

Original Article

Treatment initiation rates of patients with positive anti-hepatitis C virus results in tertiary hospitals in Turkey

Mustafa K Çelen¹, Buket Ertürk Şengel², Şafak Kaya³, Neşe Demirtürk⁴, Alpay Azap⁵, Hüsnü Pullukçu⁶, Esmâ Eroğlu⁷, Figen Yıldırım⁸, Hüseyin Ş Barut⁹, Esra Zerdali¹⁰, Ayşe Sağmak Tartar¹¹, Ayşe Ö Mete¹², Ahmet M Şahin¹³, Bedia Mutay Suntutur¹⁴, Nagehan D Sarı¹⁵, Emel Yılmaz¹⁶, Aslıhan Candevir¹⁷, Funda Şimşek¹⁸, Dilara İnan¹⁹, Sıla Akhan²⁰, Ali Asan²¹, Özgür Günel²², Onur Ural²³, Mehmet Parlak²⁴, Mehmet Çabalak²⁵, Selçuk Nazik²⁶, Kenan Hızal²⁷, Sami Kınıklı²⁸, Zehra Beştepe Dursun²⁹, Ayşe Batirel³⁰, Çiğdem Mermutluoğlu¹

¹ Department of Infectious Diseases, Dicle University Medical Faculty, Diyarbakır, Turkey

² Department of Infectious Diseases, Pendik Training and Research Hospital, İstanbul, Turkey

³ Department of Infectious Diseases, Sağlık Bilimleri University Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Turkey

⁴ Department of Infectious Diseases, Afyonkarahisar Sağlık Bilimleri University Medical Faculty, Afyonkarahisar, Turkey

⁵ Department of Infectious Diseases and Clinical Microbiology, İbn-i Sina Research and Application Hospital, Ankara University Medical Faculty, Ankara, Turkey

⁶ Department of Infectious Diseases and Clinical Microbiology, Ege University Medical Faculty, İzmir, Turkey

⁷ Department of Infectious Diseases, Konya Meram State Hospital, Konya, Turkey

⁸ Department of Infectious Diseases and Clinical Microbiology, Antalya Training and Research Hospital, Antalya, Turkey

⁹ Department of Infectious Diseases, Gaziosmanpaşa University Research and Application Hospital, Tokat, Turkey

¹⁰ Department of Infectious Diseases and Clinical Microbiology, Haseki Training and Research Hospital, İstanbul, Turkey

¹¹ Department of Infectious Diseases, Fırat University Medical Faculty, Elazığ, Turkey

¹² Department of Infectious Diseases, Gaziantep University Şahinbey Research and Application Hospital, Gaziantep, Turkey

¹³ Department of Infectious Diseases, Giresun University Prof. Dr. A. İlhan Özdemir Training and Research Hospital, Giresun, Turkey

¹⁴ Department of Infectious Diseases, Adana City Training and Research Hospital, Adana, Turkey

¹⁵ Department of Infectious Diseases and Clinical Microbiology, İstanbul Training and Research Hospital, İstanbul, Turkey

¹⁶ Department of Infectious Diseases and Clinical Microbiology, Bursa Uludağ University Medical Faculty, Bursa, Turkey

¹⁷ Department of Infectious Diseases and Clinical Microbiology, Adana Çukurova University Hospital, Adana, Turkey

¹⁸ Department of Infectious Diseases and Clinical Microbiology, Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Turkey

¹⁹ Department of Infectious Diseases, Akdeniz University Hospital, Antalya, Turkey

²⁰ Department of Infectious Diseases and Clinical Microbiology, Kocaeli University Research and Application Hospital, Kocaeli, Turkey

²¹ Department of Infectious Diseases, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey

²² Department of Infectious Diseases and Clinical Microbiology, Sağlık Bilimleri University Samsun Training and Research Hospital, Samsun, Turkey

²³ Department of Infectious Diseases, Selçuk University Medical Faculty, Konya, Turkey

²⁴ Department of Infectious Diseases and Clinical Microbiology, Atatürk University Medical Faculty Hospital, Erzurum, Turkey

²⁵ Department of Infectious Diseases, Mustafa Kemal University Research and Application Hospital, Hatay, Turkey

²⁶ Department of Infectious Diseases, Kahramanmaraş Sütçü İmam University Research and Application Hospital, Kahramanmaraş, Turkey

²⁷ Department of Infectious Diseases, Gazi University Medical Faculty Hospital, Ankara, Turkey

²⁸ Department of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, Ankara, Turkey

²⁹ Department of Infectious Diseases and Clinical Microbiology, Kayseri City Training and Research Hospital, Kayseri, Turkey

³⁰ Department of Infectious Diseases, Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey

Abstract

Introduction: The aim of this national, multicenter, cross-sectional, retrospective chart review study was to determine the proportion of patients in Turkey who received hepatitis C virus (HCV) treatment after receiving positive anti-HCV results during HCV screening.

Methodology: Data related to patients' demographics, laboratory results, time interval from obtaining a positive anti-HCV result to treatment initiation, specialty of the physician requesting anti-HCV screening, and type of hospital were analyzed.

Results: Among 1,000 patients who received a positive anti-HCV result, 50.3% were male and 78.5% were screened for HCV-RNA. Among HCV-RNA screened patients, 54.8% (n = 430) had a positive result. Among patients who tested positive for HCV-RNA, 72.8% received HCV treatment in line with their positive anti-HCV results. The median time from obtaining a positive anti-HCV result to initiation of HCV treatment was 91.0 days (interquartile range 42.0 to 178.5). Non-surgical branches requested HCV-RNA testing more frequently than surgical branches ($p < 0.001$). The rate of access to HCV treatment was higher among patients screened in university hospitals than among patients screened in training and research hospitals ($p < 0.001$).

Conclusions: Our results indicate a higher rate of treatment initiation among patients with HCV infection than is described in the published literature. Furthermore, the time from screening to treatment initiation was considerably shorter compared with other international studies. However, since HCV-RNA testing was not requested in a significant portion of patients with a positive anti-HCV test result, there might be a large patient population with HCV who do not receive treatment.

Key words: Hepatitis C; anti-HCV; screening; treatment; Turkey.

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Introduction

The World Health Organization (WHO) estimated in 2015 that 71 million people globally were living with hepatitis C virus (HCV) infection, accounting for 1% of the world population [1]. HCV infection is unevenly distributed in the world. The European and Eastern Mediterranean regions are affected more, but there are variations in HCV infection prevalence across and within countries [1]. In Turkey, HCV infection prevalence rates range between 0.95% and 2.4% [2-5].

Left untreated, hepatitis B virus (HBV) and HCV infection can lead to cirrhosis (720,000 deaths in 2015) and hepatocellular carcinoma (470,000 deaths in 2015) [1]. These long-term complications are life-threatening and account for 96% of the deaths due to viral hepatitis. Mortality from viral hepatitis has increased by 22% since 2000. Unless people with HBV and HCV infection are diagnosed and treated, the number of deaths due to viral hepatitis will continue to increase. However, currently available direct-acting antiviral (DAA) treatments can prevent these complications depending on the disease stage at which treatment is initiated. However, there are country-based variations in terms of accessibility to the treatments [1].

The virus is mainly acquired via percutaneous exposures to infected blood. Unsafe healthcare

practices (including unsafe healthcare injections) and injection drug use remain the leading modes of transmission [1,6,7].

Areas with a high rate of HCV infection are located in the Eastern Mediterranean Region (62.5 per 100,000) and the European Region (61.8 per 100,000). In the Eastern Mediterranean Region, the most common cause of transmission of HCV infection is unsafe healthcare injections [8,9]. In the European Region, injection drug use accounts for a significant proportion of infection transmission [10].

According to WHO, only 20% of patients living with HCV infection have been diagnosed and are aware of their infection. Among those diagnosed, only 7.4% were receiving treatment in 2015 [1]. Recently, potent oral short-term antiviral treatment options have become available, and the success rate of these treatments in terms of HCV eradication and cure is reaching > 90% [11]. Well-designed screening policies may help to reduce the rate of undiagnosed and untreated patients. Preoperative hepatitis serology testing is regularly conducted in major surgical clinics; however, it cannot be generalized to all regions within the country. Furthermore, information regarding the results of these serology screenings is available only through sporadic reports (mostly reported as single-center reports), and

multicenter study results that would represent Turkey are not available yet. Among patients who receive positive anti-HCV results during preoperative anti-HCV screening, more than half are neither tested further for HCV-RNA nor notified with their HCV-RNA test results [12]. Therefore, most of these patients remain unaware of their HCV infection and do not receive antiviral treatment, which results in an inaccurate and low diagnosis rate of HCV infection.

The diagnosis and treatment policies in Turkey are undergoing improvements. As per the existing protocol [13], the prescription of treatment requires a report from gastroenterology or infectious diseases specialists working at tertiary health institutions. This report includes information such as HCV-RNA positivity, the presence of cirrhosis, Child-Pugh classification of the cirrhosis, genotype in decompensated cirrhotic patients, previous HCV treatment, and the use of NS5A inhibitors in prior treatment. For treatment-naïve or treatment-experienced patients without NS5A inhibitors who are non-cirrhotic or have compensated cirrhosis, the recommended treatments are sofosbuvir/velpatasvir/voxilaprevir or glecaprevir/pibrentasvir. If the patient has decompensated cirrhosis, ledipasvir/sofosbuvir + ribavirin may be prescribed based on the genotype results. In the case of treatment experience with NS5A inhibitors, patients are assessed on an individual basis with aforementioned medications.

In this study, we aimed to determine the rate of patients who received HCV treatment after receiving positive anti-HCV results during HCV screening in Turkey within the last 3 years.

Methodology

This study was designed as a national, non-interventional, observational, multicenter, cross-sectional, retrospective chart review study that included patients screened for anti-HCV.

The study was initiated after obtaining ethics committee approval from Gaziantep University Clinical Research Ethics Committee (reference number 2020/20, 04 November 2020) in conformation with the Declaration of Helsinki, and data collection took place between 24 December 2020 and 22 June 2021. Since this was a retrospective chart review study, obtaining informed consent was not necessary and a waiver of informed consent was obtained from the same ethics committee. A total of 30 tertiary study centers, which were university hospitals or training and research hospitals located in various geographic regions in Turkey, participated in this study. Investigators in the

participating study centers retrospectively reviewed the charts of the patients who had undergone screening for anti-HCV for any reason. Adult (≥ 18 years of age) patients who received a positive anti-HCV result between 30 June 2016 and 30 June 2019 were considered eligible for this study. Laboratory result databases of the participating centers were used as the main data source for this study. All eligible patients were identified in each site from the laboratory database according to the inclusion criteria, and the treatment information was obtained from the patients' charts. Data collection was anonymized, and a code number was assigned to each patient. The investigator or delegated staff entered the available data into the electronic case report form designed for this study.

Patient demographics (e.g., gender, place of residence), laboratory results for HCV screening, including anti-HCV and, where available, HCV-RNA results, the time interval from obtaining a positive anti-HCV result to treatment initiation (if treated), specialty of the physician who requested anti-HCV screening, and type of hospital (university hospital or training and research hospital) were among collected data. In addition, physician specialties were categorized into surgical or non-surgical specialty groups.

To prevent patient selection bias, a patient selection method was defined in the protocol for sites that had a high number of eligible patients. Initially, all patients meeting eligibility criteria were identified at each site in chronological order. If the number of eligible patients in a site exceeded the local limit allowed to enroll per site ($n = 33$), then the total number of eligible patients was divided by 33 to determine the selection factor (i.e., every third or fourth patient). Then the site continued with enrollment starting with the earliest treated patient using this selection factor until the total number of patients allowed per site was reached.

This study was exploratory in nature, and hypothesis testing was not applicable. Therefore, a formal sample size calculation with the estimation of statistical power was not performed. According to available data from Turkey, 30% of the patients who were detected with positive anti-HCV during screening for any reason and who were not screened for HCV-RNA received HCV treatment only after follow-up efforts of the clinical microbiologists [14]. With this assumption, we planned to enroll 1,000 patients, which would provide a two-sided 95% confidence interval rate of 5.6% ($\pm 2.8\%$) for this study. Data were mainly analyzed using descriptive statistics. The normality assumption was determined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Median and

interquartile range (IQR) were reported where a normal distribution was not obtained. The Mann-Whitney U test was used to compare the data of two quantitative groups that did not show normal distribution. Kruskal Wallis test was used to compare the data of three quantitative groups. Fisher's exact test was used for the comparison of two categorical groups. $p < 0.05$ was considered statistically significant. All analyses were performed using the SPSS for Windows, Version 16.0. Chicago, SPSS Inc.

Results

Data from 1,000 patients were included in this retrospective chart review study, and 50.3% of the patients were male. Most patients (82.7%) were residing in cities or towns; only 15.6% were living in rural areas. More than half of the patients ($n = 570$, 57.0%) were included in the study from university hospitals, whereas 43.0% were included from training and research hospitals.

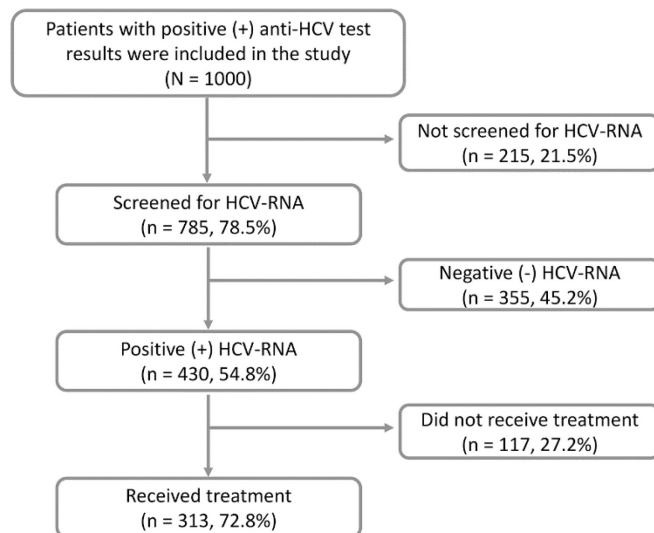
Nearly 70% of the anti-HCV screening requests were made by the non-surgical specialties. Infectious diseases (33.3%) was the specialty that most frequently requested anti-HCV tests in the non-surgical specialty group, followed by gastroenterology (20.9%) and internal medicine (19.8%). On the other hand, general surgery (27.6%) was the specialty that most frequently requested anti-HCV tests in the surgical group.

Among the 1,000 patients who received a positive anti-HCV test result, 78.5% were further screened for HCV-RNA (Figure 1). More patients were admitted to non-surgical versus surgical branches, and non-surgical

branches requested HCV-RNA testing more frequently than surgical branches ($p < 0.001$). HCV-RNA screening rates were similar in university hospitals and training and research hospitals ($p = 0.313$). A statistically significant difference was observed between the ratios of surgical and non-surgical branches requesting anti-HCV screening in different types of hospitals. Non-surgical branches requested anti-HCV screening more frequently in university hospitals, whereas surgical branches requested anti-HCV screening more frequently in training and research hospitals ($p = 0.001$). Among patients screened for HCV-RNA, 54.8% ($n = 430$) had a positive result (Figure 1). The proportion of patients with a positive HCV-RNA result was higher among patients screened by physicians in the non-surgical group ($p = 0.001$). The ratio of patients with positive HCV-RNA results was similar in university hospitals and training and research hospitals ($p = 0.663$).

Among patients testing positive for HCV-RNA, 72.8% (Figure 1) received HCV treatment in line with their positive anti-HCV test result. Considering all eligible patients with a positive anti-HCV test, this percentage corresponded to 31.3%. No statistical difference was detected in terms of access to treatment in patients screened by physicians in the surgical or non-surgical group ($p = 0.051$). Frequencies of screening and treatment of the patients according to the branches and hospital type are presented in Table 1. Patients who received HCV treatment after receiving a positive HCV-RNA result were also evaluated according to the screening departments within the surgical branches and non-surgical branches. Within the surgical branches, 49.0% of the patients who received treatment were screened in the general surgery

Figure 1. Distribution of enrolled patients with positive anti-HCV test results.



HCV: hepatitis C virus.

Table 1. Frequency of screening and treatment of the patients according to the branches and hospital type.

| | N (%) | p value [†] |
|--|------------|----------------------|
| Screening for HCV-RNA | | |
| Surgical branches | 192 (61.5) | < 0.001 |
| Non-surgical branches | 593 (86.2) | |
| Training and research hospitals | 331 (77.0) | 0.313 |
| University hospitals | 454 (79.6) | |
| HCV-RNA positivity | | |
| Surgical branches | 80 (41.7) | < 0.001 |
| Non-surgical branches | 350 (59.0) | |
| Training and research hospitals | 178 (53.8) | 0.663 |
| University hospitals | 252 (55.5) | |
| Receiving HCV treatment in line with positive results | | |
| Surgical branches | 51 (63.8) | 0.051 |
| Non-surgical branches | 262 (74.9) | |
| Training and research hospitals | 103 (57.9) | < 0.001 |
| University hospitals | 210 (83.3) | |

[†] Fisher's exact test; HCV: hepatitis C virus.

department, whereas only 2.0% of the patients who received HCV treatment were screened in the department of ear, nose, and throat surgery. Within the non-surgical branches, 46.2% of the patients receiving HCV treatment were screened in the infectious diseases department. Among patients who had access to HCV treatment, the lowest rate of access to treatment within non-surgical branches was observed in chest diseases, endocrinology, family medicine, and oncology departments. Considering the type of hospital, the rate of access to HCV treatment was higher in patients screened in a university hospital than in patients screened in a training and research hospital ($p < 0.001$).

The median time from obtaining a positive anti-HCV result to initiation of HCV treatment was 91.0 days (IQR 42.0 to 178.5). Time from anti-HCV screening to treatment initiation was categorized according to the physician’s specialty, and no statistical difference was observed in terms of access to HCV treatment among patients who were examined by different specialties ($p = 0.230$). With a similar categorization for patient residence, no statistical difference was observed in terms of access to HCV treatment among patients who were living in different residential categories such as city/town, village/rural area, or closed community areas ($p = 0.250$, Table 2). No statistical difference was detected in terms of time to reach HCV treatment in patients screened by physicians in the surgical or non-surgical group ($p = 0.942$, Table 2). However, the time to reach HCV treatment was shorter in patients screened in university hospitals than in those screened in training and research hospitals (median 70 vs. 98 days, $p = 0.006$, Table 2).

Discussion

In this study, we evaluated the rate of initiation of HCV treatment in patients who received positive anti-HCV results during routine anti-HCV screening for any reason. Among patients with a positive anti-HCV test, 31.3% received HCV treatment. HCV-RNA was tested in 78.5% of patients who had a positive anti-HCV

result; among patients with active HCV infection, 72.8% received treatment for HCV.

HCV infection is one of the most common causes of liver cirrhosis and hepatocellular carcinoma (HCC), which has an insidious course because it is asymptomatic in its early stages, and 60%-80% of the infected cases become chronic. Globally, 27% of cirrhosis cases and 25% of HCC cases are caused by HCV infection [15]. Studies have shown that HCV is the second most common cause of both liver cirrhosis and HCC in Turkey [16,17]. Today, HCV infection is a disease that can be successfully treated. With the use of DAA drugs, the success rate in the treatment of HCV infection has improved tremendously [18]. When the disease is caught at earlier stages, infected patients benefit more from the HCV treatment [19]. Published studies also indicate that HCV eradication with the use of DAA drugs reduces not only hepatic complications but also the risk of cardiovascular disease and has a positive effect on glycemic control [20,21].

The WHO aims to reduce the number of new cases of HCV by 90% and mortality due to HCV by 65% worldwide by 2030 [22]. In general, the group of patients waiting to be treated is much more than those who receive treatment. Studies show that 50%-80% of patients with HCV infection are not diagnosed, and < 20% of those who are diagnosed receive appropriate treatment [23]. Similarly, treatment initiation was reported as 21% in a Danish study conducted in patients with chronic HCV infection [24]. In our study, a higher percentage of patients (31.3%) were able to initiate HCV treatment after obtaining a positive anti-HCV result, which could be due to the high number of patients who were screened and followed up in infectious disease and gastroenterology departments.

A similar retrospective chart review study recently conducted in Mersin, Turkey, included 1,118 patients who tested positive for anti-HCV, among which, 35% were screened in gastroenterology, 37% were screened in infectious diseases, and 28% were screened in other departments. Treatment was initiated in 91% of the

Table 2. Number of days to reach HCV treatment by treatment category.

| Branch type/ geographical region/ type of hospital | n | Mean | SD | Min | Max | Median | Q1-Q3 | p value |
|--|------------------|-------|-------|------|-------|--------|------------|--------------------------|
| All | 313 [†] | 157.8 | 185.3 | 7.0 | 917.0 | 91.0 | 42.0-178.5 | - |
| Surgical branches | 71 | 157.0 | 183.4 | 14.0 | 693.0 | 91.0 | 35.0-175.0 | 0.942 [‡] |
| Non-surgical branches | 242 | 158.0 | 186.3 | 7.0 | 917.0 | 91.0 | 42.0-182.0 | |
| City/town | 265 | 21.6 | 25.8 | 1.0 | 131.0 | 11.0 | 5.00-11.00 | 0.250 [§] |
| Village/rural area | 46 | 27.8 | 30.1 | 2.0 | 99.0 | 16.0 | 6.00-39.00 | |
| Closed community areas | 2 | 27.0 | 25.5 | 9.0 | 45.0 | 27.0 | 9.00 - NA | |
| Training and research hospitals | 110 | 174.4 | 187.3 | 14.0 | 917.0 | 98.0 | 63.0-203.0 | 0.006[‡] |
| University hospitals | 203 | 148.8 | 184.1 | 7.0 | 693.0 | 70.0 | 35.0-161.0 | |

[†]Data were available for 313 patients; [‡]Mann-Whitney U test; [§]Kruskal-Wallis test. HCV: hepatitis C virus; max: maximum; min: minimum; Q1: first quartile; Q3: third quartile; SD: standard deviation.

patients identified in the gastroenterology department [25]. This result shows a high rate of treatment initiation in the gastroenterology department and might be a possible reason for obtaining the high rate of treatment initiation in our study since 37% of our patients were screened in gastroenterology and infectious diseases departments. Gastroenterology and infectious diseases are the primary departments for screening HCV infection in Turkey, and in our study, the overall treatment initiation rate in these two departments is 51.2%.

A recent single-center study conducted in Istanbul, Turkey, investigated treatment responses for chronic HCV infection. Among 1,808 patients with positive anti-HCV results, HCV-RNA was tested in 1,286 (71%) patients, and 23% of the patients ($n = 291$) had positive HCV-RNA results. Among these patients, only 44% ($n = 129$) received treatment for HCV [26]. Results of similar studies conducted in Turkey indicate that HCV-RNA was not investigated in 30%-40% of the patients who had positive anti-HCV results [27,28]. Investigation of HCV screening in a tertiary care hospital in Turkey showed that 95 patients were positive for anti-HCV and that HCV-RNA was not investigated in 47% of these patients [29]. Similarly, the results of another Turkish study showed that HCV-RNA was not tested in 51% of the patients who had positive anti-HCV results [30]. Furthermore, the studies reported higher rates of HCV-RNA negativity, ranging from 70% to 80%, among the patients with positive anti-HCV results [26,27,30]. Results of these studies may suggest that diagnosis and treatment rates of HCV infection are not sufficient in Turkey. In another study by Lee *et al.*, 53.5% of the patients had positive HCV-RNA results, and the authors suggested considering transaminase and albumin levels in conjunction with anti-HCV results to enhance the prediction of HCV infection [31]. In contrast, our study observed a lower rate of HCV-RNA negativity (45%). HCV-RNA negative results with reactive antibody may indicate either a past HCV infection, or a false-positive antibody test. However, due to the lack of enzyme and albumin levels in our study, further investigation is not possible.

We detected higher screening and treatment ratios in our study. In the present study, among 1,000 patients with a positive anti-HCV result, 78.5% were screened for HCV-RNA, 31.3% received HCV treatment, and among patients with active HCV infection, 72.8% received treatment for HCV. Nevertheless, it is crucial to investigate the reasons behind patients missing the screening and treatment. In a recent single-center study, a total of 3,249 patients with positive anti-HCV results

were evaluated, and among the subset of patients who tested positive for HCV-RNA ($n = 899$), only half of them were initiated on treatment [32]. The authors of the study highlighted that treatment failure could be attributed to various patient-related factors, including comorbidities, non-compliance with clinic appointments, or refusal of treatment. Furthermore, inadequate follow-up of test results by physicians and a lack of proper communication to patients regarding their positive results should also be considered. While there have been promising improvements in reimbursement conditions in Turkey, the process of assessing patients and initiating treatment were time-consuming, primarily due to the limited availability of medications in various centers, as well as the reimbursement being conditioned based on genotype results in patients with decompensated cirrhosis.

Another retrospective chart review study conducted in the United States in 2019 included 8,407 individuals with chronic HCV infection [33]. Of these patients, 830 initiated treatments with a DAA agent, whereas 7,577 did not, suggesting a DAA treatment initiation rate of 9.9%. The median time to initiate DAA treatment was reported as 300 days. We detected a higher treatment rate and shorter time to treatment in our study (median 91 days). However, this difference could be due to different healthcare systems present in Turkey and the United States. In the United States, despite the benefits of medicare drug coverage, studies have shown that the patients can experience escalating financial burdens associated with the HCV treatments [34]. While the exact payment figures cannot be determined in Turkey, the coverage of HCV medications through reimbursement may offer an advantage in assessment of the patients. Following categorization of screening hospitals into university or training and research hospitals, we found that the time to treatment was shorter in university hospitals (median 70 days).

Conclusions

In conclusion, our study results indicate a higher rate of treatment initiation among patients with HCV infection compared with the data in most of the published literature. Furthermore, we found that the time from screening to treatment initiation was considerably shorter compared with other international studies. We did not investigate why treatment is initiated earlier in university hospitals than in training and research hospitals since this was not among the objectives of this study. However, further research investigating factors affecting treatment initiation may help to shorten the time to treatment initiation. Despite

these promising results, there might be a considerably large population of patients with HCV who do not receive HCV treatment because further HCV-RNA testing is not requested in a significant portion of patients who test positive for anti-HCV. Raising awareness among healthcare professionals and the general population about HCV screening and treatment options, ensuring that individuals are receiving proper counseling, establishing effective communication channels with patients, and continued improvement of reimbursement policies are key recommendations for the future.

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Author contributions

All authors contributed equally for the design, data collection, analysis, preparation, and review of this manuscript.

References

- World Health Organization (2017) Global hepatitis report 2017. Available: <https://apps.who.int/iris/handle/10665/255016> Accessed: 1 June 2021.
- Örmeci N, Malhan S, Balık İ, Ergör G, Razavi H, Robbins S (2017) Scenarios to manage the hepatitis C disease burden and associated economic impact of treatment in Turkey. *Hepatology* 11: 509-516. doi: 10.1007/s12072-017-9820-3.
- Yildirim M, Çakır S, Geyik MF, Özdemir D, Güçlü E, Çakır M (2014) Seroprevalences and associated risk factors of hepatitis B and C in adults. *Turk J Med Sci* 44: 824-831. doi: 10.3906/sag-1309-25.
- Özer B, Seydaoğlu G, Özşahn AK, Demırhındı H (2012) Risk factors for higher anti-HCV positivity in a border city in southern Turkey with unique population characteristics. *Turk J Gastroenterol* 23: 574-579. doi: 10.4318/tjg.2012.0554.
- Thomas DL, Mahley RW, Badur S, Palaoglu E, Quinn TC (1994) The epidemiology of hepatitis C in Turkey. *Infection* 22: 411-414. doi: 10.1007/BF01715499.
- Chou R, Cottrell EB, Wasson N, Rahman B, Guise JM (2013) Screening for hepatitis C virus infection in adults: a systematic review for the US Preventive Services Task Force. *Ann Intern Med* 158: 101-108. doi: 10.7326/0003-4819-158-2-201301150-00574.
- Yawn BP, Gazzuola L, Wollan PC, Kim WR (2002) Development and maintenance of a community-based hepatitis C registry. *Am J Manag Care* 8: 253-261.
- Mohsen A, Bernier A, LeFouler L, Delarocque-Astagneau E, El-Daly M, El-Kafrawy S, El-Mango S, Abdel-Hamid M, Gadallah M, Esmat G, Mohamed MK, Fontanet A (2015) Hepatitis C virus acquisition among Egyptians: analysis of a 10-year surveillance of acute hepatitis C. *Trop Med Int Health* 20: 89-97. doi: 10.1111/tmi.12410.
- Khan AJ, Luby SP, Fikree F, Karim A, Obaid S, Dellawala S, Mirza S, Malik T, Fisher-Hoch S, McCormick JB (2000) Unsafe injections and the transmission of hepatitis B and C in a periurban community in Pakistan. *Bull World Health Organ* 78: 956-963.
- Mitruka K, Tsertsvadze T, Butsvashvili M, Gamkrelidze A, Sabelashvili P, Adamia E, Chokheli M, Drobeniuc J, Hagan L, Harris AM, Jiqia T, Kasradze A, Ko S, Qerashvili V, Sharvadze L, Tskhomelidze I, Kvaratskhelia V, Morgan J, Ward JW, Averbhoff F (2015) Launch of a nationwide hepatitis C elimination program - Georgia, April 2015. *MMWR Morb Mortal Wkly Rep* 64: 753-757. doi: 10.15585/mmwr.mm6428a2.
- Pham TT, Keast SL, Farmer KC, Thompson DM, Rathbun RC, Nesser NJ, Holderread BP, Skrepnek GH (2018) Sustained virologic response and costs associated with direct-acting antivirals for chronic hepatitis C infection in Oklahoma Medicaid. *J Manag Care Spec Pharm* 24: 664-676. doi: 10.18553/jmcp.2018.24.7.664.
- Yoshioka N, Okumura A, Yamamoto Y, Yamaguchi K, Kaga A, Yamada K, Hirosaki T, Ishikawa D, Kunii S, Watanabe K, Utsunomiya S, Hayashi K, Ishigami M, Goto H, Hirooka Y (2017) Promoting notification and linkage of HBs antigen and anti-HCV antibody-positive patients through hospital alert system. *BMC Infect Dis* 17: 330. doi: 10.1186/s12879-017-2438-1.
- Social Security Institution (2022) Amendments to healthcare implementation communication. Available: <https://www.resmigazete.gov.tr/eskiler/2022/06/20220601-2.pdf>. Accessed: 2 July 2023. [Article in Turkish].
- Gülmez A, Avcu A, Toparlak ÖS, Saymer AA (2017) Re-evaluation of patients who were found positive for anti HCV antibodies and were lost to follow-up with laboratory data. In: 4. National Clinic Microbiology Congress - 2017 Abstract PS-293. Available: https://www.klimud.org/public/uploads/content/files/2017_kongre_kitabi.pdf. Accessed: 1 June 2021. [Abstract in Turkish].
- Alter MJ (2007) Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 13: 2436-2441. doi: 10.3748/wjg.v13.i17.2436.
- İdilman R, Aydoğan M, Oruncu MB, Kartal A, Elhan AH, Ellik Z, Gumussoy M, Er R, Ozercan M, Duman S, Toruner M, Cinar K, Soykan I, Beyler AR, Ozkan H (2021) Natural history of cirrhosis: changing trends in etiology over the years. *Dig Dis* 39: 358-365. doi: 10.1159/000512746.
- Arhan M, Akdoğan M, İbiş M, Kılıç MY, Kaçar S, Tunç B, Şaşmaz N (2009) Data of hepatocellular carcinoma from a single center: a retrospective study. *Akad Gastroenteroloji Derg* 8: 18-23. [Article in Turkish].
- Hézode C (2018) Treatment of hepatitis C: results in real life. *Liver Int* 38 Suppl 1: 21-27. doi: 10.1111/liv.13638.
- Calvaruso V, Craxi A (2020) Hepatic benefits of HCV cure. *J Hepatol* 73: 1548-1556. doi: 10.1016/j.jhep.2020.08.006.

20. Butt AA, Yan P, Shuaib A, Abou-Samra AB, Shaikh OS, Freiberg MS (2019) Direct-acting antiviral therapy for HCV infection is associated with a reduced risk of cardiovascular disease events. *Gastroenterology* 156: 987-996.e8. doi: 10.1053/j.gastro.2018.11.022.
21. Graf C, Welzel T, Bogdanou D, Vermehren J, Beckel A, Bojunga J, Friedrich-Rust M, Dietz J, Kubesch A, Mondorf A, Fischer S, Lutz T, Stoffers P, Herrmann E, Poynard T, Zeuzem S, Dultz G, Mihm U (2020) Hepatitis C clearance by direct-acting antivirals impacts glucose and lipid homeostasis. *J Clin Med* 9: 2702. doi: 10.3390/jcm9092702.
22. Waheed Y, Siddiq M, Jamil Z, Najmi MH (2018) Hepatitis elimination by 2030: progress and challenges. *World J Gastroenterol* 24: 4959-4961. doi: 10.3748/wjg.v24.i44.4959.
23. Denniston MM, Klevens RM, McQuillan GM, Jiles RB (2012) Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: national health and nutrition examination survey 2001-2008. *Hepatology* 55: 1652-1661. doi: 10.1002/hep.25556.
24. Hansen N, Obel N, Christensen PB, Krarup H, Laursen AL, Clausen MR, Lunding S, Møller A, Schlichting P, Kromann-Andersen H, Bukh J, Weis N, DANHEP group (2009) Predictors of antiviral treatment initiation in hepatitis C virus-infected patients: a Danish cohort study. *J Viral Hepat* 16: 659-665. doi: 10.1111/j.1365-2893.2009.01126.x.
25. Akkuzu MZ, Sezgin O, Yaraş S, Özdoğan O, Yılmaz İ, Üçbilek E, Ateş F, Altıntaş E (2019) Patients lost after anti-HCV-positive finding in a tertiary care university hospital: increased awareness and action is necessary to eradicate HCV. *Sisli Etfal Hastan Tip Bul* 53: 366-370. doi: 10.14744/SEMB.2019.46656.
26. Ertürk Şengel B, Başarı T, Tükenmez Tigen E, Sarınoğlu RC, Can B, Sili U, Kortan V (2020) Chronic hepatitis C prevalence, genotype distribution and treatment responses at Marmara University Pendik Training and Research Hospital between 2014-2018. *AnkeDergisi* 34: 13-17. [Article in Turkish]. doi: 10.5222/ankem.2020.013.
27. Düzenli T, Köseoğlu H (2020) Physician awareness of hepatitis C virus among different departments. *Clin Exp Hepatol* 6: 354-358. doi: 10.5114/ceh.2020.102155.
28. Suntur BM, Kaya H, Eker HBŞ, Kara B, Bozok T, Unal N (2020) A cross-sectional study of real-life data of HCV from Turkey south region. *J Infect Dev Ctries* 14: 380-386. doi: 10.3855/jidc.11983.
29. İskender G, Mert D, Çeken S, Bahçecitapar M, Yenigün A, Ertek M (2020) Hepatitis C screening and referral for further investigation and treatment in a tertiary care hospital. *J Infect Dev Ctries* 14: 642-646. doi: 10.3855/jidc.12584.
30. Yiş R, Tosun S, Küpeli H, Demircan F (2020) Do clinicians adequately interpret HCV-RNA results in Anti-HCV-positive samples? An analysis of 10-year data. *Türk Mikrobiyoloji Cemiy Derg* 50: 78-85. [Article in Turkish]. doi: 10.5222/TMCD.2020.078.
31. Lee CH, Shin HP, Lee JI, Joo KR, Cha JM, Jeon JW, Lim JU, Min JK, Kim DH, Kang SW, Joung HJ (2013) Predicting factors of present hepatitis C virus infection among patients positive for the hepatitis C virus antibody. *Clin Mol Hepatol* 19: 376-381. doi: 10.3350/cmh.2013.19.4.376.
32. Türkoğlu E, Parlak Z, Barut HŞ (2022) Assessment of HCV-RNA test results and access rates to antiviral treatment in patients with anti-HCV positivity-a 10-year analysis. *Turk J Med Sci* 52: 1984-1990. doi: 10.55730/1300-0144.5546.
33. Kwo PY, Puenpatom A, Zhang Z, Hui SL, Kelley AA, Muschi D (2019) Initial uptake, time to treatment, and real-world effectiveness of all-oral direct-acting antivirals for hepatitis C virus infection in the United States: a retrospective cohort analysis. *PLoS One* 14: e0218759. doi: 10.1371/journal.pone.0218759.
34. Jung JK, Feldman R, Cheong C, Du P, Leslie D (2016) Coverage for hepatitis C drugs in Medicare Part D. *Am J Manag Care* 22: SP220-226.

Corresponding author

Çiğdem Mermutluoğlu, MD
 Department of Infectious Diseases, Dicle University,
 21280, Sur, Diyarbakır, Turkey.
 Tel: +90 (505) 225 27 00
 Fax: +90 (412) 241 10 00
 Email: cigdemmermut@gmail.com

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has served as a consultant for AbbVie; as a speaker for AbbVie and Gilead; and has received research funding from AbbVie, and Gilead. Özgür Günel has served as a consultant and a speaker for AbbVie, and has received research funding from AbbVie. Onur Ural has received research funding from AbbVie. Mehmet Parlak has received research funding from AbbVie. Mehmet Çabalak has served as a consultant and a speaker for AbbVie, Gilead, MSD, and Pharmactive; and has received research funding from AbbVie. Selçuk Nazik has served as a consultant for AbbVie; as a speaker

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