Research Article

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# *Epidemiological Shift in Hepatitis C Genotypes in Northern Anatolia*

## Kuzey Anadolu'da Hepatit C Genotiplerinin Epidemiyolojik Değişimi

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**ABSTRACT**

**Objectives:** Hepatitis C virus infection (HCV) is an important public health issue with large genetic diversity. Although treatment differences for genotypes have vanished with the discovery of novel drugs, genotyping enables the prediction of clinical outcomes and prevents the spread of HCV in the community by identifying risk factors. The aim of this study was to assess the genotypic changes of HCV in Northern Anatolia, Amasya, Turkey.

**Materials and Methods:** A total of 180 HCV-positive patients were included in the study between 2015 and 2022. HCV genotypes were investigated using real time polymerase chain reaction. Demographic data were obtained from medical records.

**Results:** There was a decrease in the overall incidence of HCV after 2016. A decrease in Genotypes 1 and 1b and an increase in Genotype 3 were recorded over time. The only patient with Genotype 4 detected in 2016 was an immigrant from Syria. The mean age of patients with Genotype 1 was 55.95 and Genotype 3 was 28.75. There were slightly more male patients in the Genotype 3 group and more female patients in the Genotype 1. After a year of treatment with the new regimens, all of the patients achieved viral clearance except two.

**Conclusion:** Despite Genotype 1b's continued dominance, our research showed that there was a shift in the distribution and frequency of HCV in our region, primarily due to emigration. The new treatment regimens decreased the number of patients and improved treatment success.

**Keywords:** Hepatitis C, genotype, epidemiology

**ÖZ**

**Amaç:** Hepatit C virüsü (HCV) enfeksiyonu, geniş genetik çeşitliliğe sahip önemli bir halk sağlığı sorunudur. Yeni pan-genotipik ilaçların keşfiyle, genotipler için tedavi farklılıkları ortadan kalkmış olsa da, genotiplendirme, hastaların klinik seyirlerinin tahmini ve risk faktörlerine yönelik etkin önlemlerin alınması açısından önemini korumaktadır. Bu çalışmanın amacı, Kuzey Anadolu'da yer alan Amasya ilinde HCV'nin genotipik değişimlerini değerlendirmektir.

**Gereç ve Yöntemler:** 2015-2022 yılları arasında toplam 180 HCV ile pozitif hasta çalışmaya dahil edildi. HCV genotipleri gerçek zamanlı polimeraz zincir reaksiyonu ile araştırıldı. Demografik veriler tıbbi kayıtlardan elde edildi.

**Bulgular:** 2016 yılından sonra genel HCV insidansında azalma gözlendi. Zaman içinde Genotip 1 ve 1b'de azalma ve Genotip 3'te artış kaydedildi. 2016 yılında görülen tek Genotip 4 hastası Suriye kökenliydi. Genotip 1 hastalarının yaş ortalaması 55,95, Genotip 3 ise 28,75 idi. Genotip 3 grubunda erkek hasta sayısı, Genotip 1 grubunda ise kadın hasta sayısı fazlaydı. Yeni tedavi protokolleri ile iki hasta haricinde tüm hastalarda viral klirens gözlendi.

**Sonuç:** Genotip 1b ilimizdeki hakimiyetini sürdürmesine rağmen, HCV sıklığında ve genotiplerin dağılımında, öncelikle göç nedenli değişimler olduğunu göstermiştir. Yeni tedavi rejimleri hasta sayısını azaltırken, tedavi başarısını arttırmıştır.

**Anahtar Kelimeler:** Hepatit C, genotip, epidemiyoloji

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## Introduction

Hepatitis C virus (HCV) infection is a serious public health problem that leads to liver cirrhosis, which carries a 1-5% annual risk of hepatocellular cancer, with an estimated 80 (64-103) million viremic people worldwide (1). In our country, the prevalence of HCV infection is estimated to be 1-1.9 percent (2). HCV has a significant genetic diversity including seven virus Genotypes (1-7) in addition to subtypes (a, b, c, etc.) and quasi-species (3). Genotypes 1a, 1b, 2, 3, and 4 cause the majority of infections, whereas Genotypes 5, 6, and 7 are less common or limited to specific geographic locations (4). In studies conducted in our country, the predominant HCV Genotype was 1b (5,6).

Chronic HCV infection was treated with pegylated interferon plus ribavirin and first-generation protease inhibitors depending on the HCV genotype of the patient (7). However, the need for genotype determination for treatment strategies has disappeared with the advent of novel pangenotypic direct-acting agents (DAAs) (8). Nevertheless, genotype determination remains important for epidemiological purposes because it can be influenced by migratory patterns and changes in infection routes (9-11). Although Genotype 1b was widely spread throughout the world after World War II, Genotypes 3 and 4 were spreading with an increasing trend due to intravenous drug use and migratory movements (12-14). In addition, patients with Genotypes 1 and 3 are at risk of hepatocellular cancer development, and they need to be followed up more closely (15,16).

The aim of this study was to determine the molecular epidemiological profile of the HCV in the Northern Anatolian region of Amasya, Turkey, and to establish the changes that occurred over time. In addition, the clinical follow-ups and treatment responses of all HCV-positive patients were analyzed.

## Materials and Methods

A total of 180 chronic Hepatitis C patients who were anti-HCV and HCV-RNA positive and who were tested in Amasya University Sabuncuoğlu Şerefeddin Research and Training Hospital Medical Microbiology Laboratories between January 2015-May 2022 were enrolled in this study. The anti-HCV assay was performed using a chemiluminescent microparticle immunoassay (Abbott, USA). HCV-RNA and genotypes were determined using real-time PCR according to the manufacturer's recommendations (Anatolia Geneworks, Turkey). The demographic data of the patients were reviewed retrospectively using medical records. This study was approved by the Ethics Committee of Amasya University Non-interventional Clinical Studies (approval number: 81, date: 07.07.2022).

## Results

Of the 180 chronic HCV patients, 106 (58.89%) were female and 74 (41.11%) were male. The mean age of the patients was 63.95±16.43. While most patients were in the 61 and over age range (n=106; 58.89%), 15 (8.33%) patients were in the 15-30 age group, 12 (6.67%) patients were in the 31-45 age group, and 31 (17.22%) patients were in the 46-60 age range. Of the 180 chronic HCV patients, 106 (58.89%) were female and 74 (41.11%) were male. During 2015-2022, 93.33% of the patients were in Genotype 1 (88.69% were Genotype 1b), 1.67% were in Genotype 2, 4.44% were in Genotype 3, and 0.06% were in Genotype 4. The genotype distribution according to years is presented in Figure 1. The female-to-male proportion of genotypes was as follows: 7 to 12 for Genotype 1a, 97 to 52 for Genotype 1b, 0 to 3 for Genotype 2, 1 to 7 for Genotype 3, and only 1 female for Genotype 4 (Figure 2). There were 2 immigrants from Syria; one has Genotype 1b and the other 4. The mean age of genotypes was as follows: 55.95 for 1a, 67.62 for 1b, 34.33 for 2, 28.75 for 3, and 40 for 4.

Out of the 180 patients, 71 were initiated on ombitasvir, paritaprevir, ritonavir, and dasabuvir; 37 received sofosbuvir and ledipasvir; 18 received glekaprevir and pibrentasvir, sofosbuvir and ribavirin. 50 were not followed up in our center, and two were not treated due to advanced age. Before treatment, the mean viral copy number was 1487780 international unit (IU)/mL, then decreased to 61408 IU/mL in one month. After 12 months of treatment, all patients were HCV-negative by PCR, except for two. One patient had recurrence after ombitasvir, paritaprevir, ritonavir, and dasabuvir treatment but was successfully treated with glekaprevir and pibrentasvir, and the other could not be treated with sofosbuvir and ribavirin. Thirty-five of the patients had previously used ribavirin and pegyle interpheron but were nonresponsive to treatment. Fifty-two of the patients had cirrhosis, 4 had type 1a, 46 had type 1b, 1 had type 2, and 1 had type 3. Two patients had hepatocellular carcinoma, who had type 1b HCV.

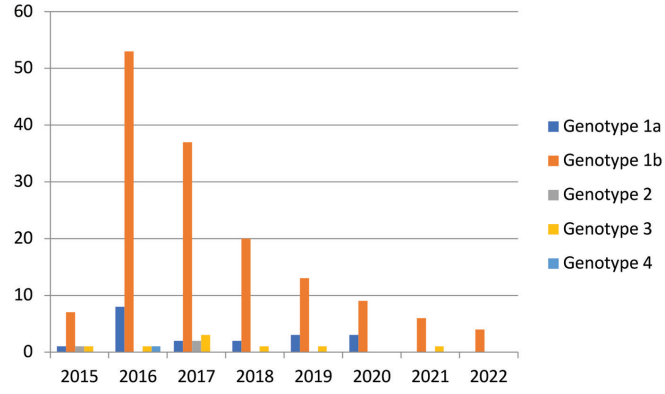


**Figure 1.** HCV genotype distribution according to age
HCV: Hepatitis C virus

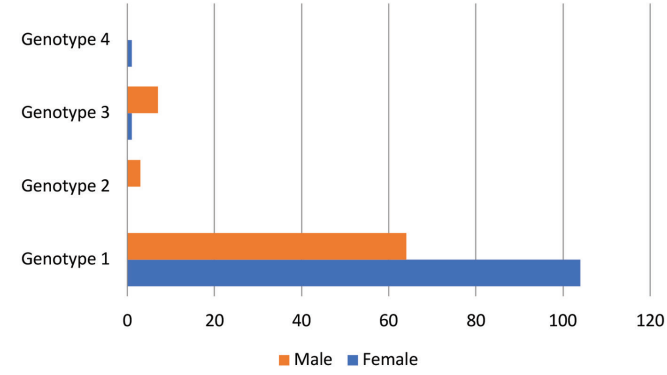


**Figure 2.** HCV genotype distribution according to gender
HCV: Hepatitis C virus

## Discussion

Our research demonstrated an increase in Genotypes 3 and 4 in our region. In a previous report from Amasya, during the 2010-2014 years, 96.34% of the patients were Genotype 1 (69.51% were Genotype 1b), 2.44% were Genotype 2, and 1.22% were Genotype 3 (17). However, during the 2015-2022 years, we found that 93.33% of the patients were Genotype 1 (88.69% were Genotype 1b), 1.67% were Genotype 2, 4.44% were Genotype 3, and 0.06% were Genotype 4. The only patient with Genotype 4 was an immigrant from Syria. According to a Syrian study, Genotype 4 infections are more common in eastern Syria, whereas Genotype 5 infections are more common in northern regions close to Turkey (18). Due to migration movements from the Middle East and Africa, Genotype 4 has become more prevalent and is most prevalent in Central Africa and the Middle East (4). Turkey's Genotype 4 distribution does not exhibit substantial regional variation, with a range of 0.5-3.4%, with Kayseri (32%) having the highest prevalence (19,20). A study from İzmir demonstrated that approximately one-third of patients with Genotype 4 were of Syrian origin (21). In our study, no Genotype 4 was detected until one patient of Syrian origin was found to have Genotype 4 in 2016.

In addition, a decreasing trend was observed in HCV positivity, especially after 2016. This result is also comparable with national and global reports of HCV (22-24). The discovery of novel agents, advent of disinfection and sterilization practices, and improved awareness of risk factors among the community can all cause the decline in HCV prevalence (22). The DAAs have had a high rate of treatment success in Turkey during the past ten years because of their potent antiviral activity, which can block a variety of targets involved in the life cycle of HCV (25). Since medications have become more widely available, more patients are receiving DAA treatment worldwide, particularly in low- and middle-income countries (26). In our study population, all patients except two had achieved complete viral clearance after 12 months of treatment.

Age-based genotype distributions may differ depending on the social structure of the community and the incidence of risk factors in that community among different age groups. According to Niu et al. (27), Genotypes 1 and 2 were more prevalent in patients aged 40-60 years, but Genotype 3 cases were more common in younger patients (27). Different studies have demonstrated that Genotype 1 patients are older than 45 years old (28-30). In Turkey, patients with Genotype 1 are typically aged 50-60 years (31-33). The mean ages of patients with Genotypes 1, 2, and 4 in a study from Maraş were comparable to those in the abovementioned studies. However, Genotype 3 patients had a mean age of 26.4 (34). In our study, patients with Genotype 1 had a mean age of 67.92 years, and those with Genotype 3 had a mean age of 28.75 years, which is concordant with global and national data.

The genotype distribution may differ according to sex. Janahi et al. (35) found that male cases of all genotypes were more common than female case. However, Genotype 3 had the lowest prevalence in female patients. Similarly, Bouacida et al. (36) reported that the prevalence of male cases was greater across all genotypes. Genotypes 1b and 2 were more prevalent in women, according to Kartashev et al. (28), whereas Genotypes 1a, 3, and 4 were more prevalent in men. Our study also demonstrated that female patients had a higher proportion of Genotype 1b patients; however, male patients were of Genotype 3.

## Conclusion

Our research revealed that despite Genotype 1b's continuous dominance, our region's HCV genotype distribution and prevalence are shifting, mostly as a result of migration. Total viral clearance was achieved in all patients, except two patients who received the new treatment protocols after 12 months. Treatment and prevention choices may be improved by tracking the epidemiology of HCV genotypes.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Amasya University Non-interventional Clinical Studies (approval number: 81, date: 07.07.2022).

**Informed Consent:** Informed consents were not obtained due to the retrospective design of the study.

### Authorship Contributions

Surgical and Medical Practices: T.Ü.A., M.A., S.E.A., Concept: T.Ü.A., Design: T.Ü.A., Data Collection or Processing: T.Ü.A., P.O., F.M.S., Analysis or Interpretation: T.Ü.A., P.O., F.M.S., Literature Search: T.Ü.A., Writing: T.Ü.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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