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Evaluation of Hepatitis C in 20 Years: A Turkish Experience

Hepatit C'nin 20 Yıllık Değerlendirilmesi: Bir Türkiye Deneyimi

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Abstract

Objective: Hepatitis C virus (HCV) infection still maintains its importance since it is one of the most important causes of liver cirrhosis and hepatocellular carcinoma. Our hospital, located in İstanbul, which is the 10th most crowded city in the world, has a patient cohort where epidemiological change can be observed due to its deep-rooted history and serving people of different nations in terms of settlement. Main aim in this study is to evaluate the change in HCV epidemiology in our country over the years.

Methods: Patients who were at the age of 18 and above and whose HCV-RNA was positive between January 2001 and January 2021 were evaluated.

Results: 1.166 patients whose HCV genotype was determined were evaluated. The mean age of the population is 52±14.75 years, 83.53% of all patients was infected with genotype 1 (GT1), 8.23% with GT3, 5.83% with GT2, 2.23% with GT4 and 0.17% of them with GT5. While the GT1 rate decreased in patients over the years, an increase was found in other GTs. GT1 and GT2 were more common in females (p<0.001); GT3 and GT4 were more dominant in males (p<0.001). The mean age of females was high in all genotypes. The mean age of GT3 was significantly lower than the other groups (p<0.001).

Conclusion: Although GT1 is still dominant in our country, GT3 and GT4 have been increasingly seen over the years, suggesting that the genotype distribution may change in the coming years due to uncontrolled migration and effective direct-acting antivirals.

Keywords: Distribution, genotype, hepatitis C, migration

Öz

Amaç: Hepatit C virüs (HCV) enfeksiyonu, karaciğer sirozu ve hepatoselüler karsinomun en önemli nedenlerinden biri olması nedeniyle önemini halen korumaktadır. Dünyanın en kalabalık 10. şehri olan İstanbul'da bulunan hastanemiz, köklü geçmişi ve yerleşim açısından farklı milletlerden insanlara hizmet vermesi nedeniyle epidemiyolojik değişimin gözlenebildiği bir hasta kohortuna sahiptir. Bu çalışmada temel amaç ülkemizde HCV epidemiyolojisinin yıllar içindeki değişimini değerlendirmektir.

Yöntem: Ocak 2001 ile Ocak 2021 tarihleri arasında HCV-RNA'sı pozitif olan 18 yaş ve üstü hastalar değerlendirildi.

Bulgular: HCV genotipi belirlenen 1,166 hasta değerlendirildi. Nüfusun ortalama yaşı 52±14,75 olup, tüm hastaların %83,53'ü genotip 1 (GT1), %8,23'ü GT3, %5,83'ü GT2, %2,23'ü GT4 ve %0,17'si GT5 ile enfekte olmuştu. Yıllar içinde hastalarda GT1 oranı azalırken, diğer GT'lerde artış saptandı. GT1 ve GT2 kadınlarda daha yaygındı (p<0,001); GT3 ve GT4 erkeklerde daha baskındı (p<0,001). Kadınların ortalama yaşı tüm genotiplerde yüksekti. GT3'ün ortalama yaşı diğer gruplara göre anlamlı derecede düşüktü (p<0,001).

Sonuç: Ülkemizde GT1 hala baskın olmasına rağmen, GT3 ve GT4'ün yıllar geçtikçe artan bir şekilde görülmesi, kontrolsüz göç ve etkili direkt etkili antiviraller nedeniyle genotip dağılımının önümüzdeki yıllarda değişebileceğini düşündürmektedir.

Anahtar kelimeler: Dağılım, genotip, göç, hepatit C

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Introduction

Hepatitis C virus (HCV) infection still maintains its importance since it is one of the most important causes of liver cirrhosis and hepatocellular carcinoma, and there is limited access to effective treatment options (1). According to the 2016 global report of the World Health Organization (WHO), it has been reported that 71 million people worldwide are infected with HCV, causing 400,000 deaths annually (2). Although its incidence rate is decreasing in developed countries, a decrease in deaths due to liver disease is expected only in the next 20 years (3,4). Again, in this report, WHO has targeted the eradication of HCV and hepatitis B virus (HBV) until 2030.

Although the seroprevalence of HCV in Turkey is in the range of 0.6-1.6%; it is responsible for 25% of all liver cirrhosis, 25-30% of hepatocellular carcinoma and also 50% of liver transplantation cases (5-7).

HCV is a single strand RNA virus from the *Flaviviridae* family. There are regions in the genome structure that are both very well preserved and highly variable. According to sequencing, it has been found that there are 7 main genotypes and nearly 67 related subtypes (3). It is important to determine the genotype in collecting epidemiological data of HCV, shaping antiviral treatment, and predicting prognosis.

The distribution of HCV genotypes varies also geographically. Genotype 1 (GT1), genotype 2 (GT2) and genotype 3 (GT3), subgroup 1a, 1b, 2a and 3a are the most common ones worldwide. These genotypes are considered as infections acquired before safe blood transfusion and epidemic subtypes thought to be spread by IV drug users. Other species (GT4-GT7) are classified as endemic and are distributed in restricted areas (3,8,9).

In our globalizing world, changes are observed in the epidemiology of infectious diseases due to the changing conditions. Our hospital, located in Istanbul, which is the 10th most crowded city in the world, has a patient cohort where epidemiological change can be observed due to its deep-rooted history and serving people of different nations in terms of settlement. Our aim in this study is to evaluate the change in HCV epidemiology in our country over the years.

Materials and Methods

In this retrospective, single-center observational study, patients who were at the age of 18 and above and admitted to the University of Health Sciences Turkey, İstanbul Training and Research Hospital between January 2001 and January 2021 and whose HCV-RNA was positive were evaluated were evaluated. The demographic characteristics, admission dates, race and HCV genotypes of the patients were obtained through the hospital information system and recorded in the prepared forms.

Inclusion Criteria

1. Patients diagnosed with HCV between January 2001 and January 2021,

2. Patients who were at the age of 18 and above,

3. Patients whose initial HCV RNA level was measured and genotype was studied were included in the study.

Exclusion Criteria

1. Patients who were under the age of 18,

2. Patients with undetectable initial HCV RNA or genotype, or both, for any kind of reason.

For HCV genotype determination, the Innolipa HCV II kit (Bayer Diagnostics, USA) was used between 2000-2010, and the HCV Genotype Plus Real-TM (Sacace Biotechnologies-Italy) kit between 2011-2020.

Statistical Analysis

Statistical analysis was performed using Software SPSS 21 (SPSS Inc., Chicago, Illinois, USA). Chi-squared and Fisher's Exact tests were used for qualitative variables. The Mann-Whitney U test was used for variables with non-normal distribution, which was determined by the Kolmogorov-Smirnov test. Comparison of HCV RNA levels among genotypes was performed by Kruskal-Wallis test. $p<0.001$ was considered as statistically significant.

Our study was conducted in accordance with the Helsinki Declaration Principles and the Ethics Committee Approval of the University of Health Sciences Turkey, İstanbul Training Research Hospital Clinical Research Ethics Committee on 19.03.2021-with the number 2776.

Results

Between January 2001 and January 2021, 1.166 patients whose HCV genotype was determined were evaluated. The mean age of the population is 52±14.75 years. When the general genotype distribution is examined, 83.53% (n=974) of all patients was infected with GT1, 8.23% (n=96) with GT3, 5.83% (n=68) with GT2, 2.23% (n=26) with GT4 and 0.17% (n=2) of them with GT5. In GT1 subgroup, 8.42% of patients

was infected with undetermined subtype, 13.04% with GT1a and 78.54% with GT1b. In GT2 subgroup, 76.47% of patients was infected with undetermined subtype, 17.65% with GT2a and 5.88% with GT2c. In GT3 subtype, 62.5% of patients was infected with undetermined subtype, 36.46% with GT3a and 1.04% of them was infected with GT3b. GT5 was detected in 2 cases, all of them were subtyped as 5a. Evaluation of demographic and genotype distributions of our patients is shown in Table 1. While the GT1 rate decreased in our patients over the years, an increase was found in other GTs. Genotype distribution percentages over the years are shown in Graphic 1, and the distribution of genotypes by years is shown in Graphic 2. GT6 and GT7 were not detected in the study group. The infection caused by more than one genotype at a time was not detected in 2 people (1b/4 and 1b/2a). These cases were Syrian.

The study population consisted of 611 (52.4%) females, 555 (47.6%) males. There was a significant difference in the distribution of genotypes by gender. While GT1 and GT2 were more common in females ($p<0.001$), GT3 and GT4 were more dominant in males ($p<0.001$) (Table 2). The mean age of the population was 52±14.75 years, while the mean age of females was 54.2±4.07 years and the mean age of males was 48.55±6.42 years. The mean age of females was high in all genotypes. The mean age of GT3 was significantly lower than the other groups ($p<0.001$) (Table 2).

Discussion

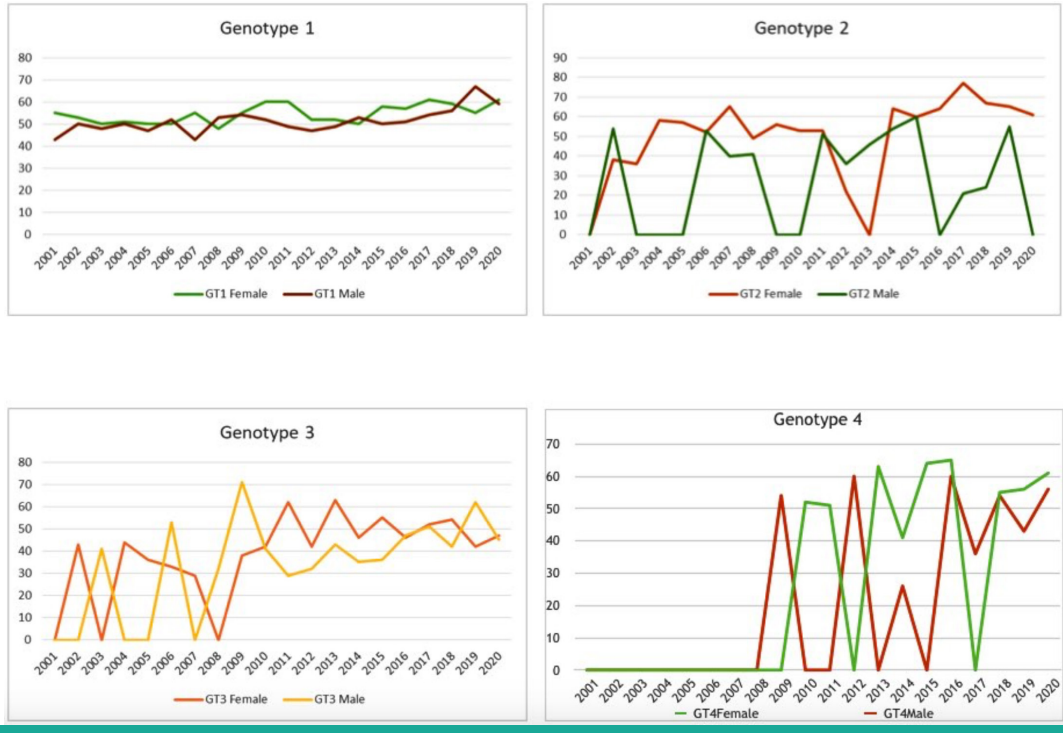
Transfusion of uncontrolled blood and blood products, invasive procedures and intravenous (IV) drug use are effective in the transmission of HCV. In developed countries, after safe transfusion procedures, its incidence is increasing in IV drug users, even if it incidence is decreasing in overall. In a multi-center study from 2013, it was reported that the incidence of HCV infection gradually decreased with the transition to safe blood transfusion practices and the number of new cases remained constant due to the low rate of IV drug users in our society. Consistent with this high incidence before 1992, a higher prevalence of HCV has been reported in patients over 50 years of age. In our study, the mean age was 52 years old (4).

The distribution of HCV genotypes varies worldwide. It is responsible for 49.1% of GT1 adult infections worldwide. It

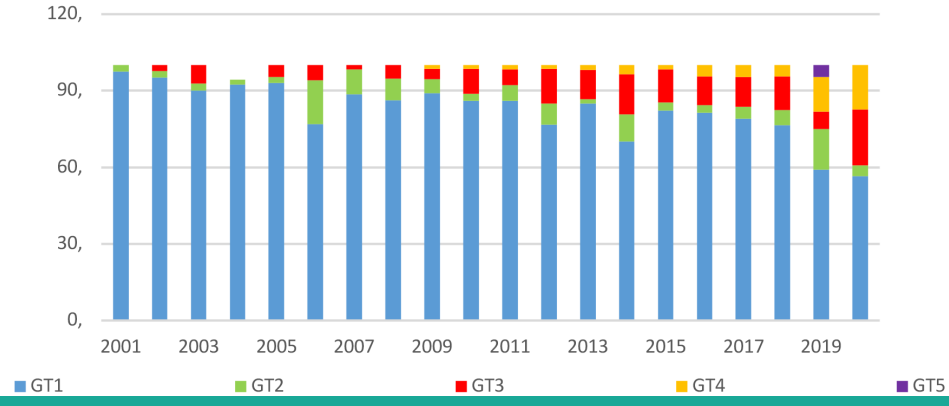
Table 1. Evaluation of demographic and genotype distributions of our patients with HCV

	Genotype 1							Genotype 2					Genotype 3					Genotype 4				
	N_t	Age_m	N_t	N_f	Age_f	N_m	Age_m	N_t	N_f	Age_f	N_m	Age_m	N_t	N_f	Age_f	N_m	Age_m	N_t	N_f	Age_f	N_m	Age_m
2001	39	51	38	28	55	10	43	1	1	38	0	0	0	0	0	0	0	0	0	0	0	0
2002	85	51	81	48	53	33	50	2	1	38	1	54	2	2	43	0	0	0	0	0	0	0
2003	70	49	63	35	50	28	48	2	2	36	0	0	5	0	0	5	41	0	0	0	0	0
2004	53	51	49	25	51	24	50	1	1	58	0	0	3	3	44	0	0	0	0	0	0	0
2005	44	49	41	28	50	13	47	1	1	57	0	0	2	2	36	0	0	0	0	0	0	0
2006	52	51	40	26	50	14	52	9	7	52	2	53	3	1	33	2	53	0	0	0	0	0
2007	62	50	55	27	55	28	43	6	5	65	1	40	1	1	29	0	0	0	0	0	0	0
2008	58	49	50	22	48	28	53	5	2	49	3	41	3	0	0	3	32	0	0	0	0	0
2009	73	55	65	38	55	27	54	4	4	56	0	0	3	2	38	1	71	1	0	0	1	54
2010	72	55	62	33	60	29	52	2	2	53	0	0	7	1	42	6	41	1	1	52	0	0
2011	65	55	56	35	60	21	49	4	3	53	1	51	4	2	62	2	29	1	1	51	0	0
2012	73	46	56	24	52	32	47	6	1	22	5	36	10	4	42	6	32	1	0	0	1	60
2013	53	50	45	21	52	24	49	1	0	0	1	46	6	1	63	5	43	1	1	63	0	0
2014	57	50	40	16	50	24	53	6	4	64	2	54	9	2	46	7	35	2	1	41	1	26
2015	62	62	51	34	58	17	50	2	1	60	1	60	8	1	55	7	36	1	1	64	0	0
2016	70	53	57	23	57	34	51	2	2	64	0	0	8	3	46	5	47	3	2	65	1	60
2017	43	55	34	17	61	17	54	2	1	77	1	21	5	1	52	4	51	2	0	0	2	36
2018	68	56	52	24	59	28	56	4	3	67	1	24	9	3	54	6	42	3	1	55	2	54
2019	44	58	26	11	55	15	67	7	3	65	4	55	3	2	42	3	62	6	3	56	3	43
2020	23	52	13	7	61	6	59	1	1	61	0	0	5	2	47	3	45	4	1	61	3	56

N_t: Total number, N_f: Total number of females, N_m: Total number of males, Age_m: Age values were given as mean, HCV: Hepatitis C virus



Graphic 1. Genotype distribution percentages over the years



Graphic 2. The distribution of genotypes by years Graphic 2. The distribution of genotypes by years

is followed by GT3 (17.9%), GT4 (16.8), GT2 (11%), GT5 (2%) and GT6 (1.4%) (3).

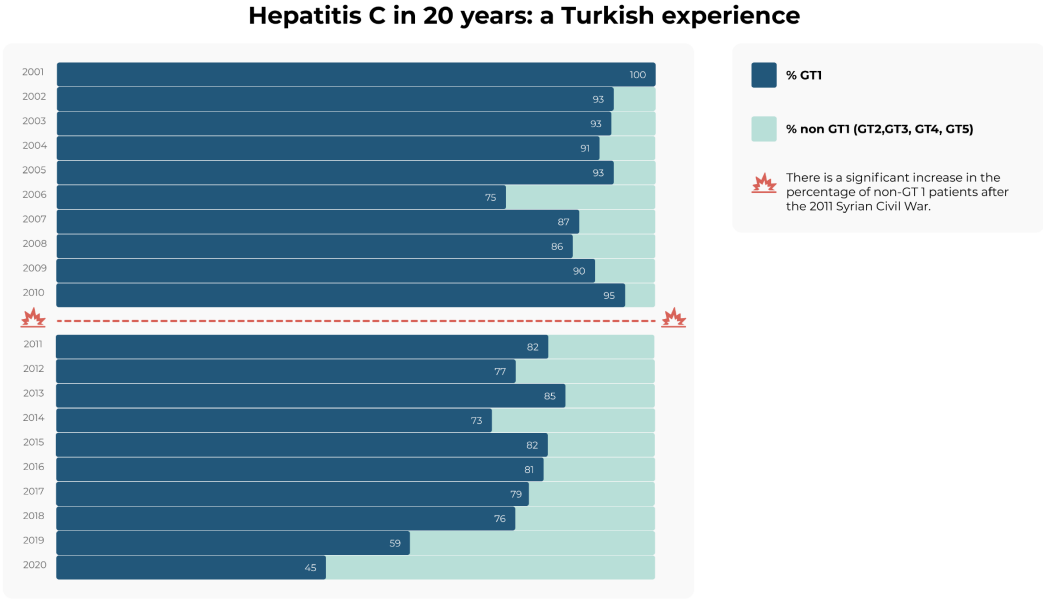
GT1, the most prevalent genotype in developed countries, is also the most prevalent worldwide and respond well to the second generation direct-acting antiviral (DAA) therapies with the viral eradication rates of >0% (10). In our study, the dominant genotype was GT1 (83.53%), followed by GT 3 (8.23%) and GT2 (5.83%). GT1 prevalence were reported between 62.4-95.3% in studies conducted in different regions of Turkey (11,12). The prevalence of GT1b, which is the most frequently observed genotype of the world (23.2-92.6%), was reported in Turkey with regional differences between 17.7% to 87%. Our study supports the general trend with a rate of 78.54% (10,11-13). Identifying previously unreported genotype "GT5" and showing relative increase of GT4 were probably caused by immigrants involved in our study group (Graphic 3).

It is known that social events such as wars and migrations play an important role in the epidemiological change of infectious diseases. GT3 is the second most common genotype, and it is the genotype that has spread among IV drug users, especially in Europe. In our previous study conducted between 2012-2019, the prevalence was 11.86% for GT3. In this study, the prevalence of GT3 was 8.23%, and two of our patients were IV drug user. In studies conducted in our country, the prevalence has been reported to be

Table 2. Difference in the distribution of genotypes by gender and age

	GT1		GT2		GT3		GT4		GT5	
	n	%	n	%	n	%	n	%	n	%
2001	38	(97.44)	1	(2.56)	0	(.00)	0	(0.00)	0	(0.00)
2002	81	(95.29)	2	(2.35)	2	(2.35)	0	(0.00)	0	(0.00)
2003	63	(90.00)	2	(2.86)	5	(7.14)	0	(0.00)	0	(0.00)
2004	49	(92.45)	1	(1.89)	3	(5.66)	0	(0.00)	0	(0.00)
2005	41	(93.18)	1	(2.27)	2	(4.55)	0	(0.00)	0	(0.00)
2006	40	(76.92)	9	(17.31)	3	(5.77)	0	(0.00)	0	(0.00)
2007	55	(88.71)	6	(9.68)	1	(1.61)	0	(0.00)	0	(0.00)
2008	50	(86.21)	5	(8.62)	3	(5.17)	0	(0.00)	0	(0.00)
2009	65	(89.04)	4	(5.48)	3	(4.11)	1	(1.37)	0	(0.00)
2010	62	(86.11)	2	(2.78)	7	(9.72)	1	(1.39)	0	(0.00)
2011	56	(86.15)	4	(6.15)	4	(6.15)	1	(1.54)	0	(0.00)
2012	56	(76.71)	6	(8.22)	10	(13.70)	1	(1.37)	0	(0.00)
2013	45	(84.91)	1	(1.89)	6	(11.32)	1	(1.89)	0	(0.00)
2014	40	(70.18)	6	(10.53)	9	(15.79)	2	(3.51)	0	(0.00)
2015	51	(82.26)	2	(3.23)	8	(12.90)	1	(1.61)	0	(0.00)
2016	57	(81.43)	2	(2.86)	8	(11.43)	3	(4.29)	0	(0.00)
2017	34	(79.07)	2	(4.65)	5	(11.63)	2	(4.65)	0	(0.00)
2018	52	(76.47)	4	(5.88)	9	(13.24)	3	(4.41)	0	(0.00)
2019	26	(59.09)	7	(15.91)	3	(6.82)	6	(13.64)	2	(4.55)
2020	13	(56.52)	1	(4.35)	5	(21.74)	4	(17.39)	0	(0.00)
Male[1]	453	(81.62)	23	(4.14)	64	(11.53)	14	(2.52)	1	(0.18)
Female[1]	521	(85.27)	45	(7.36)	32	(5.24)	12	(1.96)	1	(0.16)
Ages[2]	52.79±13.99		52.91±15.85		42.46±12.16		52.27±14.16		53.00±19.80	

[1] Chi-squared test (p<0.001) [2]Kruskal-Wallis test (p<0.001)



Graphic 3. Graphical course of hepatitis C after the 2011 Syrian Civil War

between 1.1-46%, and 0.6-71.6% from different regions in the world (10,11,14,15).

GT2 and GT4 are genotypes of African origin, and GT4 is thought to have spread iatrogenically, especially during the schistosomiasis vaccination applied in Egypt in the past, and spread to Europe due to the political relations of the countries and through frequent travels (16). In our country, it is known that it increased with the refugees coming after the Syrian civil war. In the study of Cirit et al. (17) evaluated the GTs of Syrian refugees, GT4 was found to be 48.2%. In our study, GT4 has been detected since 2009 at a rate of 2.23%. While the prevalence of GT2 is between 0.1% and 24.5% in the world, it is between 1.4-14.5% in studies conducted in our country and in our study, the prevalence was found to be 5.83% (13,18).

In the study, the low number of cases in 2020 is thought to be due to the low number of patients admitted due to the Coronavirus disease-2019 outbreak. It was observed that age and gender were effective in genotype distribution. While GT1 and GT2 were more common in females, GT3 was observed more frequently in males. In the study conducted by Karabulut et al. (19), GT1 and GT2 were observed with a higher rate in females (20).

In the GEHEP 2005 study conducted in Spain, while male gender is dominant over GT3 and GT4; female gender is dominant in GT1 and GT2 (21). Similar results were obtained in a study in which Western Europe, Russia and Israel regions were evaluated. It is thought that the prevalence in female gender is due to the fact that they are more exposed to childbirth and related invasive procedures and blood transfusion practices.

Study Limitations

Our study had limitations. Because of its retrospective nature, transmission routes, nationality, and diagnostic method (screening, presence of clinical findings), which could lead epidemiologically could not be obtained. In addition, DAAs, which were included in the scope of payment by the Social Security Institution in June 2016 in our country, are out of the scope for asylum seekers and foreign nationals, and these antivirals are not sold freely, but are distributed by the state. Since this patient group does not have a treatment opportunity, it is possible that their application will be reduced.

Conclusion

Although GT1 is still dominant in our country, GT3 and GT4 have been increasingly seen over the years, suggesting that the genotype distribution may change in the coming years due to uncontrolled migration and effective DAAs.

Ethics

Ethics Committee Approval: Our study was conducted in accordance with the Helsinki Declaration Principles and the ethics committee approval of the University of Health Sciences Turkey, İstanbul Training Research Hospital Clinical Research Ethics Committee on 19.03.2021-with the number 2776.

Informed Consent: An informed consent obtained as written forms from all of our patients to publish.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: N.D.S., İ.S., Design: N.D.S., İ.S., Data Collection or Processing: N.D.S., İ.S., Analysis or Interpretation: N.D.S., İ.S., Drafting Manuscript: N.D.S., İ.S., S.B., Critical Revision of Manuscript: N.D.S., İ.S., S.B., Final Approval and Accountability: N.D.S., İ.S., S.B., Technical and Material Support: N.D.S., S.B., Supervision: N.D.S., S.B., Writing: N.D.S., İ.S., S.B.

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