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Original Article

Hepatitis C screening and referral for further investigation and treatment in a tertiary care hospital

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Abstract

Introduction: Hepatitis C virus infection is a major cause of cirrhosis and liver cancer worldwide. The knowledge of physicians about what should they do in case of any anti-HCV positivity in screening tests is of great importance. In this study the awareness and knowledge of physicians is evaluated by analyzing the rate of the referrals of anti-HCV positive patients to HCV RNA test and their treatment by different clinics.

Methodology: The patients tested for anti-HCV in internal medicine, surgery, gastroenterology and infectious disease clinics between 1 January and 31 December 2017 were evaluated retrospectively in a tertiary care hospital.

Results: Anti-HCV testing was performed in 32,803 patients. Anti-HCV positivity was detected in 95 (0.28%) patients aged 88 years of age or younger (mean 60.89 ± 16.96 years), 57.89% of them were female. HCV RNA was tested in 50 (%52,63) of anti-HCV positive patients and it was found positive in 18 (36%) patients. In anti-HCV positive patients HCV RNA testing was requested most by infectious disease (100%) and gastroenterology (70.58%) clinics and least by surgery and other clinics (21% and 25% respectively). These differences were found to be statistically significant (χ^2=33.65, p < 001).

Conclusions: Our study highlights the significant deficiencies existed in the referring patients with anti-HCV positivity for further examination and treatment by the attending physicians especially in surgical clinics. Performing HCV screening in the different steps of medical care and using electronic reminder systems directing physicians at appropriate diagnostic and treatment protocols can maximize the likelihood of the detection and treatment of HCV- infected patients.

Key words: Hepatitis C; Hepatitis C screening; Hepatitis C treatment.

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Introduction

Hepatitis C virus (HCV) infection is an important public health concern and a major cause of cirrhosis and liver cancer worldwide [1]. It is estimated that at least 71 million people have chronic HCV viremia around the world [2]. HCV is mainly transmitted by blood transfusion, contaminated needles and devices in the medical settings, injection drug use, organ transplantation, or mother-to-infant transmission. Approximately 50–80% of individuals infected with HCV will develop chronic infection [3,4].

HCV infection has low endemicity in Turkey and its rate varies from 0.17% to 2.8%, with the highest rate in the Eastern part of the country. The most of anti-HCV positive patients are HCV RNA positive (> 50%) [4-6]. Chronic HCV infection is the second most common cause of liver transplantation in Turkey [7].

Since there is no vaccine against HCV infection, it can only be controlled by the detection and treatment of as many infected individuals as possible and prevention of transmission. This aim can be achieved by screening and treating especially risk groups that may be main reservoirs for HCV.

The revolution in HCV treatment through the development of direct-acting antivirals (DAAs) with a permanent virological response up to 100% has generated an international interest in the global elimination of the disease. A good tolerability of DAAs makes the broad screening and treatment plan for HCV infection reasonable. In 2017, the World Health Organization (WHO) called for the elimination of HCV and reductions in HCV-associated mortality by 65% and in the rate of new infections by 90% by 2030 [1].

There is no national screening program for HCV infection in Turkey and the routine HCV screening is only performing for pregnant women, the couples to be got married and the patients prior to surgical and endoscopic procedures. In addition, the knowledge level of physicians and healthcare providers about the diagnosis and treatment of HCV is not clear in our country [4]. The majority of chronic infection patients cannot be diagnosed because of the above mentioned limitations in screening.

The purpose of this study is to identify the awareness of physicians about what they should do when anti-HCV screening tests yield positive results by evaluating the rate of the referrals of these patients to HCV RNA test and their treatment by various clinics.

Methodology

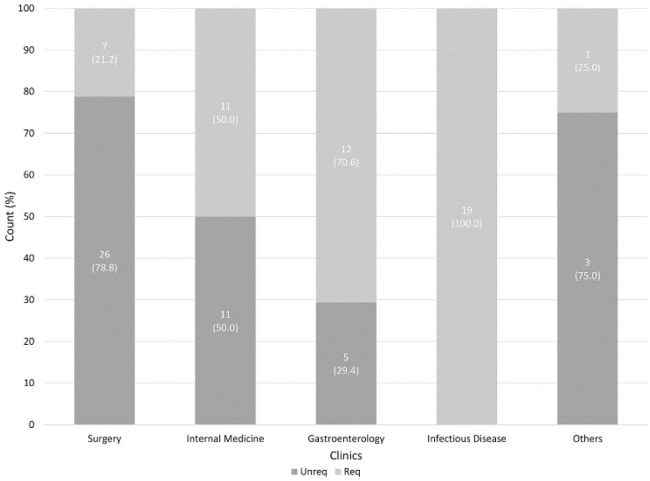
The patients tested for anti-HCV between 1 January and 31 December, 2017 were evaluated retrospectively in a tertiary care hospital (Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital). The patients were tested before surgery or endoscopic procedures or in the presence of risk factors such as intravenous drug use or elevated liver enzymes in internal medicine, surgery, gastroenterology, infectious disease and other clinics. Clinical and laboratory findings of patients were obtained from the electronic recording system of hospital. The patients were evaluated for age, gender, presence of HCV RNA testing and treatment planning for HCV viremic patients. The HCV RNA test can only be requested by infectious disease, gastroenterology or internal medicine clinics in this hospital so the patients who are found to be anti-HCV positive are directed to these clinics for this test and further evaluation

We attempted to reach by phone the patients with positive anti-HCV and without having HCV RNA test result or hepatitis C treatment report in the records of hospital to obtain information about their awareness of the disease and their treatment or follow-up status. Anti-HCV was measured by ELISA-Abbott AXSYM and polymerase chain reaction testing for HCV RNA by QIAGEN multiplex PCR.

Table 1. Clinical and demographical characteristics of study cohort.

Anti-HCV testing requested patients	**n: 32,803 (%100)**
Anti-HCV testing requested patients by clinics	
Surgery	13,020 (39.70%)
Internal medicine	11,383 (34.70%)
Gastroenterology	707 (14.34%)
Infectious disease	2,555 (7.80%)
Others	1,137 (3.46%)
Anti-HCV positive patients	**95 (0.28%)**
Female	55 (57.89%)
Male	45 (47.36%)
Age (years)	60.89 ± 16.96 years
HCV RNA testing requested patients	**50 (52.63%)**
HCV RNA positive patients	18 (18/50:36%)

Figure 1. Frequency of the requesting HCV RNA test in anti-HCV positive patients by clinics.



Statistical analysis

The statistical analyses were performed in SPSS version 21.0 (IBM, Armonk, NY). Descriptive analysis was used to identify the patients with HCV RNA testing. The differences between clinics according to the HCV RNA requested/unrequested patients were established using chi-squared test. A p value < 0.05 was considered significant.

Results

Anti-HCV testing was performed for total of 32,803 patients in the study period, in surgery, internal medicine, gastroenterology, infectious disease and other clinics (Table 1). Anti-HCV positivity was detected in 95 (0.28%) patients; 55 (57.89%) were female and 45 (47.36%) were male. The age range of the patients with anti-HCV positivity was 22 to 88 years with the mean age of 60.89 ± 16.96 years (Table 1).

Among 95 anti-HCV positive patients, HCV RNA was tested for 50 (%52.63) and it was found to be positive in 18 (18/50:36%) patients (Table 1).

For anti-HCV positive patients, the HCV RNA test was requested most by infectious disease (100%) and gastroenterology (70.6%) clinics and least by surgery and other clinics (21.2% and 25% respectively) (Figure 1). The difference between clinics in terms of requesting HCV RNA testing was established using

chi-squared test and was found to be statistically significant ($\chi^2 = 33.65$, $p < .001$).

All HCV RNA positive patients were followed and treated in gastroenterology or infectious disease clinics.

We phoned 45 anti-HCV positive patients for whom there were no hospital records of HCV RNA and among them we could only reach 21 (46.66%) patients. Among 21 patients we found only 5 (23.80%) patients that were aware of their disease (3 of them were being treated in another center and 2 of them had refused the treatment).

The patients that were unaware of their disease or untreated were encouraged to seek further examination and treatment.

Discussion

In this study we evaluated the rate of further investigation in patients who were anti- HCV positive in screening tests performed in different clinics in a tertiary care hospital. Based on the obtained data further investigation and HCV RNA testing were performed only in 52.63% of the anti-HCV positive patients. In this respect most of the patients were neglected by clinics other than infectious disease and gastroenterology.

Chronic viral hepatitis is an important health problem both in the world and in Turkey. Hepatitis B virus (HBV) and HCV virus infections are among the most common causes of advanced chronic liver diseases. HCV accounts for 27% of the cirrhosis cases and 25% of hepatocellular carcinoma (HCC) cases worldwide [3]. An estimated 115 million people are infected by HCV in the World (1.6% global anti-HCV seroprevalence) and approximately 71 million people are at viremic stage [8].

Epidemiological data derived from local studies show that Turkey has a low endemicity for HCV with an estimated rate of 0.17 to 2.8% [6,9]. In the study by Tozun *et al*. that was the largest population based study in Turkey, including 5,460 participants from the rural and urban areas of 23 cities, anti-HCV test was found to give positivity in 1% of all participants. Ages above 50 years was the only risk factor for anti-HCV positivity in this study [5]. In another epidemiological study, anti-HCV positivity was detected more commonly in subjects with the ages above 54 years [10]. According to 2016 data of The Ministry of Health of Turkey, anti-HCV positivity was found to be 3.8% in hemodialysis patients, 1.7% in peritoneal dialysis patients, 1.96% in renal transplantation patients and 7.6% in liver transplant patients [7]. In our study anti-HCV positivity was detected in 0.28% of screened patients with the mean age of 60.89 ± 16.96 years which is consistent with the above mentioned studies.

If the HCV is not treated, the burden of disease and the mortality are expected to increase gradually over the next 20 years. It is estimated that cirrhosis, liver cancer and liver-related deaths due to chronic hepatitis C will be increased by 60-70% in 2030 [11]. With the emergence of DAAs, hepatitis C has become a curable disease. It was shown that DAAs-based therapies result in HCV eradication, improvement of liver function, prevention of cirrhosis and related complications and HCC [12]. Since the acute HCV infection is asymptomatic in 60% – 70% of cases, most patients do not become aware of that they are HCV-infected until the progression of the disease and the emergence of sequelae [13]. According to the WHO 2017 Global hepatitis report the under diagnosis of HCV infection is the major barrier in HCV elimination by 2030. Undiagnosed and untreated patients are the main sources of HCV transmission in the population. This is a tough challenge, and the key factors in controlling and elimination of this disease are implementation of preventive measures, as well as diagnose and treatment of as many infected patients as possible [1,14,15]. For identifying patients with chronic HCV infection, screening with anti-HCV antibody testing followed by PCR test for HCV RNA is accurate [16].

In 2017, the Ministry of Health of Turkey introduced a national action plan to manage the viral hepatitis. Raising awareness and knowledge among the society and healthcare providers about transmission routes and diagnosis and treatment of viral hepatitis is one of the important topics of this action plan [7]. The Clinical Practice Guidelines on recommendations for screening, diagnosing and managing hepatitis C virus were updated this year (2020) by the Turkish Association for the Study of the Liver (TASL) and Viral Hepatitis Society (VHS). These guidelines describe groups that need to be prioritized for screening of HCV infection [17]. The United States Preventive Services Task Force (USPSTF) recommends screening for HCV infection in adults 79 years of age or younger to once in life in the absence of known liver disease and risk factors for HCV infection and periodically in the presence of risk factors (e.g. persons who inject drugs) [18]. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America although recommend routine HCV screening once in life for all persons 18 years and older and in persons younger than 18 years with an increased risk of HCV exposure [19].

Performing successful screening requires the identification and elimination of various barriers to screening and treatment in different populations. The knowledge and awareness about viral hepatitis is inadequate among physicians and society. It is estimated that more than three-fourths (75%) of HCV-infected patients in Turkey are not aware of their disease [5]. We could reach 21 of 45 anti-HCV positive patients without any HCV RNA testing in the hospital records and found that 76.19% of them (16 patients) were not aware of their disease. This is largely related to inadequate knowledge of physicians about further investigations and treatment of patients with anti-HCV positivity and what to do when a patient screening test yields positive result. The screening tests before any invasive procedure are generally used by physicians and health care professionals only to be careful and protect themselves from cutting tool injury during procedures. In our hospital only 52.63% (50 of 95 patients) of anti-HCV positive patients were referred for HCV RNA testing and treatment.

There are attempts toward increase awareness among physicians and patients about HCV screening and treatment. The use of physician-facing electronic medical record (EMR)- based HCV Best Practice Alert (BPA) and different modes of communication with patients such as text messaging can help in this regard [20].

The deficiencies in population screening and the cost of testing are other important factors that affect the detection of HCV-infected patients. Though the overall surveillance and screening of HCV may seem difficult, it can be considered cost-effective when compared to the costs of HCV-related cirrhosis, HCC and liver transplantation [14]. Örmeci *et al.* evaluated the cost-effectiveness of HCV diagnosis and treatment in Turkey. They found that the screening and testing are cost-effective and by implementing the WHO targets scenario, Turkey would be able to reduce HCV prevalence by 80% and the total number of related deaths by < 65% by 2030 [21]. In a 36-months study in Ireland, HBV, HCV and HIV screening was performed in 41,535 patients who underwent phlebotomy in emergency department. Among the patients 5.30% had a positive test result and 12.1% were newly diagnosed with an infection. The rates of newly diagnosed HCV, HBV and HIV positive patients were 8.26%, 2.13% and 1.72%, respectively. The researchers suggest that similar screening programs will help in the detection of new cases of HCV, HBV and HIV and will link them to care [22]. In a large scale screening initiative with the participation of four European countries, HCV infection and linkage to care were evaluated in high risk populations in community addiction, homelessness and prison services (HepCheck). Screening was performed in 2,079 individuals; 397 (19%) active HCV infections were identified and 136 (7% of total sample and 34% of identified active infections) were new cases. They suggest that the elimination of HCV will only be possible with such patient-centered approaches. The HepCheck model provides a template for HCV screening that could be introduced in many countries in accordance with local healthcare systems and resources [23].

DAAs for HCV, including sofosbuvir, ledipasvir/sofosbuvir and a "3D regimen" of paritaprevir (ritonavir boosted), ombitasvir, and dasabuvir were approved in June 2016 by the Turkish Ministry of Health. In Turkey the treatment of HCV RNA positive patients with Ishak fibrosis score of ≥ F3, cirrhosis, and decompensated cirrhosis was covered by the social security from June 2016 to January 2019. In January 2019 liver biopsy requirement was removed from the coverage in order to expand the pool of patients eligible for treatment by DDAs. Thus, it became possible to diagnose and treat a large population infected with HCV.

In conclusion, our study highlights that there are significant deficiencies in the referring patients with anti-HCV positivity for further examination and treatment by the attending physicians. Intensified screening for chronic hepatitis C and increased access to direct-acting antivirals are necessary. Performing HCV screening in the different steps of medical care and using of electronic reminder systems that direct physicians at appropriate diagnostic and treatment protocols can maximize the likelihood of the detection and treatment of HCV-infected patients.

References

1. Terrault NA (2019) Hepatitis C elimination: challenges with under-diagnosis and under-treatment. F1000 Research, 8, F1000 Faculty Rev-54.
2. Polaris Observatory HCV Collaborators: Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study (2017). Lancet Gastroenterol Hepatol 2: 161-76.
3. Alter MJ (2007) Epidemiology of hepatitis C virus infection. World J Gastroenterol 13: 2436-2441.
4. Gürbüz Y (2018) Natural course and clinical presentation in hepatitis C virus infection (Hepatitis C virus enfeksiyonlarında doğal seyir ve klinik). In Güner R, Tabak F editors. Viral Hepatit 2018. Istanbul: Tıp Publisher. 279-291. [Book in Turkish.]
5. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, Kaymakoglu S, Ergonul O (2015) Seroprevalance of hepatitis B and C virus infections and risk factors in Turkey:

a fieldwork TURHEP study. Clin Microbiol Infect 21: 1020-1026.
6. Tosun S (2013) Epidemiology of viral hepatitis in Turkey: a meta-analysis of all published papers. In Tabak F, Tosun S, editors. Viral hepatitis 2013. Istanbul: Tip Publisher. 27–79.
7. Irmak H,Yardim N, Keklik K, Temel F (2019) Turkish Viral Hepatitis Prevention and Control Program 2018-2023, Ministry of Health Ed. No.: 1140, Ankara-2019.
8. Yang RF, Liu Y, Zhao CY, Ding YX, Chen Y, Wang YD, Duan ZP (2019) A novel point-of-care oral anti-HCV assay: Is it reliable for screening hepatitis C virus infection in the era of direct-acting antivirals? PLoS One 14:e0211795.
9. Dayan S, Tekin A, Tekin R, Dal T, Hoşoğlu S, Yazgan UC, Bekçibaşı M, Gül K (2013) HBsAg, anti-HCV, anti HIV ½ and syphilis seroprevalence in healthy volunteer blood donors in southeastern Anatolia. J Infect Dev Ctries 7: 665-669.
10. Thomas DL, Mahley RW, Badur S, Palaoglu E, Quinn TC (1994) The epidemiology of hepatitis C in Turkey. Infection 22: 411–414.
11. Razavi H , Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, Vogel W, Mendes Correa MC, Hézode C, Lázaro P, Akarca U, Aleman S, Balık I, Berg T, Bihl F, Bilodeau M, Blasco A J, Brandão Mello CE, Bruggmann P, Buti M, Calleja JL, Cheinquer H, Christensen P B, Clausen M, Coelho HSM, Cramp ME, Dore GJ, Doss W, Duberg AS, El-Sayed M H, Ergör G, Esmat G, Falconer K, Félix J, Ferraz M LG, Ferreira PR, Frankova S, García-Samaniego J, Gerstoft J, Giria J A, Gonçales Jr FL, Gower E, Gschwantler M, Guimarães Pessôa M, Hindman SJ, Hofer H, Husa P, Kåberg M, Kaita KDE, Kautz A, Kaymakoglu S, Krajden M, Krarup H, Laleman W, Lavanchy D, Marinho RT, Marotta P, Mauss S, Moreno C, Murphy K, Negro F, Nemecek V, Örmeci N, Øvrehus ALH, Parkes J, Pasini K, Peltekian KM, Ramji A, Reis N, Roberts S K, Rosenberg WM, Roudot-Thoraval F, Ryder S D, Sarmento-Castro R, Semela D, Sherman M, Shiha G E, Sievert W, Sperl J, Stärkel P, Stauber R E, Thompson AJ, Urbanek P, Van Damme P, van Thiel I, Van Vlierberghe H, Vandijck D, Wedemeyer H, Weis N, Wiegand J, Yosry A, Zekry A, Cornberg M, Müllhaupt B, Estes C (2014) The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat 21 Suppl 1: 34-59. doi: 10.1111/jvh.12248.
12. Backus LI, Belperio PS, Shahoumian TA, Mole LA (2019) Impact of sustained virologic response with direct-acting antiviral treatment on mortality in patients with advanced liver disease. Hepatology 69: 487-497.
13. Westbrook RH, Dusheiko G (2014) Natural history of hepatitis C.J Hepatol 61: 58–68.
14. Alter HJ, Chisari FY (2019) Is Elimination of Hepatitis B and C a Pipe Dream or Reality? Gastroenterology 156: 294–296.
15. Abou Rached A, Abou Kheir S, Saba J, Assaf S, Kassis G, Sanchez Gonzalez Y, Ethgen O (2018) Hepatitis C in Lebanon: the burden of the disease and the value of comprehensive screening and treatment. J Infect Dev Ctries 12 Suppl 2: 27.
16. Chou R, Clark E, Helfand M (2004) Screening for Hepatitis C Virus Infection: Systematic Evidence Review No. 24. U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality.
17. Bahçecioğlu Hİ, Bektaş A, Bulut C, Günşa Fr, İnan D, Karaosmanoğlu H K, Karasu Z, Kuşçu F, Mete B, Özbakır Ö, Özdoğan O C, Parlak M, Sırmatel F, Topalak Ö, Ünsal B, Viral Hepatitis Guidelines Study Group Turkey (2017) Clinical Practice Guidelines on recommendations for screening diagnosing and managing hepatitis C virus. Turk J Gastroenterol 28 Suppl 2: 90-93.
18. US Preventive Services Task Force. Procedure Manual. Available: https://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual. Accessed 23 January 2020.
19. Ghany MG, Morgan TR (2020) AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American Association for the Study of Liver Diseases–Infectious Diseases Society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology 71: 686-721
20. Fisk R J, Kumar D, Daniel R, Murphy DR, Arya M (2018) Complementing EMR-based Interventions to Improve Hepatitis C Screening. J Transl Intern Med 6: 198-199.
21. 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. Hepatol Int 11: 509-516.
22. Grant C, O'Connell S, Lillis D, Moriarty A, Fitzgerald I, Dalby L, Bannan C, Tuite H, Crowley B, Plunkett P, Kennedy U, McMahon G, McKiernan S, Norris S, Hughes G, Shields D, Bergin C (2020) Opt-out screening for HIV, hepatitis B and hepatitis C: observational study of screening acceptance, yield and treatment outcomes. Emerg Med J 37: 102-105.
23. Barror S, Avramovic G, Oprea C, Surey J, Story A, Macías J, Cullen W, Crowley D, Horan A, Naughton AM, Iglesias M, Ianache I, Lazar S, Popa I, McHugh T, Menezes D, Tinago W, Lambert JS (2019) Hep Care Europe: a service innovation project. HepCheck: enhancing HCV identification and linkage to care for vulnerable populations through intensified outreach screening. A prospective multisite feasibility study. J Antimicrob Chemother74 Suppl 5: v39–v46.

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