New Microbiologica, 46, 3, 252-257, 2023, ISSN 1121-7138

FULL PAPER

Determination of hepatitis C virus viremia and genotype distribution in Turkish citizens and immigrants from 2018 to 2022

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SUMMARY

Hepatitis C virus (HCV) infection is an important public health problem with potential risk for Turkey. In order to contribute to the epidemiological data, we aimed to investigate the changes in seroprevalence, viremia rates, and genotypes in the last five years in HCV patients in the southern region of Turkey, which has received heavy migration in recent years, according to demographic criteria. In our study, we analyzed the results retrospectively with demographic data. Conducted at a single center, the study involved 259,875 anti-HCV antibody tests administered between January 2018 and July 2022.

The study revealed a prevalence of 0.5% for HCV antibody positivity and a viremia prevalence of 0.1%. Among Turkish nationals, the most common genotypes were GT1 (65.1%), while foreign nationals, mainly of Syrian and Ukrainian origin, showed GT4 (52.3%) as the predominant genotype ($p<0.001$ for both). Although GT2 (7.4% vs. 4.5%) and GT3 (23.3% vs. 13.6%) were relatively higher in Turkish nationals compared to foreign nationals, the difference was not statistically significant ($p=0.750$ and $p=0.154$, respectively).

This highlights the importance of continuous monitoring and public health efforts to address the potential impact of these demographic shifts on HCV epidemiology in the region.

Received March 26, 2023 *Accepted* July 23, 2023

INTRODUCTION

Hepatitis C virus (HCV) is a significant contributor to liver disease on a global scale. Roughly 85% of individuals with acute HCV infection progress to chronic HCV infection. The World Health Organization (WHO) estimates that approximately 58 million people worldwide are affected by chronic HCV infection, and around 1.5 million new infections emerge each year (Guntipalli P., 2021; WHO 2023).

HCV genotype distribution in a geographical area may change with an increase in cultural diversity (Fourati, Slim, *et al.*, 2019). Turkey's historical significance as a crossroads between the East and the West, coupled with its role as a major transit and migration route, has contributed to a diverse population in the region. In addition, especially in recent years, the settlement of foreign nationals in the region has been increasing. This suggests that HCV infection may be genotypically diverse in the region. Due to the high mutation potential of the HCV, the phenotype can change in a short period of time. The biological effects of this may be the formation of mutations that evade host defense, changes in cell tropism and virulence, and resistance to antiviral agents (Smith, David *et al.*, 2019). These immune escape mutations can make it challenging for the body to mount an effective immune response against the virus, leading to persistent infection. Although it is possible to treat individuals without identifying the HCV genotype and subtype with pangenotypic HCV drug regimens, it is still important to determine the genotype and subtype before treatment in centers where genotype-specific treatment regimens are used (EASL, 2020).

Currently, four HCV indicators, consisting of total anti-HCV antibody, HCV core antigen, HCV-RNA level determination, and HCV genotyping, are used in the viral diagnosis of HCV infection and in determining the duration of treatment (Manee, Narathon *et al.*, 2017; Hedskog, Charlotte *et al.*, 2019;

Key words:
Hepatitis C virus, prevalence, HCV viremia, HCV genotype, Immigrants.

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https://ictv.global/sg_wiki/flaviviridae/hepacivirus, 2023). As of March 2022, there are eight confirmed HCV genotypes; these genotypes contain many subtypes, and the nucleotide sequence differences among these subtypes range from 15% to 25% (Hedskog, Charlotte *et al*., 2019).

We predicted that the epidemiology of HCV infection would differ as a result of increased migration in the region due to Turkey's geographical and geopolitical location. With this study, in Turkish and immigrant patients who applied to the Training and Research Hospital in Mersin province in the south of Turkey, which that received heavy immigration in the last five years, we aimed to contribute to epidemiological data by examining HCV seroprevalence, viremia rates and changes in GTs.

MATERIALS AND METHOD

Design and patients

In this research, a total of 259,875 anti-HCV antibody tests were performed from January 2018 to July 2022, and the results of reactive anti-HCV antibody tests were analyzed retrospectively.

Patients who were found to have reactive anti-HCV antibodies and who were followed by HCV PCR and HCV genotyping tests, respectively, were included in the study. Virological test results were analyzed by correlating with the demographic data of the patients. Analysis results were obtained from the electronic Laboratory Information System (LIS). Demographic data of the patients (age, ethnicity, year) were obtained from the hospital database.

Anti–HCV antibody analysis

HCV analyses in serum samples were performed using ADVIA Centaur XPT (Siemens Healthcare Diagnostics, Deerfield, MA, USA) automatic analyzer and ADVIA Centaur anti-HCV assay (Centaur-Ab; Siemens Healthcare Diagnostics, Tokyo, Japan) chemiluminescent Immunoassay kits. Considering the cut-off (Co) value calculated automatically by the device, the results of the samples (S) were determined as S/Co.

Quantitative HCV RNA analysis

The Bosphore Ultra HCV Kit (Anatolia Geneworks, Turkey) was utilized for the detection and quantitation of HCV-RNA in the patients' samples. Bosphore Ultra HCV Quantitation/Detection Kit is a real–time PCR based in vitro diagnostic medical device.

HCV Quantification Kit detects and quantitates HCV-RNA in human serum and plasma, encompassing all the HCV GTs. An internal control was integrated into the kit to check PCR inhibition and DNA extraction. Viral nucleic acid isolation, a crucial step in the PCR-based analysis, was performed using the Magnesia 2448 Nucleic Acid Extraction and PCR Set-up equipment, also supplied by Anatolia Geneworks in Turkey.

HCV Genotyping

Bosphore HCV genotyping kit (Anatolia Geneworks, Turkey) detects and characterizes the GT of HCV in human serum or plasma, encompassing six major and most predominant HCV GTs (1, 1a, 1b, 2, 3, 4, 5, 6). The internal control can be added either during RNA extraction or PCR step. The results were evaluated in accordance with the kit manufacturer's recommendations. The analytical sensitivity of the Bosphore HCV genotyping kit was $1x10^2$ IU/mL (Bosphore HCV Genotyping Kit, 2023). This indicates that the kit can reliably detect and identify HCV genotypes in samples with a viral load as low as $1x10^2$IU/mL.

Statistical analysis

SPSS version 22 (IBM Corp.) package program was used in the statistical evaluation of the data. Median, interquartile range (IQR), minimum and maximum values for continuous variables in data analysis; number and percentage values were calculated for categorical variables. Evaluation of normal distribution as initial analysis was conducted with Kolmogorov-Smirnov and Shapiro-Wilk tests. Mann-Whitney U test and Kruskal-Wallis tests were used to compare numerical variables, and Pearson's Chi-square and Fisher's exact tests were used to compare categorical variables. Odds ratio (OR) was calculated using the relevant basic formulas. Values of $p<0.05$ were considered statistically significant.

RESULTS

A total of 259,875 anti-HCV antibody tests were performed from January 2018 to July 2022, and the results of 1460 patients were found to be reactive (HCV antibody positivity prevalence 0.5%). The prevalence and rate of HCV viremia were determined as 0.1% and 21.3%, respectively.

HCV-infected patients were categorized into seven age groups (0-18, >18-30, 31-40, 41-50, 51-60, 61-70, and >70 years). The prevalence of viremic HCV infection showed different variations with age. The highest prevalence was in the >70 years age group (0.2% of 27,935), and the lowest prevalence was in the >18-30 years age group (0.07% of 78,947) and 41-50 age group (0.07% of 33,284).

HCV antibody prevalence did not differ significantly by years ($p=0.059$). Both the prevalence of HCV viremia (0.2%) and the rate of HCV viremia (30.3%) were highest in 2018 ($p<0.001$ for both). It was determined that HCV viremia rates decreased after 2018, but increased as of the first half of 2022. The prevalence of HCV antibodies and viremia and the distri-

bution of HCV viremia rates from 2018 to 2022 are presented in *Table 1*.

The ages of 302 patients who underwent HCV genotype testing ranged from 10 to 93 years, with a median age of 44 years (IQR 31-44).

Six HCV GTs (1-6) and two GT1 subtypes were investigated and 310 HCV GTs were detected in 302 patients. Of the 302 patients, 44 were foreign nationals, with majority of Syrian and Ukrainian origin. HCV GT1 (59.3%) was found to be the most common genotype, and this was followed by GT3 (21.9%), 4 (13.6%), 2 (7.0%) and 5 (1.0%). GT6 was not detected in these patients. According to the current genotyping method, subtype 1b was detected in 61.5% of cases and subtype 1a in 37.4% of cases in GT1 patient; subtype could not be determined in only 1.1% of the samples.

Infection with only a single HCV GT was detected in 97.4% (n=294/302) of the patients. Eight (2.6%) had mixed infections with HCV GT. The most mixed infections were found between GT1 and other types (GT1/3=12.5%, GT 1a/3=12.5%, GT1b/2=12.5%, GT1b/4=25%, GT2/3=12.5%, and GT3/4=25%).

Among all GTs, GT1 was the most frequently detected GT in both males (55.9% of 204 males; GT1/other GTs OR: 1.36) and females (62.5% of 104 females; GT1/other GTs OR: 1.67) (p<0.001). GT1 (male: 55.9%, female: 62.5%, p=0.408), GT2 (male: 8.6%, female: 3.8%, p=0.124), GT3 (male: 29.3%, female: 7.7%, p<0.001) was more common in male patients, while GT4 (male: 7.6%, female: 25.0%, p<0.001) and GT5 (male: 0.0%, female: 2.9%, p<0.040) were more common in female patients than in men. GT6 could not be detected in any of the individuals.

The distribution frequency of HCV GTs among different sex groups is shown in Table 2. GT1a was more common in male patients (51.8% of 114 GT1), and GT1b was more common in female patients (86.2% of 65 GT1) (p<0.001). Mixed infections were detected in 1.9% (n=2/104) of women and 3% (n=6/198) of men; this difference was not significant (p=0.719).

HCV GT distribution by age from January 2018 to July 2022 is denoted in *Figure 1*. The median ages of patients with GT2 and GT3 were found to be lower than those with GT1, 4, and 5 (*Table 2*, p<0.001).

GT1 was the most common GT in all age groups and was most common in patients aged >70 years (86.0% of 57). This was followed by the 51-60-year age group (68.6% of 35), and the 61-70-year group (5.3% of 49) (p<0.001). GT2 was most common in the >18–30 years (11.7% of 60) and 31-40 years (11.7% of 77) age groups (p=0.165). GT3 was determined most frequently in the 41-50 age group (42.1% of 19), while GT4 was detected in the 1-18 age group (40% of 5) (p<0.001 and p=0.013, respectively).

GT5 was detected in only three patients, who were in the 51-60 (2.9% of 35) and 61-70 (4.1% of 49) age groups (p=0.156). Mixed infection was most frequently detected in the >18-30 age group (6.7% of 60), but was not observed in the 1-18, 41-50 and 51-60 age groups (p=0.639).

The distribution of different GTs among ethnicities showed significant differences. GT1 (65.1%) in Turkish nationals and GT4 (52.3%) in foreign nationals were determined to be the most common GTs (p<0.001 for both). The distribution of other HCV

Table 1 - *The prevalence of HCV antibodies and viremia, and the distribution of HCV viremia rates by age groups and years.*

Age groups	*HCV Antibody*			*HCV Viremia*			*HCV Viremia Rate*		
	Reactive (n)	*Total (n)*	*Prevalence (%)*	*HCV-RNA(+) (n)*	*Total (n)*	*Prevalence (%)*	*HCV-RNA(+) (n)*	*Total (n)*	*Rate (%)*
0-18	30	11624	0.3	6	11624	0.05	6	30	20
>18-30	173	78947	0.2	57	78947	0.07	57	173	32.9
31-40	236	50985	0.4	72	50985	0.1	72	236	30.5
41-50	152	33284	0.4	24	33284	0.07	24	152	15.8
51-60	157	29327	0.5	35	29327	0.1	35	157	22.3
61-70	343	27773	1.2	53	27773	0.1	53	343	15.5
>70	369	27935	1.3	64	27935	0.2	64	369	17.3
Total	1460	259875	0.5	311	259875	0.1	311	1460	21.3
p value		*<0.001*			*<0.001*			*<0.001*	
Years									
2018	359	61535	0.6	109	61535	0.2	109	359	30.3
2019	305	60745	0.5	87	60745	0.1	87	305	28.5
2020	247	38394	0.6	45	38394	0.1	45	247	18.2
2021	356	64019	0.6	39	64019	0.1	39	356	10.9
2022	193	35182	0.5	31	35183	0.1	31	193	16
Total	1460	259875	0.6	311	259875	0.1	311	1460	21.3
p value		*0.059*			*<0.001*			*<0.001*	

HCV, hepatitis C virus; n: number of patients.

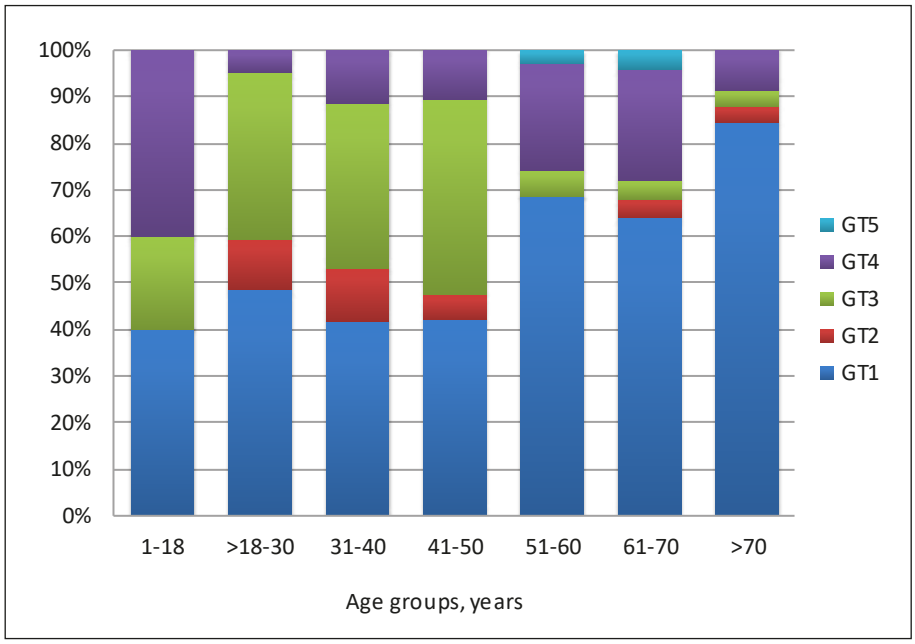

Figure 1 - *Distributions of different HCV genotypes (GT) in different age groups.*

Table 2 - *Distribution of HCV genotypes in the studied population.*

	Genotype							
Characteristic	*GT1*	*Subtype 1a*	*Subtype 1b*	*Untyped*	*GT2*	*GT3*	*GT4*	*GT5*
N (%)	179 (59.3)	67 (37.4)	110 (61.5)	2 (1.1)	21(7.0)	66 (21.9)	41(13.6)	3(1.0)
Gender, n (%)								
Female	65 (62.5)	8 (12.3)	56 (86.2)	1 (1.5)	4 (3.8)	8 (7.7)	26 (25.0)	3 (2.9)
Male	114 (57.6)	59 (51.8)	54 (47.4)	1 (0.9)	17 (8.6)	58 (29.3)	15 (7.6)	0 (0.0)
*Age, years**	58 (33-71)	33 (28-36)	69 (60-77)	44 (27-61)	34 (30-40)	32 (28-39)	58 (34-65)	61 (60-65)
Age range	14-93	14-62	24-93	27-61	23-79	18-81	10-77	59-69
Nationality								
Turkish (n=258)	168 (65.1)	58 (34.5)	109 (64.9)	1 (0.6)	19 (7.4)	60 (23.3)	18 (7.0)	0 (0.0)
Others (n=44)	11 (25.0)	9 (81.8)	1 (9.1)	1 (9.1)	2 (4.5)	6 (13.6)	23 (52.3)	3 (6.8)
Viral load†	1,66x105	1,62 x105	1,66 x105	4,51 x106	1,12 x105	2,39 x105	2,33 x105	5,43 x105
Years								
2018 (n=125)	76 (60.8)	27 (35.5)	48 (63.2)	1 (1.3)	9 (7.2)	27 (21.6)	15 (12.0)	1 (0.8)
2019 (n=87)	55 (63.2)	19 (34.5)	36 (65.5)	0 (0)	7 (8.0)	15 (17.2)	11 (12.6)	1 (1.1)
2020 (n=32)	18 (56.2)	7 (38.9)	11 (61.1)	0 (0)	1 (3.1)	9 (28.1)	6 (18.7)	0 (0)
2021 (n=36)	17 (47.2)	7 (41.2)	10 (58.8)	0 (0)	2 (5.6)	11 (27.8)	7 (19.4)	0 (0)
2022 (n=22)	13 (59.1)	7 (53.8)	5 (38.5)	1(7.7)	2 (9.1)	4 (18.2)	2 (9.1)	1 (4.5)

Data are given as percentage of rows. *median (range); †IU/ml; GT, genotype; N: number of genotypes detected; n: patient number.

GTs is presented in *Table 2*. Although GT2 (7.4% vs. 4.5%) and GT3 (23.3% vs. 13.6%) were found to be higher in Turkish nationals than in foreign nationals, the difference was not significant (p=0.750 and p=0.154, respectively). HCV GT5 was detected only in three foreign patients (6.8%) (p=0.003). When the distribution of mixed infections among ethnic origins was evaluated, no significant difference was found between Turkish (2.7%) and foreign nationals (2.3%) (p=1.000).

In this study, GT5 was associated with higher viral load (median, $5.43x10^5$) and GT2 (median, $1.12x10^5$) was associated with lower viral load, but the difference was not statistically significant (p=0.432). Although the viral load was higher in the GT1 non-classified group, the difference (compared to GT1a and GT1b) was not statistically significant (p=0.715).

DISCUSSION

HCV infection is a major public health problem. The 2016 Global Health Sector Strategy (GHSS) aims to reduce new HCV infections by 80% by 2030 (WHO, 2023). This target emphasizes the importance of pre-

venting new cases of HCV and reducing the transmission of the virus.

The prevalence of HCV infection varies depending on the geographical location of the country, population mobility (travel, migration, etc.), and socioeconomic status. The prevalence is less than 2% in developed countries and up to about 15% in developing countries (Hajarizadeh, Behzad *et al*., 2013; Gower, Erin *et al*., 2014).

There is no registry database that reveals the exact figures of HCV infection in general in Turkey. Epidemiological data are taken mostly from local studies. While the rate of anti–HCV antibody positivity was found to be between 0.4 and 2.1% in population-based studies, this rate was reported as 0.19 to 0.68% in blood donors (Akcam, Fusun Zeynep *et al*., 2009; Tozun *et al.,* 2015). In a recent meta-analysis, the prevalence of HCV infection in hemodialysis patients was found to be as high as an average of 23% (18-28%), and it was emphasized that the prevalence increase in this patient group was remarkable (Ashkani–Esfahani, Soheil *et al*., 2017).

Unfortunately, the rates of access to diagnosis and treatment for HCV infection are very low in Turkey. In an international mathematical modeling study, it was reported that the estimated diagnosis rate for HCV infection in our country was 16%, and the estimated cure rate was 0.8% (Dore *et al*., 2014). Turkey is a country in close proximity to Europe in the west, Asia in the east and the Middle East in the southeast. In a meta–analysis study evaluating the global prevalence of HCV viremia in 2014, it was determined that the prevalence of HCV viremia in North Africa and the Middle East ranged between 0.4-10% and the rate of viremia varied between 51.6 and 81.8%. In the same study, the prevalence and rate of HCV viremia were reported to be 0.8% (0.5%-1.7%) and 82.0%, respectively, in Turkish data. (Akcam, Fusun Zeynep *et al*., 2009).

In our study, HCV antibody prevalence did not differ significantly by years (p=0.059). Both the prevalence of HCV viremia (0.2%) and the rate of HCV viremia (30.6%) were highest in 2018 (p<0.001 for both). It was determined that HCV viremia rates decreased (from 30.3% to 10.9%) after 2018, but increased as of the first half (16%) of 2022. However, the prevalence and rate of viremia determined in this study were significantly lower than the rate stated in the meta–analysis results of Gower *et al*., for Turkey (Gower, Erin *et al*., 2014). Although our study does not reflect Turkey in general, we think that decreased viremia prevalence and viremia rates are promising results for the future and that there is a need for large population studies to be conducted in different regions of Turkey to support it.

In addition to gender, age groups and risk factors, the effects of regional differences, and realities such as war and migration become evident in the distribution of GTs (Niebel, Marc *et al*., 2017).

GT1 was the most common HCV infection worldwide (46-49%), followed by GT3 (17.9-30%), GT2, 4 and 6 from a total of 22.8% of all cases; GT5 contains the remaining <1%. (Messina, Jane *et al*., 2015).

Many studies have been carried out in our country to determine the distribution of HCV GTs for chronic hepatitis. When the GT distributions in our country were examined in published studies, it was seen that GT1b (52.8-87.5%) was dominant (Çetin Duran *et al*., 2020). When the GT distributions in our country are examined in the published studies, it is seen that GT1b is dominant. In general, the GT1b rate is high in interior regions; it is reported to be lower in big cities and provinces receiving immigration (Buruk, Celal Kurtuluş *et al*., 2013).

Recently, the number of foreign nationals living in the Eastern Black Sea Region has been increasing, and it was seen that GT1b was dominant (58.3%) and that GTs 2 and 3 had a prevalence above the Turkish average (both 16.7%) (Erman Dalglu, Aylin *et al*., 2021). In our study, subtype 1b was detected in 61.5% and subtype 1a in 37.4% in GT1 patients; subtype could not be determined in only 1.1% of subjects. The findings obtained in studies conducted in the same region at different times also support this data. In previous studies conducted in the south of Turkey, 78% of the patients were found to have GT1 and 11% GT3, while in the study published in 2021 it was reported that 74% of the patients had GT1 and 18% GT3. In this region, GT2 decreased from 3.5% to 1.5% over the years and GT4 increased from 1.6% to 2.8% (Saglik, Imran *et al*., 2014; Erman Daloglu, Aylin *et al*., 2021). In a study covering the western province of our country, 72% of the patients were found to be infected with GT1b, followed by GT1a (18%) and GT2a (2%), and the coexistence of GT 1a and 1b was found (6%) (Altuglu, İmre *et al*., 2013).

GT3 has been increasingly detected in Turkey over the last decade, and been found to be 4.9%- 58.6% at varying rates (Gökahmetoglu, Selma *et al*., 2011). The wide range of prevalence rates suggests possible regional variations or differences in the populations. GT4 was first found in our country in 2011 with a rate of 35.6% and attracted attention because it was quite high compared to other regions. In addition, a small number of GT6 cases has been reported from different provinces (Saglik, Imran *et al*., 2014).

HCV GT4 is known to be more common in certain regions, including the Middle East and North Africa. In Syria, the dominant GT is 4 (4c/4d), followed by GT1, GT5, GT3, and GT2, respectively. Although the predominant GT is 4 in Syria, the fact that GT1 was more dominant in refugees migrating to Turkey made us think that HCV GT rates may have been affected by migration (Messina *et al*., 2015). In our study, GT1 (65.1%) in Turkish nationals and GT4 (52.3%) in foreign nationals were determined as the most common GTs (p<0.001 for both). This data is thought to be the

reason for the mass migration movement originating from Syria and the increase in GT4 rate in our province.

The main limitation of this study could be attributed to its retrospective nature. As a retrospective study, we had limited control over data collection. Transmission routes and risk groups could not be evaluated in patients, and nucleotide sequencing could not be performed. Additionally, although the sample size was quite large, the data represents a single center's experience, thus not reflecting the whole region. Subtype definitions were limited due to the design of the kit used to identify the GT.

CONCLUSION

The increasing numbers of Syrian and Ukrainian refugees, due to recent immigration and refugee influx from countries neighboring Turkey, may cause differentiation in the prevalence, viremia, and genotype diversity epidemiology of HCV infection in the future. It is important to conduct studies that generate epidemiological data to determine the GT profile of HCV infections, to follow the clinical process, and to execute treatment.

Ethics Committee Approval

Ethical approval was obtained for this study from the Mersin Toros University Ethics Committee (Reference number: 141), September 23, 2022.

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