Changes on Hepatitis C virus genotype distribution in Western Turkey: Evaluation of twelve-year data

Alev Çetin Duran[1*], Özgül Kaya Çetinkaya[2], Ayça Arzu Sayıner[3], Gülşah Şeydaoğlu[4], Emre Özkarataş[3], Hakan Abacıoğlu[5]

[1]Clinic of Medical Microbiology and Basic Immunology, Aydın State Hospital, Aydın, Turkey
[2]Department of Medical Microbiology, Akdeniz University School of Medicine, Antalya, Turkey
[3]Department of Medical Microbiology, Dokuz Eylül University School of Medicine, İzmir, Turkey
[4]Department of Biostatistics, Çukurova University School of Medicine, Adana, Turkey
[5]İzmir University of Economics School of Medicine, İzmir, Turkey

Cite this article as: Duran AÇ, Çetinkaya ÖK, Sayıner AA, Şeydaoğlu G, Özkarataş E, Abacıoğlu H. Changes on Hepatitis C Virus Genotype Distribution in Western Turkey: Evaluation of Twelve-Year Data. Turk J Gastroenterol 2020; 31(2): 128-35.

ABSTRACT

Background/Aims: Hepatitis C virus (HCV) prevalence is 1% in Turkey with genotype 1 being the predominant type traditionally. However unique geographical location of Turkey and increasing human migration in the region influences the epidemiology of the infection. The aim of this study was to determine the changes in distribution of HCV genotypes and risk factors.

Materials and Methods: In this retrospective single-center study, HCV genotyping results of 558 patients were evaluated in between 2005 and 2016.Three different HCV genotyping assays were used during the 12-year study period;restriction fragment length polymorphism (RFLP), Abbott Real Time HCV Genotype II and Bosphore HCV genotyping kit.

Results: The most prevalent HCV genotype was genotype 1 detected in 88.4% of the patients followed by genotype 3 (5.2%),genotype 4 (2.9%),genotype 2 (2.1%), mixed genotypes (1.1%) and genotype 5 (0.3%).Genotype 1a showed an increasing prevalence.There were 19 patients (3.4%) either of foreign nationalities or Turkish citizens living abroad. Genotype 3 was the most common type among these patients which 10.3% had intravenous drug use history.Syrian migrant population differed in terms of HCV genotypes.Genotype 5 detected in two Syrian patients, which is the first report of HCV type 5 in Western Turkey. Among the HCV genotype 4 infected patients, 31.3% were Syrians.

Conclusion: Our study showed that although genotype 1b dominance continues, the distribution and prevalence of HCV genotypes are changing in our region mainly due to migration and increase in the frequency of patients with non-traditional risk factors such as intravenous drug use. Monitoring the epidemiology of HCV genotypes may provide guidance in treatment decisions.

Keywords: Hepatitis C virus genotypes, risk factors, genotype 5 infection

INTRODUCTION

Hepatitis C virus (HCV) infection is a significant public health problem worldwide due to its serious complications such as a high risk of chronic hepatitis and hepatocellular carcinoma (1, 2). Globally, 80 million (range: 64-103 million) individuals are estimated to be viremic with an HCV RNA prevalence of 1.1% (range: 0.9-1.4%) (2). The HCV prevalence is approximately 1.0 % in Turkey and approximately 1.0-1.3 million individuals are infected (3).

The identification of HCV genotypes is important for the treatment and follow-up of patients. In genotype 1 and 4 infections, the classical treatment (ribavirin and interferon) response and treatment success rate are lower than those for genotypes 2 and 3, and genotypes 1 and 4 require longer treatment duration. Even with new direct-acting antiviral therapies, treatment regimens are mostly influenced by the genotype (1).

Epidemic genotypes (genotypes 1a, 1b, 2a, 2b, 3a and 4a) are common worldwide, while genotype 5 and genotype 6, which are referred to as endemic genotypes, are more common in South Africa and South East Asia, respectively (2, 4). Genotype 1 (46%) is the most common genotype worldwide. The next most common is genotype 3 (22%), followed by genotype 2 (13%) and genotype 4 (13%) infections. Genotype 1b is responsible for 22% of HCV infections (2).While genotype 1 is dominant in Australia, Europe, Latin America, and North America, genotype 4 is dominant in North Africa and the Middle East (2, 4).

Corresponding Author: **Alev Çetin Duran; alevctndrn@gmail.com**
Received: **October 18, 2018** Accepted: **March 19, 2019**

DOI: **10.5152/tjg.2020.18798**

The aim of this study was to examine the changes in HCV genotypes and risk factors within the last twelve years at a single university hospital in Western Turkey.

MATERIALS AND METHODS

Study group

HCV genotyping results were evaluated between 2005 and 2016 in patients with HCV RNA-positive chronic liver disease in Dokuz Eylül University Hospital, Izmir. In all, 558 patients were included in this study, and one result per patient was assessed. Demographic characteristics, risk factors for transmission and therapeutic histories of patients were obtained from the medical records. The medical files of 15 patients did not have available data for samples sent from external medical centers for only the genotyping assay. This is a retrospective study and all the information about patients was anonymous. Ethics committee approval and informed consent are not necessary for this manuscript due to the retrospective design of the study.

Molecular methods

Three different HCV genotyping assays were used during the 12-year study period. A restriction fragment length polymorphism (RFLP) assay was used for the first 221 patients (2005-2012), while 75 patients (2012-2014) were tested by Abbott Real Time HCV Genotype II (Abbott Molecular Inc., USA), and 262 patients (2014-2016) were tested using the Bosphore HCV genotyping kit (Anatolia, Geneworks, Turkey).

RFLP was an in-house assay that used amplification of the 5'UTR region by nested PCR (5). Amplicons were cut with restriction endonucleases (Hae III, Rsa I, Mva I and Hinf I enzymes). The fragments were evaluated, and the genotypes were determined as described in the literature (5). Subtyping was not performed.

The Abbott Real Time HCV Genotype II assay was used as recommended by the manufacturer. Genotypes 1 to 6 were identified using the 5'UTR, and subtypes 1a-1b were determined by the NS5B target region. The Bosphore HCV genotyping kit targeted the NS5B region for the detection of genotypes 1 to 6 and the subtypes of genotype 1.

Statistical analysis

Chi square analysis was used for categorical data, while Kruskal-Wallis analysis was used for the analysis of continuous variables. The Mann-Whitney test was used for binary group comparison. Data were expressed as n (%) and the median (min-max). Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) for Windows, Version 20.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

The study group consisted of 558 patients, of whom 255 (45.7%) were male and 303 (54.3%) were female and whose mean age was 59.5±13.1 years (range: 1-91 years).

HCV genotype 1, which was detected as the predominant type, as expected, was followed by genotypes 3, 4, 2, and 5 in order of decreasing frequency. Among the 558 patient samples, 88.4% (493/558) were infected with genotype 1, 5.2% (29/558) were infected with genotype 3, 2.9% (16/558) were infected with genotype 4, 2.1% (12/558) were infected with genotype 2, and 0.3% (2/558) were infected with genotype 5. Mixed genotypes were detected in 6 samples (1.1%) where the combinations were 1a+2, 2+3, 3+4, and 1+4. Genotype 5 infection, which was not previously reported in our region, was detected in two female Syrian immigrants (Table 1). The genotype of these samples was confirmed to be genotype 5a by NS5B and 5'UTR region sequencing.

In order to evaluate the changes in the prevalence of genotypes according to year, the study period was divided into three, four-year groups (2005-2008, 2009-2012, and 2013-2016) for statistical analysis (Table 2). Although the prevalence of genotype 2 decreased, while that of genotypes 3 and 4 was increased in the last group, no statistically significant difference was observed in terms of genotype distribution between groups (p=0.221). An increase in genotype diversity was observed in the last group.

The genotype 1 subtypes could be determined after August 2012, which parallels the changes in genotyping method. The distribution of genotype 1 subtypes between 2013 and 2016 is provided in Table 3, which showed that genotype 1a has increased over the years.

The distribution of HCV genotypes according to gender and age between 2005-2016 is presented in Table 4. The mean age of the patients who were infected with genotype 1b was found to be higher than the mean age of patients infected with genotype 1a (p<0.001), genotype 3 (p<0.001), and genotype 4 (p=0.001). No significant difference in age was found among those infected with genotype 1b, genotype 2 and genotype 5.

Table 1. Distribution of HCV genotypes by year (2005-2016).

Year	Genotype 1 n (%)	Genotype 2 n (%)	Genotype 3 n (%)	Genotype 4 n (%)	Genotype 5 n (%)	Mixed types n (%)	Total n
2005	16 (80.0)	2 (10.0)	1 (5.0)	1 (5.0)	-	-	20
2006	19 (86.4)	1 (4.5)	2 (9.1)	-	-	-	22
2007	25 (92.6)	-	1 (3.7)	1 (3.7)	-	-	27
2008	26 (86.7)	2 (6.7)	1 (3.3)	1 (3.3)	-	-	30
2009	41 (100.0)	-	-	-	-	-	41
2010	29 (96.7)	-	1 (3.3)	-	-	-	30
2011	19 (79.1)	3 (12.5)	1 (4.2)	-	-	1 (Genotype 1+4) (4.2)	24
2012	24 (80.0)	-	5 (16.7)	-	-	1 (Genotype 1+4) (3.3)	30
2013	42 (97.7)	-	1 (2.3)	-	-	-	43
2014	31 (93.9)	-	1 (3.0)	-	-	1 (Genotype 1+4) (3.0)	33
2015	58 (84.1)	2 (2.9)	3 (4.3)	4 (5.8)	-	2 (Genotype 1a+2) (Genotype 3+4) (2.9)	69
2016	163 (86.2)	2 (1.1)	12 (6.3)	9 (4.8)	2 (1.1)	1 (Genotype 2+3) (0.5)	189
Total	493 (88.4)	12 (2.1)	29 (5.2)	16 (2.9)	2 (0.3)	6 (1.1)	558 (100.0)

HCV: Hepatitis C virus

Table 2. Distribution of HCV genotypes in three four-year groups during 2005-2016.

	HCV GENOTYPES n (%)					
Year	Genotype1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Mixed types
2005-2008 (n: 99)	86 (86.7)	5 (5.1)	5 (5.1)	3 (3.1)	-	-
2009-2012 (n: 125)	113 (90.4)	3 (2.4)	7 (5.6)	-	-	2 (1.6)
2013-2016 (n: 334)	294 (88.0)	4 (1.2)	17 (5.1)	13 (3.9)	2 (0.6)	4 (1.2)
Total (n: 558)	493 (88.4)	12 (2.1)	29 (5.2)	16 (2.9)	2 (0.3)	6 (1.1)

HCV: Hepatitis C virus

Table 3. Distribution of HCV genotype 1 subtypes between 2013 and 2016.

	Genotype 1 n(%) p			
	1a	1b	Subtype cannot be determined	p
2013 (n: 42)	1 (2.4)	36 (85.7)	5 (11.9)	<0.001
2014 (n: 31)	3 (9.7)	26 (83.9)	2 (6.4)	
2015 (n: 58)	8 (13.8)	50 (86.2)	-	
2016 (n: 163)	29 (17.8)	134 (82.2)	-	
Total (n: 294)	41 (13.9)	246 (83.7)	7 (2.4)	

HCV: Hepatitis C virus

Nineteen patients were either foreign nationals or Turkish individuals living abroad (Russia, Azerbaijan, England, Switzerland, Germany and Syria). HCV genotype 3 (7/19, 36.9%) was detected as the predominant type, which was followed by genotype 4 (5/19, 26.3%), genotype 5 (2/19, 10.5%), genotype 2 (2/19, 10.5%), genotype 1 (2/19, 10.5%), and mixed types (1/19, 5.3%, genotype 1+4).

Three of the seven patients (42.8%) infected with genotype 3 were intravenous drug users (IVDU) in this group. Three other IVDU were included in the study group: one

Table 4. Gender and age distribution of patients infected with different HCV genotypes between 2005 and 2016.

	Genotype 1 (n=493)			HCV GENOTYPES n (%)				
	1a	1b	1	Genotype 2	Genotype 3	Genotype 4	Genotype 5	Mixed types
Number (n=558)	41 (7.4)	246 (44.1)	206 (36.9)	12 (2.1)	29 (5.2)	16 (2.9)	2 (0.3)	6 (1.1)
Gender								
Male								
n:255 (45.7)	21 (8.2)	98 (38.4)	105 (41.2)	4 (1.6)	16 (6.3)	8 (3.1)	-	3 (1.2)
Female								
n:303 (54.3)	20 (6.6)	136 (44.9)	113 (37.3)	8 (2.6)	13 (4.3)	8 (2.6)	2 (0.7)	3 (1.0)
Age *				Age**				
Median (min-max)	49.0 (23-77)	64 (26-91)	60.0 (17-87)	57.0 (3-68)	41.0 (23-73)	52.5 (1-79)	57.0 (44-70)	60.0 (37-81)

**p<0.001, **p=0.049, HCV: Hepatitis C virus*

Table 5. Possible transmission routes in patients according to HCV genotype.

Possible transmission routes	HCV Genotypes n(%)								
	G1 (total) (n:89)								
	Sayı	1a	1b	1	2	3	4	5	Mixed
Operation/ invasive medical procedure	61 (53.5)	4 (3.5)	34 (29.8)	17 (14.9)	1 (0.9)	3 (2.6)	2 (1.8)	-	-
Hemodialysis	27 (23.7)	7 (6.1)	5 (4.4)	10 (8.8)	-	-	3 (2.6)	-	2 (1a-2/2-3) (1.8)
Blood transfusion	12 (10.6)	1 (0.9)	3 (2.6)	3 (2.6)	2 (1.8)	1 (0.9)	2 (1.8)	-	-
IVDU	6 (5.3)	1 (0.9)	-	-	1 (0.9)	4 (3.5)	-	-	-
Sexual intercourse	5 (4.4)	-	-	1 (0.9)	-	4 (3.5)	-	-	-
Familial transmission	3 (2.6)	-	2 (1.8)	1 (0.9)	-	-	-	-	-
Total	114 (100.0)	13 (11.4)	44 (38.6)	32 (28.1)	4 (3.5)	12 (10.6)	7 (6.1)	-	2 (1.8)

HCV: Hepatitis C virus; IVDU: Intravenous drug users

was infected with genotype 1a and the others with genotype 2 and genotype 3.

The five patients infected with genotype 4 (5/16, 31.3%) were Syrian and half of them experienced a medical intervention in Syria. Genotype 5 patients and a single patient with a mixed genotype (1+4) were also Syrian.

Possible transmission routes of HCV were obtained from the medical records of 114 patients (Table 5). Surgery/invasive medical procedure (61.8%, 55/89) was the most common, hemodialysis (HD) was the second most common (24.7%, 22/89), and blood transfusion (7.9%, 7/89) was the third most common transmission route in patients infected with genotype 1. The most common risk factors in patients infected with genotype 3 were intravenous drug use (33.3%, 4/12) and sexual intercourse (33.3%, 4/12) in patients infected.

We examined the genotype of newly diagnosed HCV patients for each year according to the treatment they received (ribavirin/interferon (R/I), protease inhibitor (PI), direct-acting antivirals (DAAs) regimen) (Table 6).

DISCUSSION

Genotype 1b is the most common HCV genotype in Turkey. According to a study that investigated the distribution of genotype 1b in Turkey, the HCV epidemic probably originated in Greece at the beginning of the 1900s and then spread into Turkey and increased as a result of unsafe medical practices until the end of the 1990s (6).

Table 6. Treatment regimens for newly diagnosed HCV patients according to year.

		HCV Genotypes							
Year	Number n:112 (%)	1a	1b	1	2	3	4	5	Mixed
2005	4 (3.5)	-	-	R/I (n:4)	-	-	-	-	-
2006	-	-	-	-	-	-	-	-	-
2007	6 (5.4)	-	-	R/I (n:6)	-	-	-	-	-
2008	12 (10.7)	-	-	R/I (n:10)	R/I (n:1)	R/I (n:1)	-	-	-
2009	17 (15.2)	-	-	R/I (n:17)	-	-	-	-	-
2010	8 (7.1)	-	-	R/I (n:8)	-	-	-	-	-
2011	14 (12.5)	-	-	R/I (n:11)	R/I (n:2)	R/I (n:1)	-	-	-
2012	7 (6.3)	-	R/I (n:3)	R/I (n:4)	-	-	-	-	-
2013	7 (6.3)	-	R/I (n:5)	-	-	-	-	-	-
		-	PI (n:2)	-	-	-	-	-	-
2014	11 (9.8)	-	R/I (n:1)	-	-	-	-	-	-
		-	PI (n:2)	PI (n:3)	-	-	-	-	-
		-	DAA (n:4*)	DAA (n:1*)	-	-	-	-	-
2015	6 (5.4)	-	DAA (n:5)	-	DAA (n:1)	-	-	-	-
2016	20 (17.8)	DAA (n:2)	DAA (n:12)	-	-	DAA (n:2)	DAA (n:3)	-	DAA (n:1)

** These patients waited for new treatment regimens; DAA was started after 2015, HCV: Hepatitis C virus; R/I: Ribavirin/interferon; PI: Protease inhibitör; DAAs: Direct-acting antivirals*

In recent years, the change in the epidemiology of HCV infection in Turkey has been due to factors such as tourism, the influx of Syrian refugees, and risky behaviors and has attracted substantial attention. The results of several HCV genotyping studies performed in Turkey since 1995 are summarized in Table 7 (7-17).

In our study, the most frequently identified HCV genotype was 1 (88.4%), which was similar to the results of other studies performed in Turkey. Compared with the other three studies conducted in Izmir, the results of this study show that the genotype diversity is increasing despite the predominance of genotype 1b.

The prevalence of genotype 1a increased throughout the study period and reached nearly 18% in 2016. The median age of patients infected with genotype 1a was 49 years compared with 64 years for those infected with genotype 1b. Studies in Europe note that genotype 1a is more common in younger male patients and is associated with non-iatrogenic risk factors (18, 19). The gender and transmission route of genotypes 1a and 1b were not significantly different in our study.Surgery/invasive medical procedure, HD and blood transfusion were the most important possible transmission routes in patients infected with genotypes 1a and 1b.

Immigration is an important factor that changes the epidemiology of infectious diseases. Nearly three million people who fled the current conflict in Syria are currently living in Turkey. One in every three genotype 4 cases detected in our study was of Syrian descent, which shows the effects of population movements on HCV genotypes. In addition, genotype 5 infection was detected for the first time in our region in two Syrian refugees. Although the presence of HCV genotype 5 infection in southern and southeastern Turkish cities neighboring Syria has previously been reported (17, 20), this is the first time that genotype 5 was detected in Western Turkey. HCV genotype 5 infection is commonly found in South African countries. Two global surveys reported that, in the Middle East and more specifically, in Syria, genotype 4 is the predominant type followed by genotype 1, while genotype 5 is less prevalent (2, 21). A Syrian study showed that genotype 4 infections are more widespread in eastern Syria, while genotype 5 is mostly seen in northern regions adjacent to Turkey (22). Some studies emphasize that genotype 5 infection is associated with blood transfusions and other medical interventions (22-24).

HCV is a blood-borne virus. While the most important transmission route in developed countries is intravenous drug use, in Turkey, HCV infection is primary associated

Table 7. Results of major HCV genotyping studies in Turkey.

Study (Reference)	Year	Province	Patient characteristics	Number (n)	GENOTYPES					
					Genotype 1 (total) n (%)	1a (%)	1b (%)	2 (%)	3 (%)	4 (%)	5 (%)
Abacıoğlu (7)	1995	İzmir	HD, BD,PAH	89	84 (94.4)	(19.1)	(75.3)	3 (3.4)	-	2 (2.2)	-
Bozdayı (8)	2004	Ankara	PAH	365	349 (95.0)	(11.0)	(84.0)	10 (3.0)	3 (1.0)	3 (1.0)	-
Altuğlu (9)	2008	İzmir	PAH	345	335 (97.1)	(9.9)	(87.2)	3 (0.9)	5 (1.4)	2 (0.6)	-
Gökahmetoğlu (10)	2011	Kayseri	PAH	146	90 (61.7)	(3.4)	(52.8)	4 (2.7)	-	52 (35.6)	-
Buruk (11)	2013	Trabzon	PAH	304	282 (92.8)	(5.3)	(87.5)	5 (1.6)	15 (4.9)	2 (0.7)	-
Altuğlu (12)	2013	İzmir	PAH	535	499 (93.3)	(12.9)	(80.4)	8 (1.5)	20 (3.7)	8 (1.5)	-
Sağlık (13)	2014	Antalya	PAH	422	352 (83.4)	(14.7)	(63.3)	15 (3.5)	47 (11.1)	7 (1.6)	-
Kuşçu (14)	2014	Adana	PAH	369	289 (78.3)	NA	NA	23 (6.2)	54 (14.6)	3 (0.8)	-
Çalışkan (15)	2015	Kahramanmaraş	PAH, at risk for IDU	313	162 (51.7)	NA	NA	4 (1.3)	144 (46.0)	3 (1.0)	-
Üçbilek (16)	2015	Adana-Mersin	IDU	87	10 (11.5)	NA	NA	26 (29.9)	51 (58.6)	-	-
Çetin Duran (17)	2016	Adana	PAH	119	85 (71.4)	(12.6)	(58.8)	9 (7.6)	20 (16.8)	4 (3.4)	1 (0.8)
Present Study	2005-2012	İzmir	PAH	224	199 (88.8)	NA	NA	8 (3.6)	12 (5.4)	3 (1.3)	2
	2013-2016			334	294 (88.0)	(12.3)	(70.0)	4 (1.2)	17 (5.1)	13 (3.9)	(0.6)

HD: Hemodialysis patients; PAH: Patients admitted to the hospital; IDU: Intravenous drug user; BD: Blood donor; NA: not available; -: not detected, HCV: Hepatitis C virus

with unsafe medical practices (25, 26). In the study by Altuğlu et al. (12) in Izmir, dental or surgical procedures were determined as the main risk factor in 57.5% of patients. In another study, blood transfusions and dental interventions were identified as risk factors for genotype 2 infections, while sexual activity, living abroad, multiple surgical procedures, and hemodialysis were related to genotype 3 infection (9). Interestingly, Turkish patients infected with genotype 4 generally have a history of medical intervention in Middle Eastern countries such as Saudi Arabia and Iraq (9). In this study, 31.3% of patients infected with genotype 4 were Syrian, and half of them had a history of medical intervention in Syria.

Genotype 3 (36.9%) was the most frequent genotype detected in foreign nationals and in Turkish expatriates living in countries such as Russia, Azerbaijan, England, Switzerland, and Germany. In a study conducted in Antalya, a popular coastal town, 40.4% of patients infected with genotype 3 (3a) had emigrated from Russia, Ukraine, Georgia, Kyrgyzstan, Germany, or Azerbaijan, while 13.3% of patients infected with genotype 2 were of Russian or Swiss origin (13). When HCV genotypes in these countries were examined, genotype 3 infection was the most common in the U.K. and Switzerland (43.8% and 29.2%, respectively), while genotype 3 was the second most frequent genotype after 1b (35.1% and 27.4%, respectively) in Russia and Germany (2). Reports have also shown that the prevalence of genotype 3a is increasing in Russia (27).

The most important risk factor for HCV infection in European countries today is intravenous drug use, which accounts for 23-53% of all HCV infections (28, 29).However, data on HCV infection in intravenous drug users in Turkey are limited. Uçbilek et al. (16) reported that, among intravenous drug users in the Çukurova region, 58.6% were infected with HCV genotype 3, 29.9% with genotype 2, and 11.5% with genotype 1. The prevalence of genotype 2 and 3 infections was higher in intravenous drug users compared with nonusers. In our study, only six patients were intravenous drug users, and of these, four were infected with genotype 3. While the most common possible transmission routes were IVDU and sexual intercourse in patients infected with genotype 3, surgery/invasive medical procedures, HD, and blood transfusions were the possible transmission routes in patients infected with genotype 1.

Although the combination of interferon and ribavirin has been used previously as a hepatitis C therapy, protease inhibitors after 2011 and direct-acting antiviral agents (DAAs) after 2014 have been approved for clinical use and have better viral suppression. DAAs have dramatically improved hepatitis C treatment. These new treatment regimens are providing a chance for a cure for all HCV-infected patients with cure rates over 95% (30). New treatment regimens might have a substantial effect on genotype distribution, and this change should be followed. In our study, ribavirin/interferon was used in the treatment of newly diagnosed HCV patients between 2005 and 2012, whereas ribavirin/interferon and protease inhibitors were used between 2013-2014. DAAs were used in 2015 and 2016. When we analyzed the genotypes according to year and treatment, increased genotype diversity was observed in 2016, but it was not possible to follow the effects of new antiviral agents since these were only available during the last two years of the study period. In order to determine the effect of DAA treatment on HCV genotype distribution, follow-up will be useful in the coming years.

This study has some limitations. First, this was a single-center study that only evaluated patients who were admitted to a university hospital. Therefore, the findings may not be representative of the entire region. On the contrary, this is a tertiary-care center, to which patients from the entire region are referred. Second, the genotyping method changed during the course of the study, which may have been associated with differences in sensitivity, particularly at the subtype level. However, the long study period was also a strength of this study, as it enabled a longitudinal observation of the changes in HCV genotypes.

Our study showed that although genotype 1b has continued to be dominant, the distribution and prevalence of HCV genotypes are changing in our region mainly due to migration and an increase in the frequency of patients with non-traditional risk factors such as intravenous drug use. Monitoring the epidemiology of HCV genotypes may provide guidance in treatment decisions.

Ethics Committee Approval: This study was conducted according to Declaration of Helsinki.

Informed Consent: Informed consent was not necessary due to retrospective nature of this manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.A.S., A.Ç.D.; Design - A.A.S., H.A., A.Ç.D.; Supervision - A.A.S., H.A., A.Ç.D.; Resources - A.Ç.D., A.A.S.; Materials - A.Ç.D., A.A.S., Ö.K.Ç., E.Ö.; Data Collection and/or Processing - A.Ç.D., A.A.S., G.Ş., Ö.K.Ç., E.Ö.; Analysis and/or Interpretation - A.Ç.D., A.A.S., H.A., G.Ş.; Literature Search - A.Ç.D., A.A.S., Ö.K.Ç.; Writing Manuscript -A.A.S., A.Ç.D., H.A.; Critical Review - A.A.S., H.A.

Acknowledgements: We would like to thank Prof. Dr. Mithat Bozdayı for sequencing of the genotype 5 samples and to biologists Serap Sarıalioğlu Aslan, Filiz Alkan and Yılmaz Yıldırım for their valuable contributions to the laboratory studies.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. *Ishii S, Koziel MJ. Immune responses during acute and chronic infection with hepatitis C virus. Clin Immunol 2008; 128: 133-47.* ***[CrossRef]***
2. *Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol 2014; 61: 45-57.* ***[CrossRef]***
3. *Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a field-work TURHEP study. Clin Microbiol Infect 2015; 21: 1020-6.* ***[CrossRef]***
4. *Simmonds P. Genetic diversity and evolution of hepatitis C virüs-15 years on. Gen Virol 2004; 85: 3173-88.* ***[CrossRef]***
5. *McOmish F, Yap PL, Dow BC, et al. Geographical distribution of hepatitis C virus genotypes in blood donors: an international collaborative survey. J Clin Microbiol 1994; 32: 884-92.* ***[CrossRef]***
6. *Ciccozzi M, Ciccaglione AR, Lo Presti A, et al. Reconstruction of the evolutionary Dynamics of the hepatitis C virus 1b epidemic in Turkey. Infect Genet Evol 2011; 11: 863-8.* ***[CrossRef]***
7. *Abacıoglu YH, Davidson F, Tuncer S, et al. The distribution of hepatitis C virus genotypes in Turkish patients. J Viral Hepat 1995; 2: 297-301.* ***[CrossRef]***
8. *Bozdayi AM, Aslan N, Bozdayi G, et al. Molecular epidemiology of hepatitis B, C and D viruses in Turkish patients. Arch Virol 2004; 149: 2115-29.* ***[CrossRef]***
9. *Altuglu I, Soyler I, Ozacar T, Erensoy S. Distribution of hepatitis C virus genotypes in patients with chronic hepatitis C infection in Western Turkey. Int J Infect Dis 2008; 12: 239-44.* ***[CrossRef]***
10. *Gökahmetoğlu S, Atalay MA, Kılınç A. Determination of the hepatitis C virus genotypes with 'pyrosequencing' method. Erciyes Med J 2011; 33: 99-102.*
11. *Buruk CK, Bayramoglu G, Reis A, Kaklıkkaya N, Tosun I, Aydın F. Determination of hepatitis C virus genotypes among hepatitis C patients in eastern black sea region, Turkey. Mikrobiyol Bul 2013; 47: 650-7.* ***[CrossRef]***
12. *Altuğlu I, Sertöz R, Aksoy A, Gürsel D, Tüzüner U, Günşar F. Possible transmission risks and genotype distribution of hepatitis C virus infection in Western Turkey. Turk J Gastroenterol 2013; 24: 349-55.* ***[CrossRef]***
13. *Sağlik İ, Mutlu D, Öngut G, et al. Distribution of Hepatitis C Virus Genotypes among Patients with Chronic Hepatitis C Infection in Akdeniz University Hospital, Antalya, Turkey: A Five-Year Evaluation. Mikrobiyol Bul 2014; 48: 429-37.* ***[CrossRef]***
14. *Kuşçu F, Kömür S, Seza Inal A, et al. Changing Epidemiology of Chronic Hepatitis C in Adana. Viral Hepat J 2014; 20: 15-8.* ***[CrossRef]***

15. Çalışkan A, Kirisci O, Ozkaya E, et al. Distribution and Predominance of Genotype 3 in Hepatitis C Virus Carriers in the Province of Kahramanmaras, Turkey. Hepat Mon 2015; 15: e25142. ***[CrossRef]***
16. Üçbilek E, Abayli B, Koyuncu MB, et al. Distrubition of hepatitis C virus genotypes among intravenous drug users in Çukurova Region of Turkey. Turk J Med Sci 2016; 46: 66-71. ***[CrossRef]***
17. Cetin Duran A, Kibar F, Cetiner S, Yaman A. Determination of Hepatitis C virus genotype and HCV infection transmission routes in Cukurova University Medical Faculty Hospital. Turk Hij Den Biyol Derg 2017; 74: 201-10. ***[CrossRef]***
18. Aguilera A, Navarro D, Rodríguez-Frias F, et al. Prevalence and distribution of hepatitis C virus in Spain during the 2000-2015 period (The GEHEP 005 Study). J Viral Hepat 2017; 24: 725-32. ***[CrossRef]***
19. Kartashev V, Döring M, Nieto L, Coletta E, Kaiser R, Sierra S. HCV EuResist Study group. New findings in HCV genotype distribution in selected West European, Russian and Israeli regions. J Clin Virol 2016; 81: 82-9. ***[CrossRef]***
20. Yıldırım MS, Yayla B and Cirit OS. HCV genotyping data of the Gaziantep Dr. Ersin Arslan State Hospital: Is this the first detection of genotype 5 in Turkey? Presented at 2nd National Clinical Microbiology Congress (poster number: PS432), November 2013, Antalya, Turkey (in Turkish)
21. Petruzziello A, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol 2016; 22: 7824-40. ***[CrossRef]***
22.Antaki N, Haddad M, Kebbewar K, et al. The unexpected discovery of a focus of hepatitis C virus genotype 5 in a Syrian province. Epidemiol Infect 2009; 137: 79-84. ***[CrossRef]***
23. Legrand-Abravanel F, Sandres-Sauné K, Barange K, et al. Hepatitis C virus genotype 5: epidemiological characteristics and sensitivity to combination therapy with interferon-alpha plus ribavirin. J Infect Dis 2004; 189: 1397-400. ***[CrossRef]***
24. Delwaide J, Gerard C, Reenaers C, et al. Hepatitis C virus genotype 5 in southern Belgium: epidemiological characteristics and response to therapy. Dig Dis Sci 2005; 50: 2348-51. ***[CrossRef]***
25. Epidemiology of hepatitis C in Turkey. Excerpt based on presentations of S Erensoy and H Abacıoğlu at "Burden and Prevention of Viral Hepatitis in Turkey" meeting. Viral Hepatitis 2010; 18: 8-9.
26. Yıldırım B, Tahan V, Ozaras R, et al. Hepatitis C Virus Risk Factors in the Turkish Community. Dig Dis Sci 2005; 50: 2352-5. ***[CrossRef]***
27. Kuzin SN, Samokhvalov EI, Zabotina EE, et al. Hepatitis virus genotype structure in patients with chronic hepatitis C. Zh Mikrobiol Epidemiol Immunobiol 2011; 3: 33-8.
28. Rantala M, van de Laar MJW. Surveillance and epidemiology of hepatitis B and C in Europe- a review. Euro Surveill. 2008; 13. pii: 18880. ***[CrossRef]***
29. Esteban JI, Sauleda S, Quer J. The Changing Epidemiology of Hepatitis C Virus Infection in Europe. J Hepatol 2008; 48: 148-62. ***[CrossRef]***
30. Bourlière M, Pietri O. HCV therapy: no one to let behind. Int J Antimicrob Agents 2018; pii: S0924-8579(18)30380-7.