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Distribution of HCV Genotypes in Patients with Chronic Hepatitis C Infection: A Three-Year Single-Center Retrospective Study

Kronik Hepatit C Enfeksiyonu Olan Hastaların HCV Genotiplerinin Dağılımı: Üç Yıllık Tek Merkezli Retrospektif Çalışma

Melahat Gürbüz, Cengiz Demir, Selahattin Ünlü, Betül Fatmanur Yıldırım, Yeliz Çetinkol

Afyonkarahisar Health Siences University, Faculty of Medicine, Department of Medical Microbiology, Afyonkarahisar, Türkiye

ORCID ID: Melahat Gürbüz: https://orcid.org/0000-0001-6290-1216, Cengiz Demir: https://orcid.org/0000-0002-5569-886X, Selahattin Ünlü: https://orcid.org/0009-0002-9185-0109, Betül Fatmanur Yıldırım: https://orcid.org/0000-0003-2459-5451, Yeliz Çetinkol: https://orcid.org/0000-0003-4940-4498

***Sorumlu Yazar / Corresponding Author:** Melahat Gürbüz , **e-posta / e-mail:** drmelahatgrbz@hotmail.com

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Abstract

Aim Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus belonging to the genus Hepacivirus in the Flaviviridae family. It has eight known genotypes and 93 subtypes. HCV can be transmitted through various routes, including blood transfusion, surgical procedures, sexual contact, and intravenous drug use, leading to both acute and chronic hepatitis. Genotype (GT) determination and viral load assessment are essential for selecting an appropriate antiviral treatment regimen and duration, and for monitoring treatment efficacy. We aimed to ascertain the genotype distribution over a three-year period.

Material and Method In this study, patients diagnosed with chronic HCV infection and followed at Afyon Health Sciences University Health Practice and Research Hospital between July 1, 2020, and June 30, 2023, were retrospectively evaluated for their age, gender, and HCV genotype data.

Results A total of 91 patients' HCV genotype data were included in the study. The study revealed that 95.6% of the patients were Turkish citizens, while 4.4% were of foreign nationality. Among the 91 patients, 60 (65.9%) were found to have genotype 1b, 12 (13.2%) had genotype 1a, 10 (11%) had genotype 3, 6 (6.6%) had genotype 4, 2 (2.2%) had genotype 2, and one patient (1.1%) had a co-infection of genotypes 3 and 4.

Conclusion Genotype 1b was dominant in our region. Identifying HCV genotypes is important in guiding the prognosis and treatment of chronic HCV infections and monitoring the epidemiologic changes. This information will be of great value in the health policy that targets HCV and in elimination efforts.

Keywords Genotype, hepatitis C virus, viral load

Özet

Amaç *Hepatit C virüsü (HCV), Flaviviridae ailesindeki Hepacivirus cinsine ait tek sarmallı, pozitif anlamlı bir RNA virüsüdür. Bilinen sekiz genotipi ve 93 alt tipi vardır. HCV kan transfüzyonu, cerrahi prosedürler, cinsel temas ve damar içi uyuşturucu kullanımı gibi çeşitli yollarla bulaşabilir ve hem akut hem de kronik hepatite yol açabilir. Genotip (GT) belirleme ve viral yük değerlendirmesi, uygun bir antiviral tedavi rejimi ve süresinin seçilmesi ve tedavi etkinliğinin izlenmesi için esastır. Üç yıllık bir dönem boyunca genotip dağılımını tespit etmeyi amaçladık.*

Gereç ve Yöntem *Bu çalışmada, Afyon Sağlık Bilimleri Üniversitesi Sağlık Uygulama ve Araştırma Hastanesi'nde 1 Temmuz 2020 ile 30 Haziran 2023 tarihleri arasında kronik HCV enfeksiyonu tanısı alan ve takip edilen hastalar yaş, cinsiyet ve HCV genotip verileri açısından retrospektif olarak değerlendirilmiştir.*

Bulgular *Toplam 91 hastanın HCV genotip verileri çalışmaya dahil edilmiştir. Çalışma, hastaların %95,6'sının Türk vatandaşı olduğunu, %4,4'ünün ise yabancı uyruklu olduğunu ortaya koymuştur. 91 hastanın 60'ında (%65,9) genotip 1b, 12'sinde (%13,2) genotip 1a, 10'unda (%11) genotip 3, 6'sında (%6,6) genotip 4, 2'sinde (%2,2) genotip 2 ve bir hastada (%1,1) genotip 3 ve 4 ko-enfeksiyonu olduğu tespit edilmiştir.*

Sonuç *Bölgemizde genotip 1b baskın genotip olarak saptandı. HCV genotiplerinin belirlenmesi, kronik HCV enfeksiyonlarının prognoz ve tedavisinin yönlendirilmesinde ve epidemiyolojik değişikliklerin izlenmesinde önemlidir. Bu bilgiler HCV'yi hedef alan sağlık politikalarında ve eliminasyon çalışmalarında büyük değer taşıyacaktır.*

Anahtar Kelimeler *Genotip, hepatit C virüs, viral yük*

INTRODUCTION

The Hepatitis C virus (HCV) is a single-stranded RNA virus with a positive polarity. It is classified under the Hepacivirus genus within the Flaviviridae family. Hepatitis C virus (HCV) represents a significant global public health challenge, with a high mortality rate associated with a range of complications including liver failure and chronic hepatitis C infection, as well as acute hepatitis C infection and the development of liver cancer.[1]

The HCV genome is approximately 9.4 kbp in length and is initially translated into a large polyprotein. Subsequently, the polyprotein is processed by a viral protease, resulting in the generation of ten distinct proteins. These include three structural proteins (core, E1, and E2) and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B). In particular, the NS3/4A protease and NS5B RNA polymerase have been determined to play a critical role in the pathogenesis of HCV.[2] Over the past decade, HCV strains have diversified, aided by advances in sequencing technologies, leading to variations in their geographical distribution. The number of recognized genotypes (GT) has risen from 6 to 8, with the number of subtypes increasing from 67 to 93.[3-7]

Global prevalence studies have shown that anti-HCV antibody prevalence ranges from 1% to 3.5% in the general population, whereas studies on individuals who inject drugs show a significantly higher average prevalence, ranging from 40% to 52%.[8] However, studies focusing solely on the presence of HCV antibodies require confirmation, as these data may include individuals who have spontaneously recovered or have been treated. Despite the widespread use of anti-HCV antibodies as a marker for HCV infection and their use in estimating prevalence and comparing global HCV infection levels, the classification of genetic variants remains the most critical indicator of HCV spread. Numerous studies have indicated that HCV genotype is a key determinant of both treatment outcome and disease pathogenesis.[9] It is important to understand the distribution, diversity, and patterns of HCV genotypes in order to eff e ctively control HCV infection. Genotype distribution can provide valuable insights into transmission routes and sources of infection. Moreover, HCV genotype is a determining factor in the effi cacy of direct-acting antiviral (DAA) therapy, and thus plays an essential role in the selection and duration of interferon-free DAA regimens.

Th e objective of this study was to ascertain the genotype distribution of chronic hepatitis C patients admitted to our hospital over a three-year period. Additionally, we sought to determine whether there were any changes in the distribution over the years and to investigate the relationship between genotypes and age and gender.

MATERIALS and METHODS

In this study, the age, gender, and HCV genotype data of patients diagnosed with chronic HCV infection and fol-lowed at Afyonkarahisar Health Sciences University Health Practice and Research Hospital between July 1, 2020, and June 30, 2023, were retrospectively evaluated using patient records and the hospital information system. The HCV genotype and HCV-RNA data of the patients included in the study were recorded at the time of their initial admission to our hospital. For genotype determination, samples collected until 2022 underwent extraction using the Cobas 4800 au-tomated system (Roche, USA), and testing was performed using the Roche Cobas HCV GT kit on the Cobas z 480 Real-Time PCR device. For samples collected after 2022, the Magnesia®2448 Extraction and PCR System (Anatolia Geneworks, Türkiye) was utilized. Quantitative detection of HCV-RNA was conducted using the Bosphore Ultra HCV Quantification Detection Kit, and HCV genotypes were identified using the Bosphore HCV Genotyping Kit v3 (Anatolia Geneworks, Türkiye). The PCR procedures were performed on the Montania 4896 Real-Time PCR device (Anatolia Geneworks, Türkiye). The results were interpreted according to the recommendations of the kit manufacturer. The Bosphore Ultra HCV Quantification

Detection Kit is sensitive to HCV-RNA levels as low as 8 IU/mL and can quantitatively detect HCV-RNA within a range of $1x10^1$ to $1x10^9$ IU/mL. Both systems used for HCV genotyping were capable of separately identifying genotypes 1a, 1b, 2, 3, 4, 5, and 6.

Th e study was conducted in accordance with the ethical standards set forth by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (Decision No. 443-2023/10).

Statistical Analysis

The obtained data were statistically analyzed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). The mean age and gender distributions were assessed. The chi-square test and Fisher's Exact test were employed to compare categorical variables between groups. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 91 patients with identified HCV genotypes were included in the study. Of these, 38.5% were female, and 61.5% were male, with a mean age of 51 ± 19.2 years (range 7-83 years) across all patients. The age distribution by genotypes and demographic data of the patients are presented in Table 1 and Table 2.

Table 1. Age Distribution of HCV Genotypes

	Genotypes				
	1a	1b	2	3	4
Median Age (min-max)	36 (28-72)	58 (7-83)	28 (25-28)	69 (21-51)	66 (23-67)

Of the patients, 95.6% were Turkish citizens, while 4.4% were of foreign nationality (Table 2). When examining the distribution of HCV genotypes among foreign nationals identified in this study, three of the four foreign patients were found to have GT 1b, and one had GT 4. The GT 4-positive patient was a 23-year-old Somali woman, while the other foreign patients were from Afghanistan, Uzbekistan, and Azerbaijan.

In our study, when analyzing genotype positivity by age groups, the highest rate (31.8%) was found in the group aged over 65 years (Table 2). Only one patient under 18 years of age was identified, who was a 7-year-old Afghan patient.

Table 2. Demographic Data and HCV Genotype Distribution of HCV-Positive Patients

Demographic Variables		n	%
Nationality	Turkish	87	95.6
	Foreign	4	4.4
Gender	Female	35	38.5
	Male	56	61.5
Year	2020	29	31.9
	2021	24	26.4
	2022	38	41.7
Age Group	< 18	1	1.1
	18-35	25	27.5
	36-45	11	12.1
	46-65	25	27.5
		29	31.8

Among the 91 patients followed for chronic HCV infection over the three-year period, GT 1b was identified in 60 patients (65.9%), GT 1a in 12 patients (13.2%), GT 3 in 10 patients (11%), GT 4 in 6 patients (6.6%), GT 2 in 2 patients (2.2%), and a combination of GT 3 and GT 4 in 1 patient (1.1%) (Table 3).

When examining the distribution of genotypes by gender, the difference between female and male patients with positive genotype was found to be statistically significant (p=0.0018). GT 2 and GT 3 were not detected in female patients, while the only mixed genotype (GT 3+ GT 4) in our study was identified in a female patient (Table 3).

A comparison of the data by year revealed that GT 1a was significantly higher in 2022 than in other years (p=0.0008). In contrast, no significant difference was observed for GT 1b across the years (p=0.0623) (Table 4).

Table 4. Yearly Distribution of HCV Genotypes Identified in This Study

	2020		2021		2022		Total	
	n	%	n	%	n	%	n	%
Genotype 1a	1	3.4	2	8.3	9	23.7	12	13.2
Genotype 1b	27	93.2	17	70.9	16	42.1	60	65.9
Genotype 2	-	-	-	-	2	5.3	2	2.2
Genotype 3	-	-	3	12.5	7	18.4	10	11
Genotype 4	-	-	2	8.3	4	10.5	6	6.6
Genotype 3+4	1	3.4	-	-	-	-	1	1.1
Total	**29**	**100**	**24**	**100**	**38**	**100**	**91**	**100**

Table 5. Data from HCV Genotype Studies at Different Centers in Türkiye

Study	Year	Region	Number	Genotypes (%)								
				1	1a	1b	2	3	4	5	6	Mix Type
Gökahmetoğlu et al.[10]	2011	Kayseri	146	9	5.5	85.5	2.7	-	35.6	-	-	-
Çetin et al.[11]	2016	Adana	119	-	12.6	58.8	7.6	16.8	3.4	0.8	-	-
Akgün et al.[12]	2017	Adıyaman	71	4.2	8.5	71.8	11.3	4.2	-	-	-	-
Tiryaki et al.[13]	2018	Aydın	182	2.2	18.1	69.2	1.7	7.2	1.7	-	-	-
Öz et al.[14]	2019	Sakarya	235	2.1	5.5	77.4	0.8	8.5	2.9	-	-	2.5
Sari et al.[15]	2020	İstanbul	413	12.3	12.6	53.8	5.3	11.9	2.3	0.5	-	-
Ağca et al.[16]	2021	Bursa	740	5.8	6.1	72.8	2	9.2	2.5	0.1	-	1.5
Özkaya et al.[17]	2021	Trabzon	670	3.4	3.7	82.8	1.8	6.7	0.9	-	-	0.6
Alaçam et al.[18]	2022	İstanbul	546	2.6	13.2	56.2	6.7	14	8.8	1.3	0.2	8.6
Bulut et al.[19]	2023	Van	95	-	13.7	65.3	2.1	16.8	2.1	-	-	-

DISCUSSION

Hepatitis C virus (HCV) is an infectious agent that infects approximately 3-4 million individuals annually, resulting in over 350.000 deaths. As reported by the World Health Organization (WHO), more than 71 million individuals residing in the Eastern Mediterranean and European regions, including Türkiye, are afflicted with a chronic hepatitis C infection.[20] In an effort to address the public health threat posed by HCV, the WHO has launched several global initiatives and proposed a strategy for HCV elimination in 2016. This strategy outlines principal objectives, including a reduction in the incidence of new hepatitis infections, an enhancement of access to testing and treatment, and an improvement in surveillance and monitoring systems. The objective is to achieve a reduction of 90% in chronic hepatitis C incidence and a 65% reduction in hepatitis C-related mortality by the year 2030. Despite notable progress in HCV treatment, access to care remains a challenge for many individuals, primarily due to high costs and limited healthcare resources.[21]

To date, eight HCV genotypes and 93 subtypes have been

identified, each showing around 30% genetic variability across the viral genome.[3] The considerable genetic diversity presents a significant challenge for both vaccine development and the development of effective antiviral treatments. The success and duration of therapy can be significantly influenced by the specific viral strains involved. Understanding of the HCV genotype is of significant clinical importance, as the efficacy of treatment, as measured by the sustained virologic response (SVR) rate, is heavily influenced by the distribution of genotypes and subtypes. The SVR rate is defined as the proportion of patients with persistent viremia 24 weeks after the completion of antiviral therapy.[22] Historically, the standard treatment for HCV infections was based on PEG-IFNα/RBV, which was observed to positively impact SVR rates compared to other antiviral therapies.[23] However, IFNα/RBV treatment was associated with suboptimal efficacy, extended treatment durations, and various adverse outcomes, particularly when compared to the newer and more costly direct-acting antivirals (DAAs).[24] DAAs, which inhibit viral proteins crucial for viral replication, have been reported to enhance SVR rates.[25] As a result, a deeper understanding of HCV epidemiology, particularly the global distribution of various genotypes, could assist in mitigating the impact of this serious disease.[26]

The geographical distribution of HCV genotypes exhibits considerable heterogeneity. In developed nations, "epidemic subtypes" (1a, 1b, 2a, and 3a) are common, whereas "endemic" strains are generally found in regions such as West Africa, South Asia, Central Africa, and Southeast Asia.[20] Globally, GT 1 is the most frequently identified genotype at 49.1%, followed by GT 3 (17.9%), GT 4 (16.8%), GT 2 (2%), and GT 6 (1.4%).[27] Genotypes 5, 7, and 8 together account for less than 1% of global HCV infections.[28] Genotype GT 4 is most prevalent in the Middle East, Central, and Eastern Africa, whereas GT 1 is predominantly found in North and South America, Europe, and Australia. The most common genotype in the Indian subcontinent is GT 3, while GT 2 is widespread in West Africa. GT 5 is prevalent in South Africa, and GT 6 is prevalent in Southeast Asia. The recently identified genotypes 7 and 8 are more prevalent in Central Africa and the Indian subcontinent, respectively.[29]

The phenomenon of rising human migration has contributed to the gradual shifting of the distribution of HCV genotypes, although this pattern of change has yet to be fully elucidated. The presence of distinct HCV GT1 strains has been documented in Germany and Cyprus.[30,31] In Canada, multiple distinct HCV GT 2 strains have been identified, particularly among patients of African descent.[32] Concerning HCV GT 4, Ethiopian data indicate the presence of four distinct sub-genotypes (4d, 4r, 4l, and 4v).[33] Although Simmonds et al. reported that the HCV 5a sub-genotype is the most prevalent in South Africa, they also suggested that other sub-genotypes and recombinant viruses might exist, and that recombination events play a crucial role in the evolution of RNA viruses.[34] Furthermore, studies have shown that the epidemiology of HCV GT 4 is evolving. This strain has begun to emerge in numerous Western European countries, largely as a consequence of demographic shifts, migration, and alterations in the patterns of injection drug use.[35]

Understanding the various HCV genotypes and subtypes is of paramount importance, as they can have a significant impact on the efficacy of treatment and the clinical outcomes in patients with HCV infections. For instance, interferon-based therapy has exhibited superior efficacy for genotypes 2 and 3, whereas first-generation HCV protease inhibitors demonstrated greater effectiveness for genotype 1. Fortunately, second-generation DAAs provide broader coverage across genotypes. Nevertheless, despite the considerable impact of pangenotypic treatment regimens, they are costly and frequently challenging to obtain in low- and middle-income countries.[29]

In Türkiye, recent data indicate that GT 1b remains the dominant genotype, with prevalence rates ranging from

53.8% to 85.8% (Table 5). While some studies suggest a proportional decline in GT 1b over time, others have reported no significant changes.[18,36,37] In our study, GT 1b was the most frequently detected genotype at 65.9%, and although there was a proportional decrease over the years, no statistically significant difference was observed.

Research has shown that the frequency of GT 1a in Türkiye ranges between 3.7% and 18.1% (Table 5). In our study, the GT 1a rate was 13.2%, which is consistent with the aforementioned findings. Furthermore, it was found to be significantly higher in 2022 in comparison to other years (p=0.0008). (Table 4). The results of epidemiological studies conducted in Europe indicate a decrease in genotypes 1b and 2 and an increase in genotypes 1a, 3, and 4, with a notable prevalence among younger patients and intravenous drug users. The observed increase in GT 1a in our study is consistent with these findings. However, in light of the data from our study, it is not possible to conclude that this group of patients, who are in a wide age range, are especially young or that the transmission is caused by drug use.[38]

Globally, GT 3, which typically ranks second in HCV genotype distribution, is more common in low- and middle-income countries and accounts for 25% of all HCV infections. GT 3 is also notably prevalent among intravenous drug users worldwide.[39] Studies conducted in Türkiye have reported GT 3 prevalence rates ranging from 4.2% to 16.8% (Table 5). Additionally, numerous studies have noted an increase in the number and proportion of GT 3 cases over time. This rise has been attributed to factors such as the influx of foreign patients and a notable increase in intravenous drug use.[36,37] In our study, GT 3 was detected at a rate of 11%, with a proportional increase observed over the years, aligning with the literature (Table 3).

HCV GT 4 is most prevalent in the Middle East, Central, and Eastern Africa.[29] Studies conducted in Türkiye indicate that the prevalence of GT 4 ranges from 0.9% to 35.6% (Table 5). These studies suggest that GT 4 has increased over the years, particularly in regions with a high concentration of people from the Middle East, often due to post-war migration.[40] In our study, the GT 4 rate was 6.6%, consistent with Turkish data. Among the six GT 4 cases, only one patient (a Somali national) was foreign (Table 3). Additionally, while no GT 4 cases were detected in 2020, a proportional increase was observed in 2021 and 2022, though this was not statistically significant (Table 4).

Kuru et al. emphasized the importance of detecting mixed genotype infections, as they can lead to treatment failures.[41] Recent studies from various regions of Türkiye have reported mixed genotype rates ranging from 0.6% to 8.6% (Table 5). In our study, mixed genotypes were identified at a rate of 1.1%, with a combination of genotypes 3 and 4 detected.

In a study conducted in our country, when genotypes were analyzed in terms of gender distribution, no significant difference was observed among patients with GT 1 and GT 4, whereas a statistically significant male predominance was noted in the GT 2 and GT 3 groups.[42] In the study conducted by Tezcan et al., it was determined that GT 1b is more common in women, while other subtypes apart from GT 1b are more frequently observed in men.[43] In a study conducted in Istanbul, GT 1a and GT 3 were found to be more prevalent in men, while GT 1b was more common in women.[44] In the study conducted by Selek et al., no statistically significant difference was found between gender and age groups in terms of HCV genotype distribution.[45] In another study, GT 1 was found to be more prevalent in elderly patients, while GT 3 was more common in younger patients.[46] In our study, the highest rate (31.8%) was observed in the age group over 65 years (Table 2), with GT 1b being the most frequently detected in this group. Additionally, when the distribution of genotypes by gender was analyzed, GT 1b was found to be more common in women, while other subtypes, particularly GT 1a, were more frequently observed in men. Our findings were found to be

consistent with the literature. The difference between male and female patients who tested positive for the genotype was statistically significant (p=0.0018).

Özkaya et al.'s study found that the origins of foreign patients were similar to those in our study, with an overall genotype positivity rate of 4.5%, and GT 1b being the most frequently detected genotype.[17] Consistent with these findings, our study found that three of the four foreign patients, who made up 4.4% of the total patient population, had GT 1b, and one had GT 4. The GT 4 case was a Somali female patient, while the other foreign patients were from Afghanistan, Uzbekistan, and Azerbaijan.

Guntipalli et al. reported that the most common genotypes in the Turkic republics, Russia, and surrounding countries were 1, 3, and 2, respectively. In Russia, GT 1b was prevalent at rates of 55% to 80%, but the frequency of GT 3 has increased among younger individuals due to the rise in intravenous drug use.[27]

CONCLUSION

The findings of our study indicate that GT 1b, the most prevalent genotype in Türkiye, was the predominant genotype among patients who sought care at our hospital over the three-year period. It is, however, a matter of concern that the prevalence of less common genotypes and mixed-type HCV infections is on the rise in Türkiye. In the absence of treatment for foreign patients and without the assurance of effective migrant control, there is a risk of significant shifts in the epidemiology of HCV genotypes in the coming years.

The detection of HCV genotypes is of paramount importance for the guidance of prognosis and treatment of chronic HCV infections, as well as for the surveillance of shifts in HCV epidemiology. The use of direct-acting antivirals (DAAs), particularly in regions where new variants are being identified, reinforces the confidence in achieving the strategic objective of global HCV elimination by 2030. However, continued public health eff forts are essential to ascertain further instances of novel subtypes and to observe the advent or circulation of variants that may exhibit resistance to DAA therapy.

Ethical Approval

The study was conducted in accordance with the ethical standards set forth by the Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (Decision No. 443-2023/10).

Peer-review

Externally and internally peer-reviewed.

Author Contributions

Concept: M.G., S.Ü., Y.Ç. Design: M.G., C.D., S.Ü., B.F.Y., Y.Ç., Data collection or Processing: M.G., C.D., B.F.Y., Analysis or interpretation: M.G., C.D., S.Ü., B.F.Y., Y.Ç., Literature Search: M.G., C.D., S.Ü., B.F.Y., Y.Ç., Writing: M.G., C.D., S.Ü., B.F.Y., Y.Ç.

Confli ct of Interest

The authors declare that they have no conflict of interest.

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