2.

The mean age of the 603 patients infected with genotype 1 was 59.72±16.29 years (minimum-maximum: 4-112), compared to 45.26±12.51 years (minimum-maximum: 20-77) for patients infected with other genotypes, and the difference was statistically significant ($p<0.001$). The distribution of HCV genotypes by age is shown in Table 3. Genotype 1b was detected in 63.2% of the 174 patients aged under 50 and in 89.7% of the 496 patients aged over 50 ($p<0.001$). While mixed genotypes and genotype 4 were encountered in patients aged ≥ 50 , genotype 3 and its subtypes were more common in patients aged <50 (20.1% of patients <50 compared to 2% of patients ≥ 50).

Thirty (4.5%) patients were foreign nationals, and these patients' home countries and genotypes are shown in Table 4. The most common genotype in these patients was 1b (50%) followed by genotype 3 (40%) and genotype 2 (10%).

Discussion

This study adds to the existing literature by determining the distribution of HCV genotypes, an important factor in treatment management, and by evaluating changes in genotype distributions by years in an academic center.

High rates of genotype 1b have been reported in European countries, Israel, and Japan, while genotype 1a has more frequently been reported in North America and Northern Europe (9,10). Similarly to other studies from Turkey, the most frequently identified HCV genotype in all years throughout the present study was genotype 1b (82.8%) (Table 5). HCV genotypes in the study population varied significantly with age. The genotype 1b rate among patients under 50 was significantly lower than that among patients over 50 ($p<0.001$). This may be due to a decrease with age in infection rates with HCV genotypes other than genotype 1b.

In Europe, HCV genotype infections are reported to be mostly seen in women, and at advanced ages, and to be associated with blood transfusions, dental treatment, and nosocomial infections (11). The risk factors and modes of transmission among the patients infected with HCV in the present study are unknown. However, patients ranged in age between 20 and 64, and no gender difference was observed. Globally, genotype 2 is more common in West Africa in particular, and in some regions of South America (12). This clustering is thought to be associated with migration patterns linked to the transatlantic slave trade (12). The distribution rates of genotype 2 across the world are highly heterogeneous, ranging between 0.1% and 24.5%. In the present study, HCV genotype 2 was detected in 1.8% (12) of patients, a rate higher than that in Central Europe (0.1%), but significantly lower than those in the Asian Pacific (24.5%), West Africa (23%), Western Europe (10.8%), and worldwide (9.1%) (12).

HCV genotype 3 is the second most common genotype worldwide, after genotype 1, and is particularly dominant in South Asian countries (12,13). A proportional increase was determined

Table 3. Distributions of HCV genotypes by age

		HCV genotypes n (%)									
		1		2		3		4*	Mixed	Total	
Age range (years)		1*	1a	1b	2*	2b	3*				3a
	0-4	-	-	1 (100.0)	-	-	-	-	-	-	1
	5-9	-	-	-	-	-	-	-	-	-	-
	10-14	-	1 (33.3)	2 (66.7)	-	-	-	-	-	-	3
	15-19	1 (50.0)	-	1 (50.0)	-	-	-	-	-	-	2
	20-24	-	2 (20.0)	6 (60.0)	-	1 (10.0)	1 (10.0)	-	-	-	10
	25-29	1 (5.0)	2 (10.0)	13 (65.0)	-	-	3 (15.0)	1 (5.0)	-	-	20
	30-34	3 (15.0)	1 (5.0)	8 (40.0)	2 (10.0)	-	3 (15.0)	3 (15.0)	-	-	20
	35-39	3 (10.0)	2 (6.7)	15 (50.0)	1 (3.3)	-	4 (13.3)	5 (16.7)	-	-	30
	40-44	1 (2.6)	2 (5.3)	26 (68.4)	2 (5.3)	-	-	7 (18.4)	-	-	38
	45-49	-	2 (4.0)	38 (76.0)	2 (4.0)	-	2 (4.0)	6 (12.0)	-	-	50
<50 Total		9 (5.2)	12 (6.9)	110 (63.2)	7 (4.0)	1 (0.6)	13 (7.5)	22 (12.6)	-	-	174
	50-54	1 (1.3)	2 (2.7)	63 (84.0)	2 (2.7)	-	-	3 (4.0)	2 (2.7)	2 (2.7)	75
	55-59	1 (1.1)	2 (2.1)	85 (90.4)	1 (1.1)	-	-	2 (2.1)	2 (2.1)	1 (1.1)	94
	60-64	2 (2.1)	4 (4.2)	85 (89.5)	1 (1.1)	-	1 (1.1)	-	1 (1.1)	1 (1.1)	95
	65-69	5 (6.0)	2 (2.4)	72 (86.7)	-	-	1 (1.2)	2 (2.4)	1 (1.2)	-	83
	70-74	4 (7.0)	1 (1.8)	52 (91.2)	-	-	-	-	-	-	57
	75-79	1 (2.0)	1 (2.0)	48 (94.1)	-	-	-	1 (2.0)	-	-	51
	80-84	-	-	18 (100.0)	-	-	-	-	-	-	18
	85-89	-	-	8 (100.0)	-	-	-	-	-	-	8
	>90	-	1 (6.7)	14 (93.3)	-	-	-	-	-	-	15
≥50 Total		14 (2.8)	13 (2.6)	445 (89.7)	4 (0.8)	0 (0)	2 (0.4)	8 (1.6)	6 (1.2)	4 (0.8)	496
Total		23 (3.4)	25 (3.7)	555 (82.8)	11 (1.6)	1 (0.2)	15 (2.2)	30 (4.5)	6 (0.9)	4 (0.6)	670 (100.00)

*Subtyping could not be performed. HCV: Hepatitis C virus

Table 4. Distribution of HCV genotypes detected in foreign national patients

		HCV genotypes n (%)									
Country of origin		1*	1a	1b	2*	2b	3*	3a	4*	Mixed	Total
	Azerbaijan	-	-	-	1 (50.0)	-	1 (50.0)	-	-	-	2
	Georgia	-	-	12 (60.0)	-	-	1 (5.0)	7 (35.0)	-	-	20
	Iraq	-	-	-	1 (50.0)	-	1 (50.0)	-	-	-	2
	Iran	-	-	1 (100.0)	-	-	-	-	-	-	1
	Kirgizstan	-	-	-	-	-	-	1 (100.0)	-	-	1
	Russia	-	-	1 (50.0)	1 (50.0)	-	-	-	-	-	2
	Tajikistan	-	-	1 (100.0)	-	-	-	-	-	-	1
	Ukraine	-	-	-	-	-	1 (100.0)	-	-	-	1
Total		-	-	15 (50.0)	3 (10.0)	-	4 (13.3)	8 (26.7)	-	-	30

*Subtyping could not be performed. HCV: Hepatitis C virus

in genotype 3 after 2010 in the present study. The proportion of patients aged under 50 infected with HCV genotype 3 was significantly higher than that of patients aged over 50 (20.1% and 2.0%, respectively, $p < 0.001$). It was most frequently observed in the 35-39 age group (30.0%), and the genotype is more common in males. This variation may be due to reciprocal human mobility such as tourism, education, workforce activities, and marriages, in the community comprising the study population.

Medical procedures without the use of protective measures are the basic risk factor for HCV infection in Middle Eastern and North African countries, and genotype 4 predominates in those countries (65.3%) (12). Genotype 4 is the most frequently seen genotype in Syria, at 59.0% (2,3,13,14). Turkey has a long historical relationship with these countries for reasons such as religious pilgrimages, migration, and tourism (2). In the present study, HCV genotype 4 began being detected after 2012, and this may have

Table 5. Various previous studies of HCV genotypes in Turkey

Study	Year	No. (n)	HCV genotype distribution (%)											
			1	1a	1b	2	2b	3	3a	4	4a	5	6	Mixed
Bozdayi et al. (19)	1997-2000	365	-	11.0	84.0	3.0	-	1.0	-	1.0	-	-	-	-
Cil et al. (18)	2004-2005	22		22.7	72.7			4.5					-	
İba Yılmaz et al. (20)	2008-2010	46	-	-	100.0	-	-	-	-	-	-	-	-	-
Celik et al. (21)	2010	178	-	9.0	88.2	1.1	-	1.7	-	-	-	-	-	-
Karslıgil et al. (22)	2011	51	-	9.8	78.4	7.8	-	2.0	-	2.0	-	-	-	-
Kayman et al. (2)	2010-2011	218	62.4	2.3	60.1	4.6	-	-	-	33	-	-	-	-
Oztürk et al. (23)	2010-2012	315	-	3.5	55.2	14.6	-	26.0	-	0.6	-	-	-	-
	2010-2012	324	-	0.3	86.7	9.3	-	0.9	-	2.8	-	-	-	-
Sağlık et al. (10)	2009-2013	422	83.4	14.7	63.3	3.5	0.9	-	11.1	1.6	-	-	-	0.2
Çekın et al. (5)	2011-2013	148	8.8	12.8	60.8	4.1	-	11.5	-	2	-	-	-	-
Akar et al. (24)	2012-2013	53	96.2	3.8	50.9	1.9	-	-	-	1.9	-	-	-	-
Tezcan et al. (25)	2013	236	3.8	1.7	84.7	2.1				4.2	-	0.8	-	-
Altuğlu et al. (26)	2013	535	93.3	12.9	80.4	1.5	-	3.7	-	1.5	.	-	-	-
Caliskan et al. (27)	2010-2014	313	51.7	-	-	1.3	-	46.0	-	1.0	-	-	-	-
Cirit et al. (16)	2011-2015	312	69.6			14.1		3.8		10.3		1.6	-	0.6
Çetin Duran et al. (14)	2015-2016	119	71.4	12.6	58.8	7.6		16.8		3.4		1	-	
Kulah et al. (15)	2007-2016	6.0	1.7	5.5	79.8	3.3	0.8	-	5.7	0.5	-	-	0.2	1.8
	2007-2016	336	23.0	3.6	82.8	1.2	1.2	0.3	3.3	1.5		0.3	0.6	1.8
	2007-2016	675	5.2	17.2	58.4	1.6	1.2	7.3	5.3	1.6		1.2	0.2	5 (0.7)
Kirdar et al. (17)	2011-2016	286	90.2	-	-	2.1	-	5.9	-	1.4	-	-	-	0.35
Calgin and Cetinkol (28)	2016-2018	165	2	5.6	91.4			2.5		0.5			-	

been the effect of the arrival in Turkey of refugees from Syria. HCV genotype 4 was reported in as many as 32.0% of chronic hepatitis C in one study, and since the timing coincided with times of labor force migration, the authors thought that it might have been carried by people moving to these areas (2). In the present study, however, genotype 4 was detected in only eight patients, and a more reliable interpretation when the future distribution is revealed.

The detection of HCV genotype co-presence facilitates ideal patient follow-up and increases the effectiveness of antiviral drug therapies (15). In recent years, mixed type HCV genotype reports have been issued more frequently in Turkey (15,16,17). One multi-center study from Turkey determined a mixed genotype prevalence of 1.3% (15). Genotype 1b and 4 was the most frequently seen mixed genotype combination in that study, while the lowest rates were reported for 2b+2c, 1a+3, 1a+4, 2+3, and 3+4 genotype combinations (15). High mixed genotype rates of 15.6% in Taiwan, 19.0% in the Dominican Republic, and 15.7% in Iraq have been reported. The highest rate of patients with mixed genotypes among European countries was reported in Serbia, at 8.5%. The closest rates to those of the present study were recorded from Venezuela at 0.7%, Mexico at 0.7%, and the United States of America at 0.5% (13).

Analysis of the 30 foreign national patients in this study revealed that the most common genotypes, in descending order, were 1, 3, and 2, and no other genotypes were detected. Approximately 60% of these patients were Georgians, and Georgians also represent the majority of foreign patients with genotypes 1b and 3a. Genotype 1b was observed at a lower rate, 50%, in this patient group

compared to the data for Turkey, while rates for genotype 2 and 3 were higher, at 10% and 40%, respectively. Consistent with the present study, analysis of HCV genotype distributions in Russia, Georgia, and the Turkic republics has shown that genotype 1b is dominant, followed by genotype 3, and then by genotype 2 (13). These data indicate that genotype distributions can change over time, in both our own region, in Turkey, and worldwide, especially as travel becomes easier.

Since the HCV is an RNA virus with high genetic variability, no effective vaccine is available. Therapeutic protocols and novel direct-acting antiviral drug studies are based on genotypes and subtypes (3,18).

Study Limitations

The limitation of our study is that the absence of information about the transmission routes due to the retrospective design of the study.

Conclusion

The findings of the present study revealed a time-dependent change in the general distribution of HCV genotypes and subtypes, and that HCV genotype 1b was observed at the highest rate across the years, particularly among patients over 50. Since HCV genotypes can be affected by social and cultural diversity, it is essential that the data be updated at specific intervals. In addition, determining changes in epidemiological data will serve as a useful guide for the development of vaccines and novel antiviral agents.

Ethics

Ethics Committee Approval: The study was approved by Karadeniz Technical University Faculty of Medicine Faculty Clinical Research Ethical Committee (approval number: 2020/169).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ö., C.K.B., FA., N.K., I.B., İ.T., Concept: E.Ö., C.K.B., FA., N.K., I.B., İ.T., Desing: E.Ö., C.K.B., Data Collection or Processing: E.Ö., C.K.B., Analysis or Interpretation: E.Ö., C.K.B., FA., N.K., I.B., İ.T., Literature Search: E.Ö., C.K.B., Writing: E.Ö., C.K.B., N.K., I.B., İ.T.

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