Distribution of Hepatitis C Virus Genotypes: 18-Year Experience in an Academic Center

Hepatitis C Virüs Genotip Dağılımı: Akademik Bir Merkez, 18 Yıllık Deneyim

Öz: Hepatit C virüsü (HCV) kronik hepatit, sıroz, hepatosellüler kanser gibi hastalıklara yol açması nedeniyle önemli bir halk sağlığı sorunudur. Bu çalışmada, geniş bir popülasyondaki HCV-RNA pozitif hastalarda, HCV genotip dağılımının uzun bir dönemdeki değişimin incelenmesi amaçlandı.

Gereç ve Yöntemler: HCV genotip ve subtipleri dizi analizi sonrasında dizinin referans dizilerle karşılaştırılması; “line probe assay” yöntemi veya 5'UTR ve NS5B'nin veya sadece NS5B'nin multiplex amplifikasyon yöntemlerinden biriyle gerçekleştirilmiştir.

Bulgular: Çalışmada HCV-RNA pozitif olup genotiplendirilmiş yapılan toplam 670 hasta yer alıdı. Hastalarnın 603'ünde (%90,0) genotip 1, 45'inde (%6,7) genotip 3, 12'sinde (%1,8) genotip 2 ve 6'sında (%0,9) genotip 4, 2'sinde (%0,3) genotip 1 ve 3 ve yine 2'sinde (%0,3) genotip 1 ve 4 birlikte tespit edildi. Çalışmada genotip 1b, 5, 6 ve 8'e rastlanmadı. Yıllara göre en baskın subtip genotip 1b (%82,8) idi. İkinci en sık saptanan subtip ise genotip 3a (%4,5) idi. Genotip 1b <50 yaş olan hastalarda %63,2 ve ≥50 yaş olan hastalarda %89,7 oranında (p<0,001) saptanırken, ≥50 yaş olan hastalarda genotip 3 %2,0 ve <50 yaş olan hastalarda ise %20,1 oranında saptandı (p<0,001).

Sonuç: Bu çalışmada HCV genotip 1b’nin en yüksek oranda, özellikle de 50 yaş üzerindekilerde görülüğü ortaya konmuştur.

Anahtar Kelimeler: Genotip, hepatit C virüs, subtip
Introduction

The hepatitis C virus (HCV), a member of the genus hepacivirus from the family flaviviridae, infects an estimated 130-200 million individuals worldwide (1,2). According to World Health Organization figures for 2018, 71.1 million individuals worldwide are infected with HCV, and approximately 475,000 die from the infection every year (3). Since the prevalence of HCV varies among different regions, countries are grouped in terms of the incidence of HCV infection. Eighty percent of HCV infections are seen in 31 countries. Six countries in particular (China, Pakistan, Nigeria, Egypt, India, and Russia) are host to 50% of all cases (4). HCV is also an important public health problem with a high probability of chronicization and still with no effective vaccine, that leads to severe liver diseases such as hepatocellular carcinoma and cirrhosis (2,5).

There are eight confirmed HCV genotypes and 86 subtypes to date (4). The distribution of HCV genotypes and subtypes exhibits geographic variations. Genotype 1 is responsible for 44% of all HCV infections worldwide, and for 60% of infections in high and middle-income countries (4). Globally, the leading genotypes are 1a, 1b, 2a, 2b, and 3a. Approximately one in three genotype 1 infections are seen in East Asia. Genotype 3 infections are more widespread in lower-middle-income countries than in high-income, upper-middle-income, and lower-income countries and constitute 25% of all HCV infections (4). Approximately 75% of HCV genotype 3 infections are seen in South Asia. Genotype 4 has been detected more widely in Central Africa and the Middle East, and genotypes 2 and 6 in East Asia (1,4). Genotype 5, 7, and 8 represent less than 1% of all HCV infections, with several cases emerging from southern and central sub-Saharan Africa (1,4). HCV genotypes have been shown to vary in terms of disease severity, prognosis, and response to antiviral drugs (4,6). Therefore, HCV genotyping is an important component of pre-treatment diagnostic algorithms, especially as it guides the therapeutic regimen process (7). Knowing the genotypes is the most important factor determining the selection of an effective antiviral agent, the length of treatment, and the expected virological response (6,8). A knowledge of regional HCV genotype distributions is therefore essential for the development of international and domestic HCV infection management strategies.

The purpose of this study was to examine the HCV genotype distribution in the previous 18 years among HCV-RNA-positive patients in a broad population.

Material and Methods

Research Type and Study Group

HCV genotype results from HCV-RNA-positive blood specimens studied at the Karadeniz Technical University Clinical Microbiology Laboratory, Turkey, between 2002 and 2019 were evaluated retrospectively. Patients’ demographic data were retrieved from the hospital information system.

Specimens from the patients included in the study were investigated in the academic clinical microbiology laboratory of a 960-bed tertiary university hospital in the Eastern Black Sea region of Turkey. The study population consisted of patients infected with HCV, the great majority living in the region (approximate population 2.9 million individuals per year). Six hundred seventy patients were enrolled in the study, the first specimen being evaluated in case of repeated specimens.

The study was approved by Karadeniz Technical University Faculty of Medicine Clinical Research Ethical Committee (approval number: 2020/169).

HCV-RNA Quantitation

The HCV-RNA load in specimens was determined using bDNA (Branching DNA, HCV 3.0 bDNA assay, Bayer Diagnostics, USA) or one of various real time PCR applications (COBAS® AmpliPrep/ COBAS®TaqMan® HCV test, Roche Diagnostics Corporation, USA, Abbott RealTime HCV Assay, Abbott Molecular Inc., USA, and Bosphore® HCV Quantification Kit, Anatolia Geneworks, Turkey).

HCV Genotyping Procedure

Following HCV genotype and subtype “5’untranslated region (5’UTR)” or “non-structural 5B” (NS5B) amplification and sequence analysis, the comparison of the sequence with reference sequences were studied with either using the “line probe assay” method (INNO-LiPA HCV II, Innogenetics, Belgium) or two different commercial Real-Time PCR kits, by the method of multiplex amplification of the 5’UTR and NS5B (Abbott RealTime HCV Genotype II Assay, Abbott Molecular Inc., USA) or only NS5B (HCV Genotyping Kit v1 Bosphore, Geneworks Anatolia, Turkey).

Statistical Analysis

Statistical analysis was performed on SPSS version 21 software (SPSS Inc., Chicago, IL, USA). Non-parametric data not conforming to normal distribution at the Kolmogorov-Smirnov test were compared using the Mann-Whitney U test. The chi-square test and Fisher’s exact test were employed in the comparison of categorical variables. P-values <0.05 were regarded as statistically significant.

Results

Three hundred fifty-nine (59.6%) of the 670 patients in the study were men and 311 (46.4%) were women. The patients’ mean age was 58.27±16.53 years (minimum-maximum: 4-112). Genotype distributions by gender are shown in Table 1. No significant difference in genotype distribution was observed between the genders (p=0.461).

Table 1. Distributions of HCV genotypes by gender

| Gender | 1 (4.2) | 1a (2.9) | 1b (83.9) | 2 (1.9) | 2b (1.9) | 3 (3.5) | 3a (1.0) | 4 (1.0) | Mixed (0.6) | Total n (%) |
|--------|---------|---------|----------|--------|---------|--------|---------|--------|-------------|-------------|
| Female | 13       | 9       | 261      | 6      | -       | 6      | 11      | 3      | 2           | 311 (46.4)  |
| Male   | 10       | 16      | 294      | 5      | 1       | 9      | 19      | 3      | 2           | 359 (53.6)  |

*Subtyping could not be performed. HCV. Hepatitis C virus
Table 2. Distribution of HCV genotypes by years

| Year | Genotype 1 (%) | Genotype 2 (%) | Genotype 3 (%) | Genotype 4 (%) | Mixed (%) | Total (n) |
|------|----------------|----------------|----------------|---------------|-----------|-----------|
| 2002 | -              | 5 (100.0)      | -              | -             | -         | 5         |
| 2004 | -              | 10 (90.9)      | -              | 1 (9.1)       | -         | 11        |
| 2005 | -              | 4 (66.7)       | -              | 1 (16.7)      | -         | 6         |
| 2006 | -              | -              | -              | -             | -         | 4         |
| 2007 | -              | 1 (50.0)       | -              | -             | -         | 2         |
| 2008 | -              | 5 (100.0)      | -              | -             | -         | 5         |
| 2009 | -              | 49 (96.1)      | -              | -             | -         | 51        |
| 2010 | 5 (5.8)        | 72 (82.8)      | 1 (1.2)        | 3 (3.5)       | 4 (4.6)   | 1 (1.2) (genotip 1b+3a) |
| 2011 | 3 (4.9)        | 55 (90.2)      | 2 (3.3)        | -             | -         | 61        |
| 2012 | 2 (3.2)        | 50 (79.4)      | 2 (3.2)        | 2 (3.2)       | 2 (3.2)   | 1 (1.6) (genotip 1b+4) |
| 2013 | -              | 63 (85.1)      | 1 (1.4)        | 2 (2.7)       | 2 (2.7)   | 1 (1.4) (genotip 1b+4) |
| 2014 | 2 (4.4)        | 38 (84.4)      | -              | 1 (2.2)       | 1 (2.2)   | 1 (2.2)   |
| 2015 | -              | 23 (85.2)      | -              | 1 (3.7)       | -         | 27        |
| 2016 | 8 (11.9)       | 52 (77.6)      | 1 (1.5)        | 4 (6.0)       | -         | 67        |
| 2017 | 1 (1.9)        | 48 (90.6)      | 1 (1.9)        | -             | 2 (3.8)   | 1 (1.9) (genotip 1b+3a) |
| 2018 | 1 (1.8)        | 43 (75.4)      | 1 (1.8)        | -             | 7 (12.3)  | 2 (3.5)   |
| 2019 | 1 (1.9)        | 33 (63.5)      | 2 (3.9)        | 1 (1.9)       | 2 (3.9)   | 10 (1.9) |
| Total| 23 (3.4)       | 555 (82.8)     | 11 (1.6)       | 1 (0.2)       | 15 (2.2)  | 30 (4.5)  | 6 (0.9) | 4 (0.6) | 670 |

*Subtyping could not be performed. HCV: Hepatitis C Virus

Genotype 1 was determined in 603 patients (90.0%), genotype 3 in 45 (6.7%), genotype 2 in 12 (1.8%), genotype 4 in six (0.9%), combined genotypes 1 and 3 in two (0.3%), and genotypes 1 and 4 in two (0.3%). Genotypes 5, 6, 7, and 8 were not encountered. The most frequently identified subtypes were genotype 1b (82.8%) and genotype 3a (4.5%). Detailed distributions by years of genotypes and subtypes are shown in Table 2.

The mean age of the 603 patients infected with genotype 1 was 59.72±16.29 years (minimum-maximum: 4-112), compared to 45.26±12.51 years (minimum-maximum: 20-77) for patients infected with other genotypes, and the difference was statistically significant (p<0.001). The distribution of HCV genotypes by age is shown in Table 3. Genotype 1b was detected in 63.2% of the 174 patients aged under 50 and in 59.7% of the 496 patients aged over 50 (p<0.001). While mixed genotypes and genotype 4 were encountered in patients aged ≥50, genotype 3 and its subtypes were more common in patients aged <50 (20.1% of patients <50 compared to 2% of patients ≥50).

Thirty (4.5%) patients were foreign nationals, and these patients’ home countries and genotypes are shown in Table 4. The most common genotype in these patients was 1b (50%) followed by genotype 3 (40%) and genotype 2 (10%).

Discussion

This study adds to the existing literature by determining the distribution of HCV genotypes, an important factor in treatment management, and by evaluating changes in genotype distributions by years in an academic center.

High rates of genotype 1b have been reported in European countries, Israel, and Japan, while genotype 1a has more frequently been reported in North America and Northern Europe (9,10). Similarly to other studies from Turkey, the most frequently identified HCV genotype in all years throughout the present study was genotype 1b (82.8%) (Table 5). HCV genotypes in the study population varied significantly with age. The genotype 1b rate among patients under 50 was significantly lower than that among patients over 50 (p<0.001). This may be due to a decrease with age in infection rates with HCV genotypes other than genotype 1b.

In Europe, HCV genotype infections are reported to be mostly seen in women, and at advanced ages, and to be associated with blood transfusions, dental treatment, and nosocomial infections (11). The risk factors and modes of transmission among the patients infected with HVC in the present study are unknown. However, patients ranged in age between 20 and 64, and no gender difference was observed. Globally, genotype 2 is more common in West Africa in particular, and in some regions of South America (12). This clustering is thought to be associated with migration patterns linked to the transatlantic slave trade (12). The distribution rates of genotype 2 across the world are highly heterogeneous, ranging between 0.1% and 24.5%. In the present study, HCV genotype 2 was detected in 1.8% (12) of patients, a rate higher than that in Central Europe (0.1%), but significantly lower than those in the Asian Pacific (24.5%), West Africa (23%), Western Europe (10.8%), and worldwide (9.1%) (12).

HCV genotype 3 is the second most common genotype worldwide, after genotype 1, and is particularly dominant in South Asian countries (12,13). A proportional increase was determined...
in genotype 3 after 2010 in the present study. The proportion of patients aged under 50 infected with HCV genotype 3 was significantly higher than that of patients aged over 50 (20.1% and 2.0%, respectively, \( p<0.001 \)). It was most frequently observed in the 35-39 age group (30.0%), and the genotype is more common in males. This variation may be due to reciprocal human mobility such as tourism, education, workforce activities, and marriages, in the community comprising the study population.

Medical procedures without the use of protective measures are the basic risk factor for HCV infection in Middle Eastern and North African countries, and genotype 4 predominates in those countries (65.3%) (12). Genotype 4 is the most frequently seen genotype in Syria, at 59.0% (2,3,13,14). Turkey has a long historical relationship with these countries for reasons such as religious pilgrimages, migration, and tourism (2). In the present study, HCV genotype 4 began being detected after 2012, and this may have

### Table 3. Distributions of HCV genotypes by age

| HCV genotypes n (%) | 1' | 1a | 1b | 2' | 2b | 3' | 3a | 4' | Mixed | Total |
|---------------------|----|----|----|----|----|----|----|----|-------|-------|
| **Age range (years)** | 1' | 1a | 1b | 2' | 2b | 3' | 3a | 4' | Mixed | Total |
| 0-4                 |    |    | 1 (100.0) |    |    |    |    |    |       | 1     |
| 5-9                 |    |    |    |    |    |    |    |    |       |       |
| 10-14               |    | 1 (33.3) | 2 (66.7) |    |    |    |    |    |       | 3     |
| 15-19               | 1 (50.0) |    | 1 (50.0) |    |    |    |    |    |       | 3     |
| 20-24               |    | 2 (20.0) | 6 (60.0) |    | 1 (10.0) | 1 (10.0) |    |    |       | 10    |
| 25-29               | 1 (5.0) | 2 (10.0) | 13 (65.0) |    | 3 (15.0) | 1 (5.0) |    |    |       | 20    |
| 30-34               | 3 (15.0) | 1 (5.0) | 8 (40.0) | 2 (10.0) |    | 3 (15.0) | 3 (15.0) |    |       | 20    |
| 35-39               | 3 (10.0) | 2 (6.7) | 15 (50.0) | 1 (3.3) |    | 4 (13.3) | 5 (16.7) |    |       | 30    |
| 40-44               | 1 (2.6) | 2 (5.3) | 26 (88.4) | 2 (5.3) |    | 7 (18.4) |     |    |       | 38    |
| 45-49               |    | 2 (4.0) | 38 (76.0) | 2 (4.0) |    | 6 (12.0) |     |    |       | 50    |
| <50 Total           | 9 (5.2) | 12 (6.9) | 110 (63.2) | 7 (4.0) | 1 (0.6) | 13 (7.5) | 22 (12.6) |    |       | 174   |
| 50-54               | 1 (1.3) | 2 (2.7) | 63 (84.0) | 2 (2.7) |    | 3 (4.0) | 2 (2.7) | 2 (2.7) |     | 75    |
| 55-59               | 1 (1.1) | 2 (2.1) | 85 (90.4) | 1 (1.1) |    | 2 (2.1) | 2 (2.1) | 1 (1.1) |     | 94    |
| 60-64               | 2 (2.1) | 4 (4.2) | 85 (89.5) | 1 (1.1) |    | 1 (1.1) | 1 (1.1) | 1 (1.1) |     | 95    |
| 65-69               | 5 (6.0) | 2 (2.4) | 72 (86.7) |    | 1 (1.2) | 2 (2.4) | 1 (1.2) |     |       | 83    |
| 70-74               | 4 (7.0) | 1 (1.8) | 52 (91.2) |    |    |    |    |    |     | 57    |
| 75-79               | 1 (2.0) | 1 (2.0) | 48 (94.1) |    |    | 1 (2.0) |    |    |     | 51    |
| 80-84               |    |    | 18 (100.0) |    |    |    |    |    |     | 18    |
| 85-89               |    |    | 8 (100.0) |    |    |    |    |    |     | 8     |
| >90                 | 1 (6.7) | 14 (93.3) |    |    |    |    |    |    |     | 15    |
| ≥50 Total           | 14 (2.8) | 13 (2.6) | 445 (89.7) | 4 (0.8) | 0 (0) | 2 (0.4) | 8 (1.6) | 6 (1.2) | 4 (0.8) | 496   |
| Total               | 23 (3.4) | 25 (3.7) | 555 (82.8) | 11 (1.6) | 1 (0.2) | 15 (2.2) | 30 (4.5) | 6 (0.9) | 4 (0.6) | 670 (100.00) |

*Subtyping could not be performed. HCV: Hepatitis C virus

### Table 4. Distribution of HCV genotypes detected in foreign national patients

| HCV genotypes n (%) | 1' | 1a | 1b | 2' | 2b | 3' | 3a | 4' | Mixed | Total |
|---------------------|----|----|----|----|----|----|----|----|-------|-------|
| **Country of origin** | 1' | 1a | 1b | 2' | 2b | 3' | 3a | 4' | Mixed | Total |
| Azerbaijan          |    |    |    |    |    |    |    |    |       | 2     |
| Georgia             |    |    | 12 (60.0) |    | 1 (5.0) | 7 (35.0) |    |    |       | 20    |
| Iraq                |    |    | 1 (50.0) |    | 1 (50.0) |    |    |    |       | 2     |
| Iran                |    |    | 1 (100.0) |    |    |    |    |    |       | 1     |
| Kirgizstan          |    |    |    |    |    |    |    |    | 1 (100.0) | 1     |
| Russia              |    | 1 (50.0) | 1 (50.0) |    |    |    |    |    |       | 2     |
| Tajikistan          |    | 1 (100.0) |    |    |    |    |    |    |       | 1     |
| Ukraine             |    |    |    |    |    |    | 1 (100.0) |    |    |       | 1     |
| Total               |    | 15 (50.0) | 3 (10.0) |    | 4 (13.3) | 8 (26.7) |    |    |       | 30    |

*Subtyping could not be performed. HCV: Hepatitis C virus
been the effect of the arrival in Turkey of refugees from Syria. HCV genotype 4 was reported in as many as 32.0% of chronic hepatitis C in one study, and since the timing coincided with times of labor force migration, the authors thought that it might have been carried by people moving to these areas (2). In the present study, however, genotype 4 was detected in only eight patients, and a more reliable interpretation when the future distribution is revealed.

The detection of HCV genotype co-presence facilitates ideal patient follow-up and increases the effectiveness of antiviral drug therapies (15). In recent years, mixed type HCV genotype reports have been issued more frequently in Turkey (15,16,17). One multicenter study from Turkey determined a mixed genotype prevalence of 1.3% (15). Genotype 1b and 4 was the most frequently seen subtype (3,18). Direct-acting antiviral drug studies are based on genotypes and subtypes (3,18).

The findings of the present study revealed a time-dependent change in the general distribution of HCV genotypes and subtypes, and that HCV genotype 1b was observed at the highest rate across the years, particularly among patients over 50. Since HCV genotypes can be affected by social and cultural diversity, it is essential that the data be updated at specific intervals. In addition, since the HCV is an RNA virus with high genetic variability, no effective vaccine is available. Therapeutic protocols and novel direct-acting antiviral drug studies are based on genotypes and subtypes (3,18).

**Study Limitations**

The limitation of our study is that the absence of information about the transmission routes due to the retrospective design of the study.

**Conclusion**

The findings of the present study revealed a time-dependent change in the general distribution of HCV genotypes and subtypes, and that HCV genotype 1b was observed at the highest rate across the years, particularly among patients over 50. Since HCV genotypes can be affected by social and cultural diversity, it is essential that the data be updated at specific intervals. In addition, determining changes in epidemiological data will serve as a useful guide for the development of vaccines and novel antiviral agents.
Ethics

Ethics Committee Approval: The study was approved by Karadeniz Technical University Faculty of Medicine Faculty Clinical Research Ethical Committee (approval number: 2020/169).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.Ö., C.K.B., F.A., N.K., I.B., İ.T.

Concept: E.Ö., C.K.B., F.A., N.K., I.B., İ.T.

Data Collection or Processing: E.Ö., C.K.B., F.A., N.K., I.B., İ.T.

Literature Search: E.Ö., C.K.B., F.A., N.K., I.B., İ.T.

Writing: E.Ö., C.K.B., N.K., I.B., İ.T.

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References

1. Bouacida L, Suin V, Hutse V, Boudewijns M, Cartuyvels R, Debaies L, De Laere E, Hallin M, Hougardy N, Lagrou K, Oris E, Padalko E, Reynolds M, Roussel G, Senterre JM, Stalpaert M, Ursi D, Vael C, Vaira D, Van Acker J, Verstrepen W, Van Gucht S, Kabamba B, Quoillot S, Muyldermans G. Distribution of HCV genotypes in Belgium from 2006 to 2015. PLoS One. 2018;13:e0207584.

2. Kayman T, Polat C, Ergür G, Abacioglu YH. Characterization of HCV genotype 4d infections in Kayseri, Turkey. Turk J Med Sci. 2015;45:547-552.

3. Salam M, Batarseh R, Natseheh A, Abbadi J, Al-Fraihat E, Yaseen A, Kaddomi D, Khamees N, Mahaffza A, Sahin GO. An update on hepatitis C virus genotype distribution in Jordan: a 12-year retrospective study from a tertiary care teaching hospital in Amman. BMC Infect Dis. 2019;20:3.

4. Spearman CW, Dusheiko GM, Heald M, Sonderup M. Hepatitis C. Lancet. 2019;394:1451-1466.

5. Çekin Y, Gür N, Çekin AH, Altuğlu I, Yazan Sertöz R. Investigation of hepatitis C virus genotype distribution in patients with chronic hepatitis C infections in Antalya Training and Research Hospital, Turkey. Mikrobiyol Bul. 2014;48:484-490.

6. Buruk CK, Bayramoglu G, Reis A, Kalikikkaya N, Tosun I, Aydin F. Determination of hepatitis C virus genomes among hepatitis C patients in Eastern Black Sea Region, Turkey. Mikrobiyol Bul. 2013;47:650-657.

7. Vince A, Židovec Lepej S, Bingulac-Popović J, Miletic M, Kuret S, Sardeleć S, Srakela IB, Kurelec I. Distribution of hepatitis C virus genotypes and subtypes in Croatia: 2008-2015. Cent Eur J Public Health. 2018;26:159-163.

8. Karabulut N, Alacam S, Yolcu A, Onel M, Agacfidan A. Distribution of hepatitis C virus genotypes in Istanbul, Turkey. Indian J Med Microbiol. 2018;36:192-196.

9. Seleke MB, Baylan O, Karagöz E, Özyurt M. Changes in hepatitis C virus genotype distribution in chronic hepatitis C infection patients. Indian J Med Microbiol. 2018;36:416-421.

10. Sağlık I, Mutlu D, Öngut G, İnan D, Oğuzhan, Can Sarınoğlu R, Özak Baysan B, Gütekim M, Çolak D. 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;48:429-437.

11. Petruzzello A, Marigiano S, Loquercio G, Cacciapuoti C. Hepatitis C virus (HCV) genotypes distribution: an epidemiological update in Europe. Infect Agent Cancer. 2016;11:53.

12. Messina JP Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61:77 87.

13. 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(Suppl1):S45-57.

14. Çetin Duran A, Kibar F, Çetiner S, Yaman A. Determination of hepatitis C virus genotype and HCV infection transmission routes in Cukurova University Medical Faculty Hospital. Turk Hij Den Biyol J. 2017;74:201-210.

15. Kulah C, Altindis M, Akyar I, Gokahmetoglu S, Sayiner A, Kaleli I, Fidan I, Altuglu I, Aydin F, Topkaya A, Us T, Findik D, Ozdemir M, Oztürk E, Ulger ST, Karakuyuk T, Cakar Y, Aksaray S, Uzunoglu E, Aktas O, Uslu H, Cetinkiol Y, Gureasir AS, Ege O, Tophan H, Koroglu M, Comert F. The prevalence of mixed genotype infections in turkish patients with hepatitis c: a multicentered assessment. Clin Lab. 2019;65:485-490.

16. Ciril OS, Uzala Mizrakli A, Vurupalmaz Y, Gümrüş HH, Özturhan H, Barış A. Genotyping Distribution of Hepatitis C Virus in Şanlıurfa Province and Effect of Syrian Patients. Viral Hepat J. 2019;25:62-66.

17. Kirdar S, Aydin N, Tiryaki Y, Ertugrul B, Coskun A, Bilgen M. Dynamics of HCV epidemiology in Aydın province of Turkey and the associated factors. APMS. 2018;126:109-113.

18. Çil T, Ozekinci T, Goral V, Altıntaş A. Hepatitis C virus genotypes in the southeast region of Turkey. Turkiye Klinikleri J Med Sci. 2007:27:496-500.

19. Bozdai A, Aslan N, Bozdai G, Türkylmaz AR, Sengür T, Wend U, Erkan O, Aydemir F, Zahirhadjeav S, Orucov S, Bozkaya H, Gerlich W, Karrayülçin S, Yurdadıvin C, Uzunalmılgıç O. Molecular epidemiology of hepatitis B, C and D viruses in Turkish patients. Arch Virol. 2004;149:2115-2129.

20. İba Yılmaz S, Erol S, Özbek A, Parlık M. Distribution of viral genotypes and extrahepatic manifestations in patients with chronic hepatitis C in Eastern Turkey. Turk J Med Sci. 2015;45:70-75.

21. Çelik C, Bakici MZ, Kaygusuz R, Ertürk R. The searching of HCV genotyping distributions in the region of Sivas. Viral Hepat J. 2010;16:106-110.

22. Karslıgil T, Savaş E, Savaş MC. Genotype distribution and 5′UTR nucleotide changes in hepatitis C virus. Balkan Med J. 2011;28:232-236.

23. Öztürk AB, Doğan UB, Öztürk NA, Ozyazici G, Demir M, Akin MS, Böngöl AS, Hepatitis C virus genotypes in Adana and Antalya regions of Turkey. Turk J Med Sci. 2014;44:661-665.

24. Akar T, Aynoğlu A, Dindar G, Babür T. Contribution to determination of hepatitis C virus genotypes in Black Sea region: data from single high volume center in Zonguldak, Turkey. Mikrobiyol Bul. 2014;48:518-520.

25. Tezcan S, Ulger M, Aslan G, Yaraş A, Alttıntaş E, Sezgin O, Ermekdaş G, Gürer Giray B, Sungur MA. Determination of hepatitis C virus genotype distribution in Mersin province, Turkey. Mikrobiyol Bul. 2014;47:332-338.

26. Altuğlu I, Sertos R, Aksoy A, Gürsel D, Tüzün er U, Güncar F Possible transmission risks and genotype distribution of hepatitis C virus infection in Western Turkey. Turk J Gastroenterol. 2013;24:349-355.

27. Caliskan A, Kirisci O, Ozkaya E, Ozden S, Turner S, Catlar S, Guler SA, Senol H. Distribution and predominance of genotype 3 in hepatitis c virus carriers in the province of Kahramanmaras, Turkey. Hepat Mon. 2015;15:e25142.

28. Calign MK, Cetinkol Y. Hepatitis C virus genotype distribution in Ordu province. J Clin Anal Med. 2019;10:372-375.