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Hepatitis C Genotype Distribution in Türkiye; Are Genotypes Distributions Changing? A Meta-Analysis

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Abstract

Backround: Hepatitis C virus is one of the leading causes of viral hepatitis in humans. It is clinically characterized by chronic hepatitis developing after acute infection. There are seven genotypes of HCV. Each genotype, numbered one to seven, has several subtypes. Genotype differences play a role in the course of HCV infection, basic pathological features, and response to treatment. In this study, we aimed to determine the genotype distribution of HCV in Türkiye and whether there is a change in the HCV genotype distribution over the years.

Methods: PubMed, Scopus and TR Dizin databases are used to select the appropriate publications to use data in the study. 103 studies were included in this study. Of these, 32036 data were evaluated. This study protocol was developed keeping in view the requirements of the PRISMA guidelines.

Result: A total of 32036 genotype data were found from the studies included in the evaluation. Genotype 1 (82.6%) was the most common genotype. The genotype distribution rates for genotype 2, genotype 3, genotype 4 and other groups are 3.9%, 8.7%, 3.9% and 0.9%, respectively. There was a significant difference between the genders Genotype 1 incidence is significantly higher in females compared to males, while genotypes 2 and 3 have a higher incidence in males. There was a significant difference between the regions for all genotypes. When the distribution was analyzed according to the years, there was a significant difference according to the years. After 2011, a significant decrease in genotype 1 and a significant increase in genotype 3 were detected.

Conclusion: The most common HCV genotype in Türkiye is genotype 1. The most common genotype has not changed over the years, but we observed that the distribution of genotypes has changed at various rates. This may increase in the future for various reasons.

Keywords: Hepatitis C, HCV, genotype, Türkiye

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Türkiye'de Hepatit C Genotip Dağılımı; Genotip Dağılımları Değişiyor mu? Bir Meta-Analiz

Öz

Giriş: Hepatit C virüsü insanda viral hepatitin önde gelen nedenlerinden biridir. Klinik tablo akut enfeksiyondan sonra gelişen kronik hepatit ile karakterizedir. HCV' nin yedi genotipi vardır. Birden yediye kadar numaralandırılan her bir genotipin de birkaç alt tipi bulunur. Genotip farklılıkları HCV enfeksiyonunun seyri, temel patolojik özellikleri ve tedaviye yanıtta rol oynar. Bu çalışmada, Türkiye'de HCV' nin genotip dağılımını ve HCV genotip dağılımında yıllara göre değişim olup olmadığını belirlemeyi amaçladık.

Yöntemler: Çalışmada veri kullanmak için uygun yayınların seçilmesinde PubMed, Scopus ve TR Dizin veri tabanları kullanıldı. 103 çalışma bu çalışmaya dahil edilmiştir ve bunlar arasından 32036 veri değerlendirilmiştir. Bu çalışma protokolü PRISMA kılavuzlarının gereklilikleri göz önünde bulundurularak uygulandı.

Sonuç: Değerlendirmeye alınan çalışmalarda toplam 32036 genotip verisi bulunmuştur. Genotip 1 (%82.6) en sık görülen genotip olmuştur. Genotip 2, genotip 3, genotip 4 ve diğer grup için genotip dağılımı oranları sırasıyla %3.9, %8.7, %3.9 ve %0.9'dur. Cinsiyetler arasında anlamlı fark bulunmuştur. Genotip 1 görülme sıklığı kadınlarda erkeklere göre anlamlı olarak daha yüksek iken, genotip 2 ve 3 erkeklerde daha fazla görülme sıklığına sahiptir. Tüm genotipler için bölgeler arasında anlamlı fark bulunmuştur. Yıllara göre dağılım incelendiğinde yıllara göre anlamlı fark bulunmuştur. 2011 yılından sonra genotip 1'de anlamlı azalma, genotip 3'te ise anlamlı artış tespit edilmiştir.

Sonuç: Türkiye'de görülen en yaygın HCV genotipi genotip 1'dir. En yaygın görülen genotip yıllara göre değişmemiştir, ancak genotiplerin dağılımının çeşitli oranlarda değiştiğini gözlemledik. Bu durum gelecekte çeşitli nedenlerle artabilir.

Anahtar kelimeler: Hepatit C, HCV, genotip, Türkiye.

INTRODUCTION

Hepatitis C is an infectious disease caused by an RNA virus in the *Flaviviridae* family called hepatitis C virus (HCV). HCV infection can cause acute hepatitis C and after acute infection, the majority of patients develop chronic hepatitis C. Chronic hepatitis C infection; it triggers the formation of a serious and chronic inflammatory disease that can progress to liver fibrosis, cirrhosis, hepatocellular carcinoma and death. Hepatitis C infection is one of the important indications for liver transplantation in many region of the world[1].

Hepatitis C virus is in the *Viruses* superkingdom, *Riboviria* clade, *Orthornavirae* kingdom, *Kitrinoviricota* phylum, *Flasuviricetes* class, *Amarillovirales* order, *Flaviviridae* family, *Hepacivirus* genus[2].

The hepatitis C virus has different genotypes, numbered 1 to 7, each with several subtypes[3]. Genotype differences play a role in the basic pathological features of HCV infection. Insulin resistance, progression to steatosis, cirrhosis and fibrosis and hepatocellular carcinoma develop by genotype-specific mechanisms. The pathways involved in cell proliferation, apoptosis, lipid metabolism, insulin and interferon signaling vary at different levels between genotypes, and this leads to the emergence of different pathological formations. For instance, genotype 1 is associated with a more aggressive disease with increased insulin resistance, minimal response to therapy, higher risk of cirrhosis and development of hepatocellular carcinoma, while genotype 3 is associated with increased steatosis and fibrosis[4]. Besides their pathological effects, genotype differences affect in terms of the pharmacological treatment of infection, drug use dose and duration[4].

The hepatitis C virus is as primary transmissions with blood, and most infections occur in unsafe injection practices and healthcare services, unscreened blood transfusions, injection drug use, and sexually transmitted[5].

Acute HCV infections are usually asymptomatic and most do not cause life-threatening illness. In about 30% (15-45%) of infected people, the virus disappears spontaneously without any treatment within 6 months of infection. The remaining 70% (55-85%) develop chronic HCV infection. The risk of developing cirrhosis in patients with chronic HCV infection varies between 15-30% within 20 years[5].

According to the data shared by the World Health Organization (WHO) in June 2022, it has been reported that approximately 58 million people have chronic hepatitis C infection. It has been reported that this number is mostly seen in the Eastern Mediterranean Region and the European Region, 12 million in both regions, an estimated 10 million people in both regions in the Southeast Asian Region and the Western Pacific Region, 9 million in the African Region and 5 million in the Americas Region[5]. In addition, it has been reported that approximately 1.5 million new infections occur each year and there are approximately 3.2 million adolescents and children with chronic hepatitis C infection[5].

In this study, we aimed to determine the genotype distribution of HCV in Türkiye, which is the cause of hepatitis C infection, which is widely seen in the world and causes serious consequences.

METHOD

Study protocol

This study protocol was developed keeping in view the requirements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[6].

Search strategy

PubMed, Scopus and TR Dizin (created by the Scientific and Technological Research Council of Türkiye, TUBITAK) databases are used to select the appropriate publications to use data in the study. Screening were made using the words "HCV, genotype, Türkiye" "Hepatitis C, genotype, Türkiye", "HCV, genotip, Türkiye", "Hepatit C, genotip, Türkiye", "HCV, genotype, distribution, Türkiye", "Hepatitis C, genotype, distribution, Türkiye", "HCV, genotip, dağılım, Türkiye", "Hepatit C, genotip, dağılım, Türkiye".

Eligibility criteria for inclusion in the study

Studies obtained from specified databases; (i) The publication year of the studies is between 01.01.2000-30.06.2022, (ii) The publication language is Turkish or English, (iii) Studies must have full text access, (iv) Genotypes 1, 2, 3 and 4 must be included among the genotypes investigated in the studies, (v) The data in the studies should not show inconsistency within themselves, (vi) Data from before 2000 should not be available, (vii) Studies should be in original research, original article and short communication format that has a search of must include genotypes 1, 2, 3, 4 in the data distribution. It should not be a type of publication in review, case report, meta-analysis, non-data-based short communication format.

The publications obtained from the databases were evaluated in terms of compliance with the criteria. Publications that did not meet at least one of the eligibility criteria were excluded from the study. Data obtained from studies that met the eligibility criteria for the study were recorded electronically.

Data extraction

Study data were grouped as genotype distribution, sex data if available, year (2011 and before and after 2011), geographical region where the study was conducted, and included in the statistical analysis.

In genotype distribution, the data were separated as G1, G2, G3, G4 and other. G5, G6, those who could not be genotyped and mixed genotype (e.g. Genotype 1+3) were included in the other group. Mixed infections caused by sub-genotypes belonging to a single genotype were included in the genotype (eg. Genotype 1a+1b was included genotype 1).

In studies with have sex distribution, sex distribution data were recorded as genotype distributions for female and male.

In order to examine the genotype changes according to the years, the distribution by years was made according to the data collection date as 2011 and before and after 2011. In the studies covering the data of both periods, distribution was made according to the date range in which the data were collected. (For example, a study in which data was collected between 2009-2012 was included in the 2011 and before group because it was predominantly for the period 2011 and before, and a study for which data was collected between 2010-2015 was included in the after 2011 group because it was predominantly the period after 2011). Among the studies whose dates of study were not specified in the study text, those belonging to 2011 and before the publication year were included in the 2011 and before group, and studies published after 2011 were included as uncertain. Studies that were equally interval in both groups (eg, studies that collected data between 2010 and 2013) were considered as a common group. Studies that were considered to be uncertain and were equally interval between both groups were not included in the statistical evaluation in the distribution by years, and were only used in the genotype distribution data and sex distribution data, if any.

The geographical region distribution of the study was taken as the geographical region (such as Marmara, Aegean, Black Sea) where the city is located in Türkiye. Multicenter studies in different geographical regions (eg, containing data from the cities of Diyarbakır, Ankara, Istanbul) were grouped as multicenters. Multicenter studies in the same region were specified as the geographical region (eg, the study containing the data of Gaziantep, Diyarbakır and Adıyaman was taken as Southeastern Anatolia). Multicenter studies conducted in more than one region were included in the statistical total, but not in the statistical comparison between regions. Statistical comparison between regions was made only according to seven geographical regions in Türkiye.

The raw data recorded in the electronic media were recalculated as a percentage within the data of each study itself. Values resulting from the calculation were added to the results. The data obtained in the study were expressed as frequency and percentage values. The Jamovi Project (2022) Jamovi (Version 2.3) computer program was used in the analysis. Chi-square test was used for statistical analysis. The significance level was considered $p<0.05$.

Ethics Committee Approval

Since the study is a research study examining data from studies published in the literature, it was exempt from ethics committee approval.

RESULTS

A total of 449 studies were identified in the three databases; among these, 127 studies were excluded due to duplication and 24 due to not access of full-text access. The remaining 298 studies were evaluated according to eligibility criteria. 195 studies were excluded because they did not meet the eligibility criteria, and 103 articles were included in the study (Figure 1).

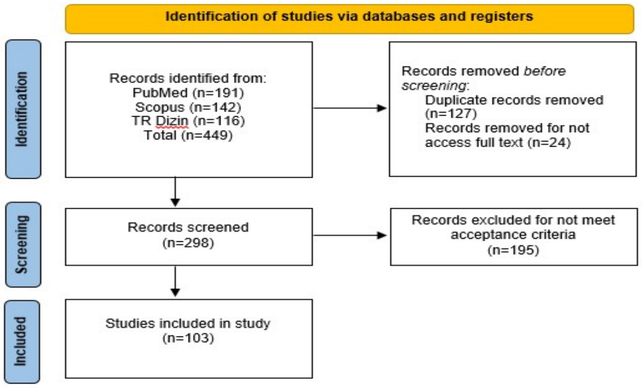

Figure 1. Flow Chart

General information about the study is shown in Table 1. A total of 32036 genotype data were found from the studies included in the evaluation. Genotype 1 (82.6%) was found the most common genotype. Genotype distribution percentages for genotype 2, genotype 3, genotype 4 and other group are 3.9%, 8.7%, 3.9%, and 0.9%, respectively. In studies with genotype distribution by sex, genotype and sex distributions were examined. Genotype 1 was the most common genotype in both female and male, and this rate was 85.9% in female and 68.7% in male, and a statistically significant difference was observed. There is a statistically significant difference between male and female in genotype 2 and genotype 3 distribution, and both genotypes were found to be higher in male (Table 2). There was a significant difference between genotype distribution and geographical regions. Genotype 1 was the most frequently detected genotype in each region. While the region where genotype 1 was most frequent was East Anatolia (96%), genotype 2 was most prevalent in Southeast Anatolia (10%), genotype 3 was most prevalent in Mediterranean (23.2%) and genotype 4 was most prevalent in Central Anatolia (6.5%) (Table 3). When the period 2011 and before and the period after 2011 are compared, genotype 1 was determined at the highest level in both periods. A statistically significant difference was found between the rates of genotype 1 and genotype 3 according to the periods. While genotype 1 was determined as 86.6% in 2011 and before, this value decreased to 80.6% after 2011. On the contrary, while genotype 3 was detected at the rate of 6.1% in 2011 and before, this rate increased to 11.3% after 2011 (Table 4).

Table I: General characteristics and genotype distributions of the studies included in the study

Genel Information					Genotypes				
	Publication date	Region	Data Collection Date	Sex Distribution	G1 N (%)	G2 N (%)	G3 N (%)	G4 N (%)	Other N (%)
Ağca et al.[7]	2015	Marmara	07.10-12.12	-	214 (92.6)	1 (0.4)	9 (3.9)	7 (3)	0 (0)
Aksu et al.[8]	2012	Multicenter	Unspecified	-	88 (86.3)	10 (9.8)	3 (2.9)	1 (1)	0 (0)
Aktaş et al.[9]	2010	Black Sea	05.07-07.09	-	39 (88.6)	0 (0)	0 (0)	0 (0)	5 (11.4)
Aktaş et al.[10]	2014	Eastern A.	01.11-02.14	-	103 (95.4)	0 (0)	4 (3.7)	1 (0.9)	0 (0)
Altındiş et al.[11]	2006	Mediterranean	2000-2001	-	52 (98.1)	1 (1.9)	0 (0)	0 (0)	0 (0)
Altındiş et al.[12]	2015	Multicenter	2009-2014	-	5675 (81)	329 (4.7)	467 (6.7)	514 (7.3)	17 (0.2)
Altuğlu et al.[13]	2013	Aegean	2005-2010	+	499 (93.3)	8 (1.5)	20 (3.7)	8 (1.5)	0 (0)
Altuğlu et al.[14]	2008	Aegean	02.03-02.07	+	335 (97.1)	3 (0.9)	5 (1.4)	2 (0.6)	0 (0)
Altuntaş Aydın et al.[15]	2014	Marmara	01.06-11.13	-	5 (55.6)	1 (11.1)	2 (22.2)	0 (0)	1 (11.1)
Aşgın and Satılmış[16]	2019	Black Sea	01.16-03.19	-	3 (42.8)	0 (0)	2 (28.6)	2 (28.6)	0 (0)
Aşgın and Satılmış[17]	2019	Black Sea	01.16-12.18	+	8 (66.7)	0 (0)	0 (0)	4 (33.3)	0 (0)
Atilla et al.[18]	2015	Black Sea	2003-2013	-	161 (98.8)	0 (0)	1 (0.6)	1 (0.6)	0 (0)
Aydın[19]	2021	Marmara	01.15-06.20	-	353 (88.5)	14 (3.5)	25 (6.3)	7 (1.8)	0 (0)
Aydın et al.[20]	2019	Black Sea	01.16-05.18	-	18 (90)	0 (0)	1 (5)	1 (5)	0 (0)
Aygen et al.[21]	2014	Multicenter	04.11-04.13	-	145 (86.8)	0 (0)	0 (0)	22 (13.2)	0 (0)
Borcak et al.[22]	2015	Central A.	06.11-01.14	-	142 (83.5)	25 (14.7)	2 (1.2)	1 (0.6)	0 (0)
Bozkaya et al.[23]	2000	Multicenter	2000	-	36 (97.3)	1 (2.7)	0 (0)	0 (0)	0 (0)
Bulut et al.[24]	2021	Marmara	01.16-06.19	+	313 (81.3)	13 (3.4)	34 (8.8)	11 (2.9)	14 (3.7)
Buruk et al.[25]	2013	Black Sea	01.09-12.12	-	282 (92.8)	5 (1.6)	15 (4.9)	2 (0.7)	0 (0)
Cirit et al.[26]	2019	Southeastern A.	01.11-12.15	+	217 (69.6)	44 (14.1)	12 (3.8)	32 (10.3)	7 (2.2)
Çabalak and Bal[27]	2020	Mediterranean	01.17-12.19	+	7 (9.1)	7 (9.1)	32 (41.5)	30 (39)	1 (1.3)
Çalışkan et al.[28]	2015	Mediterranean	03.10-08.14	+	162 (51.7)	4 (1.3)	144 (46)	3 (1)	0 (0)
Çekın et al.[29]	2014	Mediterranean	01.11-06.13	-	122 (82.4)	6 (4.1)	17 (11.5)	3 (2)	0 (0)
Çetin Duran et al.[30]	2017	Mediterranean	01.15-08.16	+	85 (71.4)	9 (7.6)	20 (16.8)	4 (3.4)	1 (0.8)
Çetin Duran et al.[31]	2020	Aegean	2005-2012	+	493 (88.4)	12 (2.1)	29 (5.2)	16 (2.9)	8 (1.4)
Çil et al.[32]	2007	Southeastern A.	01.04-01.05	+	21 (95.5)	0 (0)	1 (4.5)	0 (0)	0 (0)
Çizmeci[33]	2016	Marmara	06.09-02.12	+	93 (86.1)	7 (6.5)	0 (0)	1 (0.9)	7 (6.5)

Değertekin et al.[34]	2020	Multicenter	06.15-01.20	-	3894 (94.8)	40 (1)	83 (2)	77 (1.9)	14 (0.3)
Demircili et al.[35]	2016	Central A.	12.10-02.12	-	62 (95.5)	1 (1.5)	1 (1.5)	1 (1.5)	0 (0)
Dilek et al.[36]	2013	Black Sea	Unspecified	-	38 (90.5)	0 (0)	3 (7.1)	1 (2.4)	0 (0)
Erensoy et al.[37]	2002	Multicenter	2002	-	45 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Erman Daloğlu et al.[38]	2021	Mediterranean	01.14-03.19	-	555 (77.1)	11 (1.5)	129 (17.9)	20 (2.8)	5 (0.7)
Ertürk Şengel et al.[39]	2020	Marmara	01.14-12.18	-	109 (84.5)	2 (1.6)	7 (5.4)	2 (1.6)	9 (6.9)
Genç et al.[40]	2020	Black Sea	01.17-05.19	-	137 (93.2)	2 (1.4)	8 (5.4)	0 (0)	0 (0)
Gökahmetoğlu et al.[41]	2007	Central A.	2007	+	57 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Gülseren et al.[42]	2020	Central A.	2016-2018	-	186 (77.2)	13 (5.4)	34 (14.1)	7 (2.9)	1 (0.4)
Gürbüz et al.[43]	2016	Multicenter	2005-2013	-	869 (91.8)	38 (4)	16 (1.7)	24 (2.5)	0 (0)
Hacıseyitoğlu et al.[44]	2021	Marmara	01.15-12.18	-	236 (74)	3 (0.9)	62 (19.4)	6 (1.9)	12 (3.8)
Harman et al.[45]	2017	Southeastern A.	2012-2016	-	157 (98.1)	1 (0.6)	2 (1.3)	0 (0)	0 (0)
İba Yılmaz et al.[46]	2015	Eastern A.	12.08-04.11	-	46 (100)	0 (0)	0 (0)	0 (0)	0 (0)
İdilman et al.[47]	2019	Multicenter	04.15-01.16	-	189 (98.4)	0 (0)	0 (0)	3 (1.6)	0 (0)
İrvem et al.[48]	2017	Marmara	01.12-09.13	-	38 (84.4)	2 (4.4)	5 (11.1)	0 (0)	0 (0)
Kabakçı Alagöz et al.[49]	2014	Central A.	Unspecified	-	490 (98)	2 (0.4)	0 (0)	2 (0.4)	6 (1.2)
Kalaycı et al.[50]	2010	Aegean	09.07-03.08	-	26 (86.7)	0 (0)	0 (0)	4 (13.3)	0 (0)
Kandemir and Gültekin[51]	2017	Mediterranean	2000-2016	-	120 (50.4)	22 (9.2)	81 (34)	15 (6.3)	0 (0)
Kandemir et al.[52]	2020	Eastern A.	01.08-12.17	-	18 (90)	0 (0)	0 (0)	2 (10)	0 (0)
Kara et al.[53]	2021	Mediterranean	07.17-03.18	-	20 (52.6)	1 (2.6)	12 (31.6)	5 (13.2)	0 (0)
Karabulut et al.[54]	2018	Marmara	01.13-09.16	+	340 (82.5)	19 (4.6)	44 (10.7)	9 (2.2)	0 (0)
Kayman et al.[55]	2015	Central A.	2010-2011	+	136 (62.4)	10 (4.6)	0 (0)	72 (33)	0 (0)
Keskin et al.[56]	2010	Marmara	2010	-	91 (84.3)	7 (6.5)	6 (5.6)	1 (0.9)	3 (2.7)
Keten et al.[57]	2016	Mediterranean	05.14-05.15	-	1 (3)	0 (0)	32 (97)	0 (0)	0 (0)
Kırdar et al.[58]	2015	Aegean	08.07-12.10	-	48 (96)	1 (2)	1 (2)	0 (0)	0 (0)
Kırdar et al.[59]	2016	Aegean	03.13-02.15	-	98 (90.7)	2 (1.9)	5 (4.6)	3 (2.8)	0 (0)
Kırdar et al.[60]	2018	Aegean	01.11-12.16	-	258 (90.2)	6 (2.1)	17 (5.9)	4 (1.4)	1 (0.4)
Kirişçi et al.[61]	2013	Mediterranean	03.10-08.12	+	60 (60)	0 (0)	40 (40)	0 (0)	0 (0)
Kirişçi and Çalışkan[62]	2019	Mediterranean	09.14-02.18	+	124 (45.3)	6 (2.2)	122 (44.5)	22 (8)	0 (0)
Tekin Koruk et al.[63]	2012	Southeastern A.	04.07-03.11	-	102 (82.3)	22 (17.7)	0 (0)	0 (0)	0 (0)
Kuru and Hamidi[64]	2020	Black Sea	01.16-12.19	-	152 (89.9)	1 (0.6)	10 (5.9)	6 (3.6)	0 (0)
Küçköztaş et al.[65]	2010	Marmara	02.07-09.08	-	41 (78.8)	2 (3.8)	5 (9.6)	4 (7.7)	0 (0)
Mutay Suntur et al.[66]	2020	Mediterranean.	06.16-10.18	-	395 (52.4)	85 (11.3)	216 (28.6)	31 (4.1)	27 (3.6)
Mutlu Sarıgüzel et al.[67]	2015	Central A.	06.12-12.12	-	70 (70)	4 (4)	2 (2)	24 (24)	0 (0)
Nar et al.[68]	2013	Southeastern A.	2012-2013	-	23 (85.2)	3 (11.1)	0 (0)	1 (3.7)	0 (0)
Oral Zeytinli et al.[69]	2017	Marmara	01.16-01.17	+	442 (79.8)	3 (0.5)	94 (17)	3 (0.5)	12 (2.2)
Öksüz et al.[70]	2022	Mediterranean	01.17-09.20	-	110 (61.4)	27 (15.1)	34 (19)	8 (4.5)	0 (0)
Özatağ et al.[71]	2021	Aegean	01.17-10.19	-	12 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Özbek et al.[72]	2009	Southeastern A.	04.07-10.08	-	68 (91.9)	2 (2.7)	4 (5.4)	0 (0)	0 (0)
Özdoğan et al.[73]	2020	Mediterranean	05.16-01.18	-	117 (96.7)	3 (2.5)	0 (0)	1 (0.8)	0 (0)
Özdoğan and Yaraş[74]	2020	Mediterranean	2006-2010	-	132 (97.8)	2 (1.5)	0 (0)	1 (0.7)	0 (0)
Özer Etik et al.[75]	2019	Central A.	06.16-05.17	-	30 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Ozger et al.[76]	2017	Multicenter	2014-2016	-	31 (31.3)	1 (1)	66 (66.7)	1 (1)	0 (0)
Özkaya et al.[77]	2021	Black Sea	2002-2019	+	603 (90)	12 (1.8)	45 (6.7)	6 (0.9)	4 (0.6)
Özmen and Gökahmetoğlu[78]	2022	Central A.	2018	+	138 (65.1)	21 (9.9)	21 (9.9)	30 (14.2)	2 (0.9)
Öztürk et al.[79]	2014	Mediterranean	12.10-12.12	+	467 (73.1)	76 (11.9)	85 (13.3)	11 (1.7)	0 (0)
Rota et al.[80]	2013	Central A.	Unspecified	-	85 (89.5)	6 (6.3)	2 (2.1)	2 (2.1)	0 (0)
Sağlık et al.[81]	2014	Mediterranean	2009-2013	-	352 (83.4)	15 (3.6)	47 (11.1)	7 (1.7)	1 (0.2)
Sarı et al.[82]	2020	Marmara	01.12-12.19	+	325 (78.7)	22 (5.3)	49 (11.9)	15 (3.6)	2 (0.5)
Sarıgül et al.[83]	2019	Mediterranean	06.16-06.17	-	88 (87.1)	2 (2)	8 (7.9)	3 (3)	0 (0)
Sayan et al.[84]	2020	Multicenter	07.17-09.19	-	48 (90.6)	2 (3.8)	3 (5.7)	0 (0)	0 (0)
Selçuk et al.[85]	2006	Central A.	Unspecified	-	121 (93.1)	0 (0)	0 (0)	9 (6.9)	0 (0)
Selek et al.[86]	2018	Marmara	01.15-04.16	+	86 (81.1)	3 (2.8)	17 (16)	0 (0)	0 (0)
Süleymanlar et al.[87]	2010	Mediterranean	2010	+	29 (69)	0 (0)	0 (0)	0 (0)	13 (31)
Şanlıdağ et al.[88]	2009	Aegean	2002-2005	-	92 (92)	2 (2)	0 (0)	5 (5)	1 (1)
Şanlıdağ et al.[89]	2017	Multicenter	2015	-	88 (90.7)	2 (2.1)	4 (4.1)	3 (3.1)	0 (0)

Tabak et al.[90]	2021	Multicenter	06.17-12.17	-	895 (87.9)	19 (1.9)	36 (3.5)	13 (1.3)	55 (5.4)
Taheri et al.[91]	2015	Central A.	2010-2013	-	123 (90.4)	0 (0)	0 (0)	13 (9.6)	0 (0)
Taşkın et al.[92]	2020	Black Sea	2014-2017	+	771 (89.9)	24 (2.8)	39 (4.5)	24 (2.8)	0 (0)
Tezcan et al.[93]	2013	Mediterranean	03.10-05.12	+	218 (92.4)	5 (2.1)	10 (4.2)	2 (0.8)	1 (0.4)
Tiftikçi et al.[94]	2009	Marmara	2009	-	44 (88)	3 (6)	3 (6)	0 (0)	0 (0)
Tiryaki et al.[95]	2018	Aegean	2014-2018	+	163 (89.6)	3 (1.6)	13 (7.1)	3 (1.6)	0 (0)
Tüzüner et al.[96]	2018	Central A.	01-10-05.17	+	432 (90)	18 (3.8)	16 (3.3)	12 (2.5)	2 (0.9)
Us et al.[97]	2017	Central A.	2009-2014	-	192 (94.5)	3 (1.5)	4 (2)	4 (2)	0 (0)
Uzun et al.[98]	2014	Aegean	01.10-12.13	-	271 (88)	8 (2.6)	15(4.9)	5 (1.6)	9 (2.9)
Üçbilek et al.[99]	2016	Mediterranean	05.10-05.14	+	10 (11.5)	26 (29.9)	51 (58.6)	0 (0)	0 (0)
Ünal et al.[100]	2021	Mediterranean	2011-2017	+	548 (54.2)	136 (13.4)	287 (28.4)	27 (2.7)	14 (1.3)
Vatansever et al.[101]	2018	Aegean	04.08-12.17	-	10 (76.9)	0 (0)	3 (23.1)	0 (0)	0 (0)
Yamazhan et al.[102]	2020	Aegean	05.16-12.16	-	98 (94.2)	0 (0)	3 (2.9)	3 (2.9)	0 (0)
Yetim and Şahin[103]	2018	Mediterranean	04.13-06.17	-	22 (61.1)	2 (5.6)	12 (33.3)	0 (0)	0 (0)
Yıldırım et al.[104]	2006	Marmara	2006	-	32 (86.5)	2 (5.4)	3 (8.1)	0 (0)	0 (0)
Yıldırım et al.[105]	2015	Central A.	2012	-	42 (95.4)	0 (0)	1 (2.3)	1 (2.3)	0 (0)
Yıldız et al.[106]	2002	Mediterranean	2002	-	77 (97.5)	1 (1.3)	0 (0)	1 (1.3)	0 (0)
Yıldız Kaya et al.[107]	2017	Marmara	01.08-12.15	-	105 (89.7)	3 (2.6)	9 (7.7)	0 (0)	0 (0)
Yılmaz et al.[108]	2014	Central A.	09.08-09.09	-	41 (70.7)	3 (5.2)	0 (0)	0 (0)	14 (24.1)
Ziyade et al.[109]	2020	Marmara	2014-2018	+	16 (40)	2 (5)	11 (27.5)	2 (5)	9 (22.5)
Total					26476 (82.6)	1265 (3.9)	2783 (8.7)	1234 (3.9)	278 (0.9)

A: Anatolia, G: Genotype

Table II: Genotype distribution according to gender

Gender	Genotype 1 N (%)	Genotype 2 N (%)	Genotype 3 N (%)	Genotype 4 N (%)	Other N (%)
Female	3774 (85.9)	170 (3.8)	225 (5.1)	179 (4.1)	45 (1)
Male	3424 (68.7)	323 (6.5)	1016 (20.4)	170 (3.4)	52 (1)
p	< 0.05	< 0.05	< 0.05	0.090	0.929

Table III: Genotype distribution according to region

Region	Genotype 1 N (%)	Genotype 2 N (%)	Genotype 3 N (%)	Genotype 4 N (%)	Other N (%)	Total
Mediterranean	3873 (65)	447 (7.5)	1379 (23.2)	194 (3.2)	63 (1.1)	5956
Black Sea	2212 (90.8)	44 (1.8)	124 (5.1)	47 (1.9)	9 (0.4)	2436
Eastern A.	167 (96)	0 (0)	4 (2.3)	3 (1.7)	0 (0)	174
Southeastern A.	588 (81.8)	72 (10)	19 (2.6)	33 (4.6)	7 (1)	719
Central A.	2347 (85.7)	106 (3.9)	83 (3)	178 (6.5)	25 (0.9)	2739
Marmara	2883 (82)	109 (3)	385 (11)	68 (2)	69 (2)	3514
Aegean	2403 (91.3)	45 (1.7)	111 (4.2)	53 (2)	19 (0.7)	2631
Multicenter	12003 (86.6)	442 (3.2)	678 (4.9)	658 (4.7)	86 (0.6)	13867
p	< 0.05	< 0.05	< 0.05	< 0.05	< 0.05	32036

A: Anatolia

Table IV: Genotype distribution according to years

Years	Genotype 1 N (%)	Genotype 2 N (%)	Genotype 3 N (%)	Genotype 4 N (%)	Other N (%)	Total
2011 and before	6088 (86.6)	265 (3.8)	429 (6.1)	191 (2.7)	58 (0.8)	7031
After 2011	13200 (80.6)	639 (3.9)	1851 (11.3)	492 (3)	188 (1.1)	16370
p	< 0.05	0.625	< 0.05	0.229	0.026	23401

DISCUSSION

Although the genotype distribution of HCV varies in different parts of the world, genotype 1 is the most common genotype globally. The data obtained in this study showed that genotype 1 is the most common HCV genotype in Türkiye. Similarly, different studies confirm this result[110-112]. Genotype 1 is the most common genotype in Europe (excluding Norway and Finland), North and South America, Australia, New Zealand, Russia, China, South Korea, Japan, Central Asia and Iran. Genotype 2; it has been reported to be more common in Kenya, Ghana, Burkina Faso, Guinea Bissau, Gambia and Suriname. Genotype 3; it is more common in Southeast Asian countries such as Thailand and Malaysia, and South Asian countries such as Afghanistan, Nepal, Pakistan, and India. In addition, although genotype 1 is the predominant genotype across Europe, interestingly, genotype 3 is more common in Finland and Norway[112]. Genotype 3 is significantly associated to IVDU (intravenous drug use) and it has been reported that the most common route of transmission HCV infection in Finland is IVDU[113,114]. Genotype 4; it is common in Central Sub-Saharan African countries, Chad, Ethiopia, Burundi, Egypt and Arabic Middle East countries[112]. In a study assessment Middle Eastern countries, Egypt has been shown to have a higher level of genotype 4 (86.22%) distribution when compared to other countries[110]. On the other hand, mixed infections are more common in Libya (53.5%), genotype 5 in South Africa, genotype 6 in Southeast Asian countries such as Cambodia, Laos, Vietnam and Myanmar (Figure 2)[112].

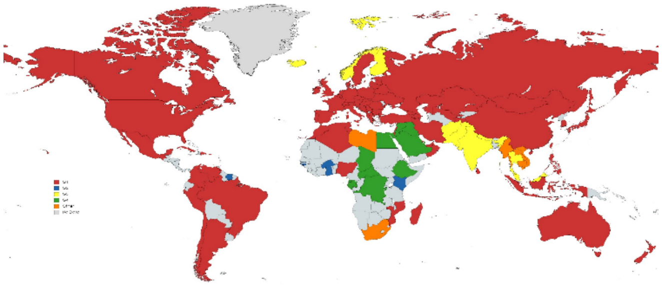

Figure 2. Global Distribution of HCV Genotypes (The results for Türkiye were added according to the data obtained from this study. The data of other countries are arranged by obtaining from reference no:112).

There are seven geographical regions in Türkiye: Marmara, Aegean, Mediterranean, Central Anatolia, Southeastern Anatolia, Eastern Anatolia and Black Sea. We stated that genotype 1 is the most common genotype in Türkiye. Genotype 1 was seen proportionally most frequently in the Eastern Anatolia region, but this may be due to the smaller study group population compared to other regions. When examined according to the situation of the regions, it was detected that the most common genotype in each region was genotype 1. However, it was determined that there was a statistically significant difference between the distribution of all genotypes between regions. Genotype 2 was found at a higher rate in Southeast Anatolia compared to other regions. Some studies included in this study reported that genotype 2 was the most common genotype in the region after genotype 1 in the Southeastern Anatolia region[26, 63, 68]. On the contrary, in other studies conducted in Southeastern Anatolia, the incidence of genotype 2 is lower[32,45,72]. The difference in these results may be due to the small number of studies conducted in Southeastern Anatolia and the fact that they were conducted on a lower number of people compared to other regions except Eastern Anatolia. It has been reported that the incidence of genotype 2 decreased in Şanlıurfa, a province in Southeastern Anatolia. In addition, it has been reported that there is an increase in genotypes 4 and 5 due to Syrian patients migrating to the region[26]. Genotype 3 has statistically significantly higher rates in the Mediterranean. When various studies included in this study were examined, it was seen that this situation was related to the illicit drug use and inmates[27,28,38,57]. Therefore, IVDU (intravenous drug use) increases genotype 3 dominance in the population, but in addition to this situation, irregular migration from regions dominated by genotype 3 may cause this situation to increase statistically in the future. The effect of irregular migrations on HCV genotype distribution in Türkiye is not clear. Otherwise, we have emphasized before that genotype 3 is common in Pakistan, Afghanistan and India. According to the data of the Turkish Immigration Administration, Afghanistan and Pakistan are among the countries where Türkiye receives the most irregular migration[115]. For this reason, the effect of this situation on genotype 3 distribution seems worthy of discussion. Genotype 4 is more common in Central Anatolia compared to other regions. Especially in the studies conducted in Kayseri (a province in Central Anatolia), the genotype 4 rate is higher than the country average obtained in this study[55,67,78]. Kayman et al.[55] showed that HCV genotype 4d virus entered Kayseri province between 1936 and 1981 by molecular clock analysis method. It has been shown that this situation indicates its endemic nature and is also compatible with the dates of labor migration from Türkiye. For this reason, it was stated that it would be plausible to think that the virus was brought here by infected people in the Middle East or North Africa regions and kept in the population by local transmission routes. It has been reported that the incidence of genotype 4 has increased in Greece, a Mediterranean country similar to Türkiye[116]. Ansaldi et al.[117] reported in their studies that genotypes 3 and 4 were mainly in the[31-60] age group and compatible with intravenous drug use and migration.

According to the report Sarasvat et al.[118], the prevalence of HCV is generally higher in males than in females. For Genotypes 1, 2 and 3, significant differences were observed between males and females in this study ($p < 0.05$), while for Genotype 4 and others, no significant differences were observed between males and females. Genotype 1 is the most common genotype in both males and females. Genotype 1 ratio is higher in females compared to males, while genotype 2 and 3 ratios are higher in males. Niu et al.[119] showed that among all genotypes, genotype 1 was highest in both male and female patients, followed by genotype 2. In the same study, it was stated that Genotype 1, 2 and 6 were more common in female patients than males, and no significant gender difference was observed for genotype 6. In addition, they were stated the frequently of HCV genotype 3 was equivalent in male and female patients. Also, the frequency of all different HCV genotypes was reported to be higher in female patients than in males, but they added that the rate of females was higher in the study. The reason for the difference in this study may be due to the gender distribution in the study groups. Genotype 3 difference is thought to be due to the fact that the male population is higher in studies where genotype 3 is more frequent[38,57].

When the HCV genotype distribution was analyzed by years, a significant difference was observed in genotypes 1 and 3 between in the period 2011 and before versus after 2011 ($p < 0.05$). While a decrease was observed in genotype 1, there was an increase in genotype 3. The rate of increase in genotype 3 (5.2%) and the rate of decrease in genotype 1 (6%) are close to each other. No official data could be found regarding the IVDU rate in Türkiye. However, the United Nations reported that 269 million people worldwide used drugs in 2018, 30 percent more than in 2009[120]. This shows the increase in drug use globally. This increase may increase the risk of transmission of infections such as HCV. As we mentioned before, genotype 3 is significantly associated with IVDU, and in the studies included in this study, genotype 3 is seen at a higher rate in inmates and drug users. Therefore, it is closely possible that this increase in genotype 3 is related to this situation. After 2011, migration in Türkiye due to the Syrian civil war has increased. Again, according to the report of the Turkish Migration Administration, as of 2022 December 8, there are more than 3.5 million Syrian refugees in Türkiye[121]. Genotype 4 is common in Syria. Migration to Türkiye from Syria took place especially from the northern part of the country. Antaki et al.[122] in their study in 2009, they reported that Genotype 4 (46%) was most frequent in the northern region of Syria. Isenring et al.[123] in their systematic review study published in 2018, they stated that the risk of hepatitis B and C in Syrians is very low. In addition they stated the risk of hepatitis C in Syria and the Middle East is also very low except for at-risk groups such as drug users presenting high incidences. However, increasing population rates may affect this situation in the future and cause changes in genotype 4 incidence. The distribution of genotypes in the geographical regions included in the study according to year groups is shown in Figure 3.

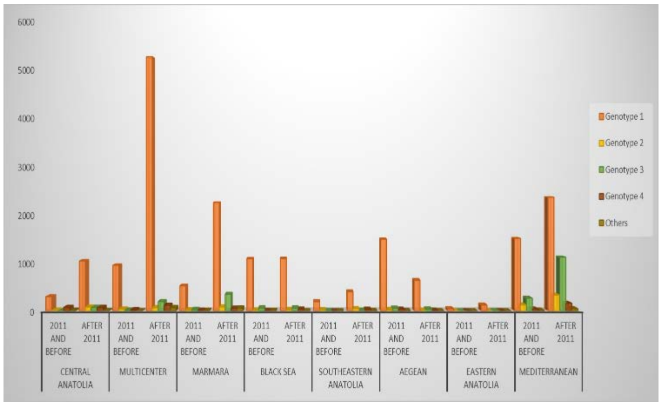

Figure 3. Distribution of HCV genotypes by year groups in the regions included in the study.

CONCLUSIONS

In this study, we observed that the most dominant genotype did not change in genotype distribution in Türkiye, but different genotypes changed at various rates. Changes that will occur due to various risk factors can affect health policy both economically and in terms of planning. Therefore, studies that provide comprehensive data not only for HCV but also for many other infectious diseases are needed.

Ethics Committee Approval: Since the study is a research study examining data from studies published in the literature, it was exempt from ethics committee approval.

Conflict of Interest: The authors declared no conflicts of interest.

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