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Original Article

A cross-sectional study of real life data of HCV from Turkey south region

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Abstract

Introduction: This study investigated demographic characteristics and the prevalence of viremia among anti-HCV-positive patients.
Methodology: Hospital records of adult patients with anti-HCV positivity between June 2016 and October 2018 were screened retrospectively. Demographic characteristics, genotype distribution, history of injection drug use (IDU), treatment data of HCV RNA-positive patients were investigated.
Results: The rate of anti-HCV seropositivity was 1.7% and 54.5% of these were viremic. 69.5% of the 869 viremic patients were male. The mean age was 62 ± 15 (18–95) years for women and 42 ± 19 (18-90) years for men ($p < 0.0001$). 42.7% of these patients had IDU history. Regarding age, patients with IDU history accounted for 95% of the 18–29 age group. The most common genotype in patients younger than 40 was genotype 3, and genotype 1b in those older than 40. Only 52% of viremic patients had received DAA therapy. Also, 62.2% of patients aged < 40 and 36% of patients > 40 did not receive treatment ($p < 0.0001$). The SVR12 rate in patients receiving DAA treatment and follow-up was 100%; SVR24 was 99.5%.
Conclusions: A shift in the demographic structure of HCV-infected patients due to the changing trends of the HCV transmission mode was observed in this study. On the other hand, the proportion of patients who received DAA therapy was low. A substantial proportion of untreated patients were young with a history of IDU. This indicates that without strategies targeting the patients, the patient load due to HCV-related cirrhosis and hepatocellular carcinoma may persist in the future.

Key words: hepatitis C virus; genotype; injection drug use; direct-acting antiviral.

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Introduction

It is estimated that approximately 71 million people worldwide are infected with the hepatitis C virus (HCV) and 700,000 people die each year due to cirrhosis or hepatocellular carcinoma (HCC) caused by HCV [1,2]. The seroprevalence of anti-HCV in Turkey is reported to range between 0.6–1.6% [3-5]. HCV infection is responsible for 25% of cirrhosis cases, 25–30% of HCC, and is the second most common cause of liver transplantation in Turkey [6]. In 2016, the World Health Organization (WHO) announced an action plan to eliminate hepatitis B and hepatitis C by the year 2030. This elimination program aims to diagnose 90% of people infected with HCV and treat 80% of diagnosed patients in order to reduce newly infected cases by 90% and hepatitis C-related deaths by 65% by 2030 [7]. In parallel to this call to action from the WHO, in October 2018 the Turkish Ministry of Health announced a national action plan called the "Turkish Viral Hepatitis Prevention and Control Program (2018–2023)" [6]. Although there is no HCV vaccine available yet, it is thought that HCV elimination may now be possible with DAA drugs which have very high treatment success rates. DAA drugs became available in Turkey in June 2016. Although for the short time, there were some restrictions regarding reimbursement, these drugs are now covered by unconditional reimbursement.

This observational cross-sectional retrospective study, initiated simultaneously with the introduction of DAA drugs in Turkey. The study has been conducted to determine the proportion of patients diagnosed with active HCV infection at anti-HCV screening in our hospital and to evaluate the viremic patients' demographic characteristics, genotype distribution, rates of DAA therapy.

Methodology

The HCV RNA results required to confirm active infection following HCV screening were examined retrospectively from the hospital records of adult patients who were anti-HCV-positive at our hospital between June 2016 and October 2018. Patients positive

for HCV RNA were analyzed regarding demographic data, genotype distribution, previous treatment experience, histopathological status, history of injection drug use (IDU), whether they received DAA therapy, end-of-treatment HCV RNA results, and post-treatment sustained virological response (SVR).

Of the viremic patients, who discontinued follow-up after HCV RNA or genotype testing were classified as unfollowed; those who did not attend follow-up after HCV RNA testing following DAA therapy were classified as unfollowed post-treatment; and those who attended follow-up at 12 weeks after completing treatment were classified as followed. Of the followed patients, those with negative HCV RNA results at 12 and 24 weeks were classified as having achieved SVR12 and SVR24, respectively. Patients who were diagnosed with active HCV infection at our hospital yet received treatment and follow-up at other centers were not included in the study.

Regarding to the social security institution reimbursement rules in Turkey, based on categorization of the patients as either treatment-experienced, treatment-naïve, cirrhotic or non-cirrhotic, certain treatment protocols were applied; for instance; for genotype 1b it is one of the following; paritaprevir + ritonavir + ombitasvir + dasabuvir (PROD) 12 week, sofosbuvir + ledipasvir + ribavirin (SL-R) 12 week or sofosbuvir + ledipasvir (SL) 24 week; for genotype 1 and genotype 1a, protocols are consisted of paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin (PROD-R) 12 week, SL 24 week or PROD-R 24 week; also regarding genotype 2 and for genotype 3, protocols are application of sofosbuvir + ribavirin (S-R) 12 week and S-R 24 week respectively; next is the protocol for genotype 4 which includes application of one of the following; paritaprevir + ritonavir + ombitasvir + ribavirin (PRO-R) 12 week, SL-R 12 week or SL 24 week; finally for genotype 5, it is either as SL 24 week or SL-R 12 week.

Anti-HCV testing was performed using the ELISA method on an Architect SR2000i device (Abbott Diagnostics, Wiesbaden, Germany). HCV RNA was measured with the RT-PCR method using Abbott RealTime HCV (Abbott Molecular Inc., Des Plaines, IL, USA) kits. The Abbott RealTime HCV Genotype II (Abbott Molecular Inc., Des Plaines, IL, USA) kit was used for HCV genotyping. The lower limit of HCV RNA detection was 12 IU/mL. Samples with HCV RNA > 500 IU/mL underwent genotyping.

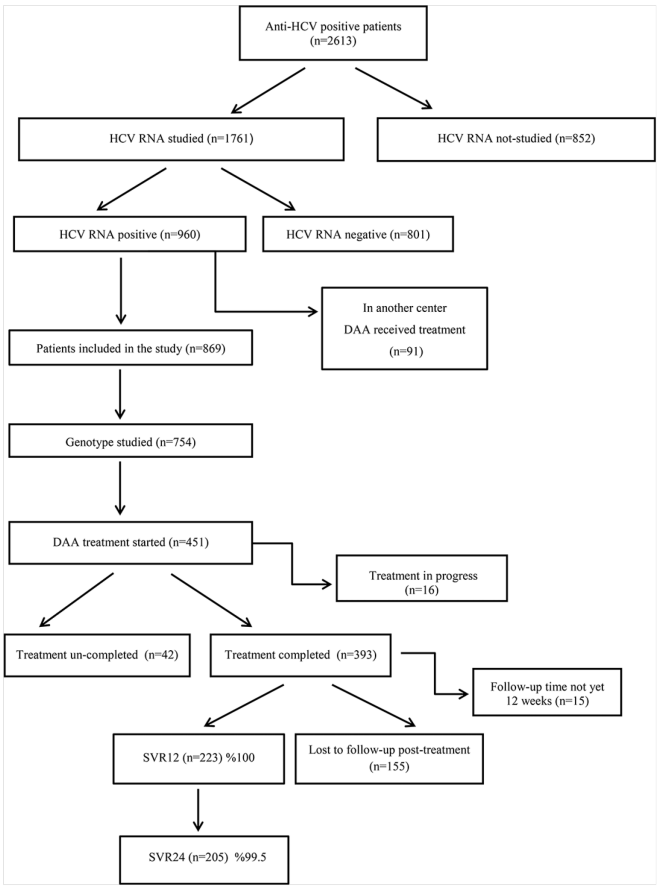
Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Descriptive analyses were presented in terms of percentages, median, minimum, maximum, mean, and standard deviation. The variables were tested using the Kolmogorov–Smirnov test to determine whether they were normally distributed. Student's t-test for continuous variables and chi-square or Fisher's exact test for discrete variables were used between groups for univariate analysis. A p-value less than 0.05 was considered statistically significant.

Results

A total of 146,342 anti-HCV tests were performed in the study period and anti-HCV was positive in 2613 (1.7%) patients. HCV RNA was analyzed in 1761 of these anti-HCV positive patients and was positive in 960 patients (54.5%). Of the 960 patients with active HCV infection, 91 had received DAA therapy at another center. The remaining 869 patients were included in the study (Figure 1).

Of the 869 HCV RNA-positive patients in the study, 604 (69.5%) were male, 265 (30.5%) were female, and the overall mean age was 48 ± 20 (18–95) years. The mean age was 62 ± 15 (18–95) years for the women and 42 ± 19 (18–90) years for the men ($p < 0.0001$).

Figure 1. Chronic HCV infection care cascade among the patients included in the study between June 2016-October 2018.



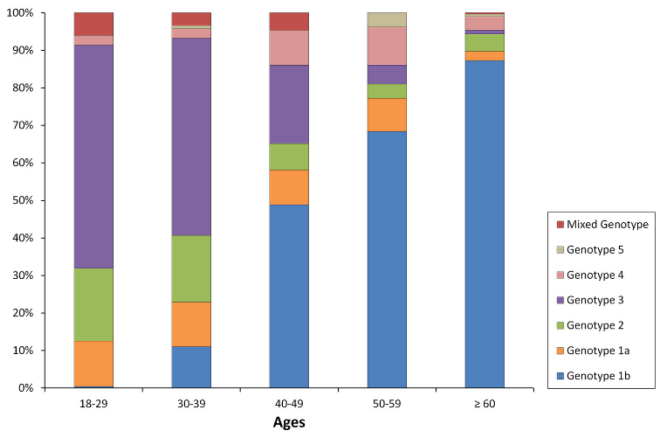
History of IDU was present in 42.7% (371/869) of the patients and 19.2% (167/869) of the patients were prison inmates (94.6% (158/167) of them had a history of IDU). Approximately, 7.8% (65/869) of the patients were Syrian refugees; 3.5% (30/869) had chronic kidney disease (CKD) and were under chronic hemodialysis; finally, 0.6% (5/869) had blood disorders that required frequent blood transfusions.

HCV genotype was determined in 754 patients. In those, genotype 1b was detected in 43.1% (325/754), genotype 3 in 28.6% (216/754), genotype 2 in 11.3% (85/754), genotype 1a in 8% (60/754), genotype 4 in 4.1% (31/754), genotype 1 in 1.3% (10/754), genotype 5 in 0.8% (6/754), and mixed genotype in 2.8% (21/754) patients.

Genotyping analysis by age group yielded the following distribution typing patterns: between 18–29 years: 59.5% (138/232) genotype 3, 19.4% (45/232) genotype 2, and 12.1% (28/232) genotype 1a; 30–39 years: 50% (59/118) genotype 3, 17.8% (21/118) genotype 2, and 11.9% (14/118) genotype 1a; 40–49 years: 41.9% (18/43) genotype 1b, 20.9% (9/43) genotype 3, 9.3% (4/43) genotype 4, and 9.3% (4/43) genotype 1a; 50–59 years: 67.1% (53/79) genotype 1b, 10.1% (8/79) genotype 4, and 8.9% (7/79) genotype 1a; >60 years: 85.1% (240/282) genotype 1b, 4.6% (13/282) genotype 2, and 3.5% (10/282) genotype 4 (Figure 2 and Table 1). Fortythree were genotyped on the 65 patients who were Syrian refugees. Genotype 4 (48.8%), genotype 5 (14%), and genotype 1a (11.6%) were the most common genotypes in these patients.

Of the patients with history of IDU, 97.8% (363/371) were male and 2.2% (8/371) were female ($p < 0.0001$). The mean age of these patients was 29 ± 6 (18–48) years, while the mean age of those without IDU history was 63.9 ± 14 years ($p < 0.0001$). When evaluated based on age range, rates of IDU were 95% (241/254) in the 18–29 year group, 83% (110/133) in the 30–39 year group, and 45% (20/44) in the 40–49 year group. Prison inmates accounted for 40.8% (158/371) of these patients. In the 322 patients with IDU history who underwent genotyping, the distribution was 61.5% (198/322) genotype 3, 20.8% (67/322) genotype 2, 11.2% (36/322) genotype 1a, 5.3% (17/322) mixed genotype, 0.6% (2/322) genotype 1b, and 0.6% (2/322) genotype 4. The genotype distribution of patients with IDU history was significantly different from that of the other patients ($p < 0.0001$) (Figure 3).

Figure 2. The genotype distribution of patients according to age groups.



In terms of previous treatment, 25.5% (222/869) of the patients were treatment-experienced, while 74.5% (647/869) were treatment-naive. Histopathological examination of the liver was performed on 46% (399/869) of the patients. According to histopathological examination, Ishak fibrosis score was 0 in 3% (12/399), 1 in 19.3% (77/399), 2 in 35.8% (143/399), 3 in 13.5% (54/399), 4 in 5.5% (22/399), 5 in 6.3% (25/399), and 6 in 16.5% (66/399) of the patients.

Fifty-two percent (451/869) of patients diagnosed with active HCV infection had received DAA therapy. Thirty-seven percent (167/451) of these patients were

Table 1. The genotype distribution of 754 patients according to age groups (Genotype 1 and genotype 3a have been included in genotype 1b and genotype 3, respectively).

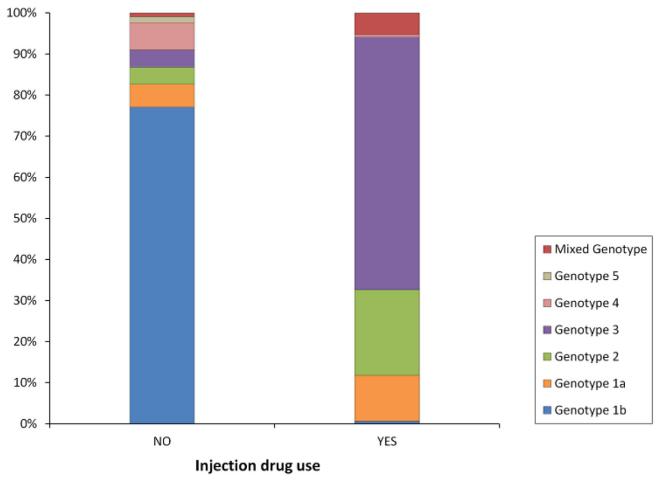
	G 1b (%)	G 1a (%)	G 2 (%)	G 3 (%)	G 4 (%)	G 5 (%)	mixed genotype (%)
18-29 age (232/754)	0.4	12.1	19.4	59.5	2.6	-	6
30-39 age (118/754)	11	11.7	17.8	52.5	2.5	0.8	3.4
40-49 age (43/754)	48.8	9.3	7	20.9	9.3	-	4.6
50-59 age (79/754)	68.3	8.9	3.8	5	10.1	3.8	-
≥ 60 age (282/754)	87.2	2.5	4.6	1	3.5	0.7	0.3

treatment-experienced and 42.3% (130/303) who underwent histopathological examination had an Ishak fibrosis score ≥ 3. Of the treated patients, regimens used were SL 24 week in 143 patients (31.7%), PROD 12 week in 118 (26.2%), S-R 24 week in 97 (21.5%), PROD-R 12 week in 29 (6.4%), S-R 12 week in 33 (7.3%), SL-R 12 week in 23 (5.1%), PRO-R 12 week 7 (1.5%) and PROD-R 24 week in 1 patient. Of the patients prescribed DAA therapy, 84.5% (381/451) completed treatment, 2.7% (12/451) completed treatment with poor treatment compliance, 9.3% (42/451) did not complete treatment, and 3.5% (16/451) were still under treatment. DAA therapy was initiated for 36.6% (136/371) of patients with history of IDU; however only 66.2% of those with the history of IDU (90/136) completed treatment, while 25% (34/136) discontinued the follow-up and therefore did not complete treatment, finally remaining 8.8% (12/136) were still under treatment.

HCV RNA was negative at the end of treatment in all 393 patients who completed DAA therapy. Of these patients, 155 were unfollowed post-treatment, while 15 had not yet completed the post-treatment 12-week follow-up period for SVR. SVR12 was achieved in all 223 patients who were followed after treatment and tested for HCV RNA at 12 weeks. SVR24 was achieved in 204 (99.5%) of the patients who were followed and tested for HCV RNA at 24 weeks, while 1 patient was found to be HCV RNA-positive. Of the 42 patients who did not complete DAA therapy, 16 were lost to follow-up after treatment was planned. Of those who were followed, 15 were HCV RNA-negative and 11 were HCV RNA-positive (Figure 1).

Forty-eight percent (418/869) of the viremic patients did not received DAA therapy. Further evaluation of these patients' characteristics revealed that 56.2% (235/418) had history of IDU (40.4% [95/235] of whom were also prison inmates), 0.9% (4/418) were prisoners with no history of IDU, 10.5% (44/418) were Syrian refugees, 4% (17/418) were CKD patients in a hemodialysis program, and 6% (25/418) were being followed due to malignancy. In terms of genotype, 59% (50/85) of those infected with genotype 2, 57% (124/216) with genotype 3, 45% (27/60) with genotype 1a, 45% (14/31) with genotype 4, and 23% (75/325) of patients infected with genotype 1b did not received DAA therapy. When analyzed regarding age, 62.2% (250/402) of patients under 40 years of age and 36% (168/467) of patients over 40 years of age did not received treatment ($p < 0.0001$).

Figure 3. Genotype distribution of patients amoung IDU and not-IDU.



Discussion

In this study, the seroprevalence of anti-HCV was found to be 1.7%, and 54.5% of patients were viremic. Turkey is among the countries with a moderate HCV prevalence (0.6–1.6%) [3-5]. In a multicenter study based on the year 2013, it was reported that after peaking in 1991, the incidence of HCV infection in Turkey declined gradually with the transition to safe blood transfusion practices and that the number of new cases remained stable due to the low rate of IDU among infected patients [8]. Consistent with this higher incidence before 1992, a higher prevalence of HCV is reported in individuals over the age of 50 [4,8]. In our study, patients aged 18–29 (30%) and > 60 years (38%) comprised the largest proportions of the study group. This finding was notable as a reflection of the changing dynamics of transmission mode for HCV. History of IDU was present in 42.7% of the patients in our study and 95% of those aged 18–29 years. While the younger patient group probably reflected transmission related to IDU, the older patient group reflected the history of transmission associated with unsafe blood transfusion and other medical practices. Moreover, when age and sex were evaluated together, there was a statistically significant sex-based age difference (62 ± 15 vs. 42 ± 19 years for women and men, respectively). Considering that 98% of patients with IDU were male, the fact that female patients were significantly older than males was also associated with the change in virus transmission mode.

It is also reported that the demographic structure and genotype distribution of HCV-infected patients have changed worldwide over the last 20 years. This change is attributed to the shift to IDU as the main mode of HCV transmission that occurred after the widespread use of safe blood and blood products [9]. IDU is the

most important risk factor for HCV infection in the USA and European countries [10]. It is also reported that 39.2% of global injection drug users are infected with HCV, that 8.5% of HCV-infected individuals are injection drug users, and that injection drug users account for 23% of new infections [11]. Our findings are consistent with the literature in terms of reflecting this global change. According to previous studies, the rate of IDU among HCV-infected patients in Turkey varied between 1.3 and 3.1% [12,13]. More recently, a 2016 report by the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) stated that Turkey is among six European countries in which anti-HCV prevalence rose among injection drug users between 2008 and 2014 [14]. The prevalence of anti-HCV among injection drug users in Turkey was reported to be as 28.9% in a publication based on the year 2009, 39.8% according to the 2018 report by the EMCDDA, and 51.9% according to the results of a multicenter national study [15-17].

In our study, genotype 1b was still the dominant genotype (43.1%), followed by genotypes 3 (28.6%) and 2 (11.3%). Compared to previous studies in our region, the relative frequency of genotype 1b decreased while that of genotype 3 increased [18,19]. When analyzed by age, genotype 3 was the most common in the 18–29 and 30–39 age groups, whereas genotype 1b was the most common in patients over 40 years of age. In addition, the difference between the genotype distributions of injection drug users and other patients was statistically significant. Mixed genotype rate was 2.8% in all cohort versus 5.3% incases with history of IDU. This was compatible with the concept that is propably due to reinfections with other genotypes more common in the IDU subgroup [20]. These findings suggest that the distribution of genotypes in our region has changed as a result of IDU-related transmission becoming more predominant in the young patient group. The results of previous studies conducted in this region also provide clues about this genotypic shift [18,19]. Our findings were consistent with literature indicating that genotype 1b is on the decline while genotype 3 is increasing worldwide [9]. Detection of genotype 5, which was not reported previously in Turkey, and the relative increase of genotype 4 in our study were probably due to their presence in the Syrian refugees who were included in our study group [21].

According to our findings, only 52% of patients with active HCV infection received DAA therapy. Furthermore, considering some of the patients who did not complete the diagnostic algorithm after anti-HCV testing may be viremic, and it can be said that the number of untreated patients is even higher. Infected patients who remain undiagnosed or untreated are considered the main obstacle to HCV elimination [22,23]. Modeling studies have shown that WHO goals can only be achieved by increasing anti-HCV screening [24]. However, the results of our study indicate that even a substantial proportion (48%) of diagnosed viremic patients discontinued follow-up and could not be treated. Moreover, the fact that 56.2% of the untreated patients in our study had a history of IDU reflects a serious handicap in terms of controlling transmission in our region due to the risky behaviors of these patients. It is emphasized that injection drug users, who serve as a reservoir for HCV, are one of the barriers to elimination and should be a primary target for treatment [22,25]. Beyond treating the infected individual, antiviral therapy is critical in this patient group in order to break the transmission chain at the social level, which is referred to as "treatment as prevention" [26,27]. Injection drug users are thought to be difficult to treat due to their low treatment compliance and their risk of reinfection during the interferon period. However, clinical studies during the DAA period indicate that treatment compliance improved and SVR rates were also high [28]. In our study, DAA therapy was initiated for only 36.6% of patients with history of IDU, of whom 66.2% completed treatment and 25% discontinued treatment. The results of a meta-analysis showed that rates of loss to follow-up are higher and rates of treatment completion and SVR are lower in observational studies of injection drug users compared to clinical studies, which supports the findings of our study, which is based on real-life data [29]. Establishing an active surveillance network that includes family physicians to help ensure injection drug users continue follow-up and treatment after diagnosis may increase the proportion of patients who are treated. Due to the high prevalence and incidence of HCV among prison inmates, these patients are regarded as another priority patient group for treatment [30]. However, the low treatment rate among prisoners in our study reveals that prison doctors should also play a proactive role in the follow-up and treatment of these patients.

On the other hand, our genotype analysis showed a statistically significant difference between the genotype distributions of treated and untreated patients. Fifty-seven percent of patients infected with genotype 3, 59% of those infected with genotype 2, and 23% of those infected with genotype 1b were untreated. These findings suggest that genotype 2 or 3 may become the dominant genotype in our region in coming years.

Despite the introduction of safe blood transfusion practices, the current HCV-related cirrhosis and HCC patient load consists of patients with past transfusion-transmission. In our study, 36% of patients aged > 40 and 62.2% of patients aged < 40 were untreated. These findings indicate that if the young infected population is not treated, the cirrhosis and HCC patient load will persist in the future. In other words, we can assume that the future patient load with HCV-related complications in our region will be comprised of current HCV-infected injection drug users.

Conclusions

In conclusion, the findings of our study demonstrate a shift in the demographic characteristics of HCV-infected patients in our region, primarily due to the change of trends in the transmission of the virus. Thus, injection drug users should comprise the target patient group in future strategies both to reduce the patient load and to control virus transmission. Although DAA drugs are a definitive treatment and are unconditionally reimbursed in Turkey, the proportions of patients receiving and completing treatment are considerably lower than WHO goals, suggesting that it may not be possible to reach elimination goals. In our opinion, more coordinated work by local health managers, family physicians, prison physicians, drug addiction treatment centers, and specialist physicians in HCV treatment hospitals will contribute to achieving HCV elimination targets.

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