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Determination of Confirmation Rate of Anti-HCV Test Pozitivity with HCV-RNA

Anti-HCV Test Pozitifliğinin HCV-RNA ile Doğrulanma Oranının Belirlenmesi

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Abstract

Objective: Timely diagnosis of the disease is important to prevent late complications in hepatitis C infection. Anti-hepatitis C virus (HCV) tests are regularly requested in screening test panels. However, it is seen that even seropositive patients cannot be followed appropriately. In this study, it was aimed to reveal the missed opportunities in terms of diagnosis and treatment of HCV infection in the seropositive patient group detected by screening tests.

Methods: It was investigated retrospectively whether the seropositive patients for HCV were followed up in accordance with the diagnosis of HCV infection protocol in our hospital.

Results: A total of 9.878 anti-HCV tests were studied between November 2016 and February 2019, and 133 Anti-HCV positivity (1.3%) were detected. In total, HCV-RNA test was requested from only 58 (45%) of 129 patients. HCV-RNA was found positive in 12 (20.7%) patients. It was observed that S/CO value was above 10 in 28 (21.7%) of 71 patients in whom HCV-RNA was not wanted, and the probability of virus RNA being positive was high. Infectious diseases consultation was not requested from any of these patients; it was thought that there were missed opportunities for diagnosis of HCV infection.

Conclusion: It will be very important to consult the infectious diseases branch of patients with anti-HCV positive, to organize in-service training seminars for physicians of other specialties, and to provide warnings in case of anti-HCV positivity on the hospital automation system in order to increase awareness and ensure that the patients are followed appropriately.

Keywords: Hepatitis C virus, screening tests, HCV-RNA

Öz

Amaç: Hepatit C enfeksiyonunda geç dönem komplikasyonların önlenmesi için hastalığın zamanında tanısı önemlidir. Tarama test panellerinde anti-hepatit C virüsü (HCV) testleri düzenli istenmektedir. Ancak seropozitif bulunan hastaların bile uygun takip edilemediği görülmektedir. Bu çalışmada tarama testleri ile tespit edilen seropozitif hasta grubunda HCV enfeksiyonunun tanı ve tedavisi açısından kaçırılan fırsatların ortaya konması amaçlanmıştır.

Yöntem: Hastanemizde seropozitif saptanan hastaların HCV tanısı açısından protokole uygun takip edilip edilmediği geriye dönük olarak araştırılmıştır.

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Öz

Bulgular: Kasım 2016 ile Şubat 2019 arasında toplam 9,878 anti-HCV testi incelenmiş ve 133 anti-HCV pozitifliği (%1,3) tespit edilmiştir. Toplamda 129 hastanın sadece 58'inden (%45) HCV-RNA testi istendiği görülmüştür. On iki (%20,7) hastada HCV-RNA pozitif bulunmuştur. Anti-HCV pozitif iken HCV-RNA istenmeyen 71 hastanın 28'inde (%21,7) S/CO değerinin 10'un üzerinde olduğu saptanmış ve virüs RNA'sının pozitif olma olasılığının yüksek olduğu tahmin edilmiştir. Bu hastaların hiçbirinden enfeksiyon hastalıkları konsültasyonu talep edilmediği görülmüş ve bu durumun HCV tanısı açısından kaçırılan fırsat oluşturduğu düşünülmüştür.

Sonuç: Anti-HCV pozitif bulunan hastaların enfeksiyon hastalıkları branşına danışılması, diğer uzmanlık branşları için hizmetiçi eğitim seminerleri düzenlenmesi ve hastane otomasyon sistemi üzerinde anti-HCV pozitiflik durumunda uyarıların çıkmasının sağlanması farkındalık artırarak hastaların uygun şekilde takip edilmesinin sağlanması açısından çok önemli olacaktır.

Anahtar Kelimeler: Hepatit C virüsü, tarama testleri, HCV-RNA

Introduction

Hepatitis C virus (HCV) infection is one of the important causes of liver cirrhosis and hepatocellular carcinoma. It is reported that approximately 185 million people in the world are infected with HCV and more than 70 millions of those patients have chronic hepatitis[1]. The prevalence of HCV infection is reported as 0.6-1.9% in Turkey[2,3].

Enzyme immunoassay or chemiluminescence microparticle immunoassay tests are used for the first step of the diagnosis of hepatitis C. These tests cannot distinguish between acute or past HCV infections. The specificity of these antibody-based tests has increased due to new generation anti-HCV tests include antigens of certain regions of the HCV genome (such as NS3, core and NS4 regions), but it is reported that these tests are not much diagnostic value in countries with low HCV prevalence[3]. Determination of HCV RNA level by nucleic acid tests is necessary for the diagnosis of active infection[4]. Following acute infection, approximately 20% of patients recover and anti-HCV positivity remains as a marker of previous infection. In the remaining patients, chronic liver inflammation continues, and the risk of cirrhosis and hepatocellular carcinoma increases as 1-4% per year[1-3].

In Turkey, anti-HCV test is often requested as a screening test, from people who do not have any specific signs and symptoms, as a part of some processes such as recruiting and marriage procedures, pregnancy follow-ups, and pre-surgical examinations. These tests, whose medical necessity can be discussed, should be well evaluated as an opportunity to detect patients with HCV carriers as long as process continues. However, since most of these tests are requested from physicians other than infectious diseases specialists, it is seen that the positive test results remain without proper consideration or totally unconsidered[5].

Due to the recent availability of effective antiviral therapy, timely diagnosis of patients has become more important to prevent long-term complications. For definitive diagnosis, screening test results should be confirmed by positive HCV-RNA test[2,3,6].

In this study, we aimed to show that there are deficiencies in the follow-up, interpretation and validation of positive anti-HCV test results and that there is a patient group that cannot be referred to treatment.

Materials and Methods

It was investigated that whether anti-HCV seropositive patients were followed up in accordance with the HCV screening protocol of the laboratory of our hospital retrospectively. According to the microbiology laboratory operating procedure in our hospital; in case of anti-HCV (Architect i1000, Abbott, USA) positivity, the test is repeated from the same blood sample. In recurrent reactivity, a new blood sample is requested from the patient and reported in case of third test positivity. In the final report, an annotation is made for the clinician to request a confirmatory test with HCV-RNA. Physician is notified in case of HCV-RNA (COBAS AmpliPrep/COBAS AMPLICOR HCV Test; Roche Diagnostics, Switzerland) result positivity.

In this study, we used the information on the hospital information processing system.

Anti-HCV results are calculated as normalized signal-to-cut-off (S/CO) ratios obtained by measuring the signal strength of sample and the signal strength of an internal cut-off. Samples with an S/CO ratio of ≥1.0 are defined by the manufacturer as positive.

HCV RNA results are reported as IU/mL.

The study was approved by the University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee with the date of 23.08.2019 and decision number 14/6.

Statistical Analysis

Categorical variables are given as percentage distribution. Microsoft Excel and manual statistical formulas were used for analysis.

Results

A total of 9.878 anti-HCV tests were studied between November 2016 and February 2019, and 133 anti-HCV positivity (1.3%) were detected. Four test positivity were excluded from the study due to duplication. In total, it was observed that HCV-RNA has been requested from only 58 (44.9%) of 129 anti-HCV positive patients. HCV-RNA was found positive 12 (20.7%) patients among HCV-RNA tested patients. It was thought that there were many missed opportunities in diagnosis because HCV-RNA tests were not studied from samples with high S/CO values such as above 10 and the probability of virus RNA being positive was high at least in 28 of 71 patients (21.7%). The results are given in Figure 1. It was observed that 90 (69.8%) of the patients were not asked for infection consultation, and patients who did not receive HCV-RNA despite having a high S/CO result were included in this group.

Except for two of the HCV-RNA positive cases, the S/CO value was above 10. One case was determined as 8.36 and the other as 9.08. However, although HCV-RNA was negative in four cases, S/CO was found to be above 10. It was most likely considered as a past infection.

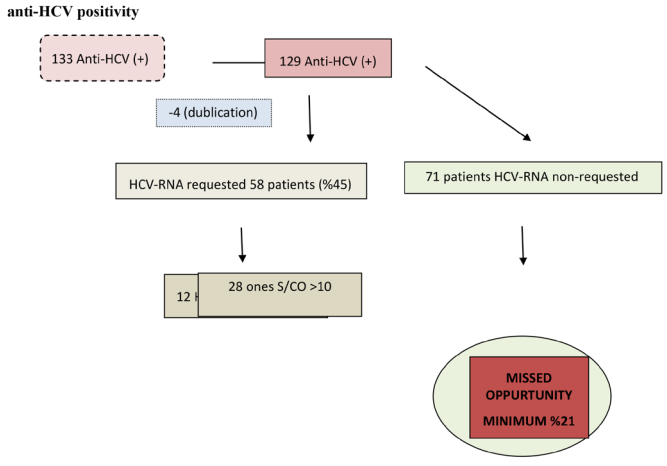

Figure 1. Analysis of patients with anti-HCV positivity
S/CO: Signal-to-cut-off, HCV: Hepatitis C virus

It is seen that infection consultation was requested from only 20 (15%) patients with anti-HCV positivity.

It is seen that anti-HCV positive results were detected in 45 patients at the surgical branches, and 33 (74%) patients did not receive ongoing follow-up and referral. It is observed that the procedure was fully implemented in 19 patients who were followed up in the infectious diseases outpatient clinic. The remaining 65 patients were requested to be tested by the internal branches, and it was observed that 38 (58%) patients were not followed up properly. Although there was a mathematical difference between the internal and surgical branches in terms of directing the patients correctly, it was not statistically significant (p>0.05).

Patients' demographical data and test features were given in Table 1.

Discussion

Anti-HCV screening tests are considered cost-effective in the presence of risk factors in low endemic countries for detection of HCV infection. Major risk factors can be listed as blood transfusion, intravenous drug use, frequent tattooing and acupuncture in the region with high HCV incidence,

Table 1. Some demographical and laboratory features of patients

	Number	Tested for HCV-RNA positive/negative	Non-tested for HCV-RNA
Age	17-82 years (mean 36.78 years)	-	-
Gender	35 female, 94 male	-	-
Internal branches	65	3/24	38
Surgical branches	45	0/12	33
Primary infectious diseases	19	9/10	0
S/CO 1-4	70	0/39	31
S/CO 5-10	17	2/3	12
S/CO >10	42	10/4	28
All S/CO	129	12/46	71

S/CO: Signal-to-cut-off, HCV: Hepatitis C virus

occupational exposure, family history of HCV hepatitis, and having multiple sexual partners[6,7].

In Turkey, according to Ministry of Health Turkey Viral Hepatitis Prevention and Control Program some risk groups were defined such as those who have frequent blood and blood product transfusions, intravenous drug users, haemodialysis patients, having surgery and other interventional procedures. In addition, sexual transmission and from mother to baby it is also among the other modes of transmission[8].

False and/or previous HCV-related positivity that can be encountered in screening tests in people who do not have risk factors cause increased costs and cause concern in patients until confirmation results are obtained. Anti-HCV tests were designed to provide high sensitivity, however in case of S/CO was taken 5 instead of 1, which is the manufacturer's recommendation, will increase the specificity over 95% without significant loss in sensitivity. A study conducted by the manufacturer itself and some other studies support this situation[9-12]. These test results, which currently have high sensitivity but relatively low specificity, therefore require good interpretation, correct orientation and enlightenment of the patient. All our HCV-RNA positive patients had a S/CO index of 8 and above.

In some studies, published in Turkey, their results were consistent with our results. Sarıbaş and Aksoy[13] found that HCV-RNA positivity is not usually associated with results close to the anti-HCV threshold value, and very few samples would require confirmation when the threshold value for the anti-HCV screening test was set as 7.8. Aydın et al.[14] had notified that Anti-HCV S/CO below 7.13, considering the high negative predictive value of this threshold; a false positive result in a patient presenting for screening can be predicted without waiting for the HCV RNA result.

Organizations such as World Health Organization and Centres for Disease Control and Prevention recommend that the anti-HCV result be reported with the recommendation of additional tests by giving the S/CO ratio to guide the clinician[1,9,15].

In fact, the main subject of this study was to underline the importance of sending patients to the relevant specialists in case of test positivity, rather than the low specificity of low S/CO values in the anti-HCV test. In our study indicates that at least 21% of patients have a missed chance of being diagnosed and treatment.

Inadequate follow-up of patients with HCV seropositivity is not seen as a problem unique to Turkey. In a study conducted within the scope of the HCV elimination project in Italy, it was seen that HCV-RNA was not requested from 54% of the patients with anti-HCV positivity in a health centre with similar prevalence results (1.83%), and the patients were recalled. HCV-RNA was requested from 123 patients who returned from 123 patients, and direct-acting antiviral treatment was started in 10 patients (38%) who were found to be positive[16].

In surgical branches, screening tests are generally requested in order to make the surgical personnel feel safe. Almost every study indicated that detecting rate of HCV infection stayed lower than expected[7,17]. In a study conducted in Germany, anti-HCV seropositivity was found in 21 (1.5%) of 1.373 patients undergoing arthroplasty, but it was reported that 7 (33%) of 21 patients were not aware of HCV infection before[18]. Erbay et al.[19] stated that the number of people who did not know that they were anti-HCV positive before the surgical operation was determined as 21 (26.9%) to be quite high. In our study, the anti-HCV screening tests were requested more by the internal branches in our hospital, but the proportional lack of follow-up rate was more in the surgical branches (74% vs. 58%). Based on these results, it was thought that awareness training should be given to surgical branches primarily.

In our study HCV-RNA was negative in four cases, although S/CO was found to be above 10. It was thought as a past infection. Substantially HCV infection cannot be called directly without repeating the HCV RNA test after a certain period. If a negative result is obtained again, it can be merely asserted that there is no active HCV infection. Since the study is retrospective, our cases cannot be evaluated by that means. It can be said that laboratory-clinician approach algorithm application is also important in this respect.

Ministry of Health Turkey Viral Hepatitis Prevention and Control Program recommends eight strategies for struggle of viral hepatitis. First strategy is the increasing the awareness[8]. Hospital automation systems are important in awareness regulations. Toka et al. [20] reported that with the pop-up warnings on the automation system, gastroenterology or infectious diseases consultation of anti-HCV positive patients increased from 5.5% to 22.5%. Sayar et al. [21] indicated that the referral rate to gastroenterologists after the "pop-up" alert system has improved from 61% to 88.6% and patients who received treatment increased from

37.2% to 52.9%. Admission to a specialist as an in-patient or immediately after discharge increased from 21.8% to 54.6%.

Study Limitations

The low number of samples is the main limitation of this study.

Conclusion

It is essential that demanding anti-HCV test should be accurate and rational. Following the requested test results appropriately and guiding the patient correctly are important points. In hospital practise, emphasizing the HCV infection is a treatable infectious disease but early diagnosis and treatment will contribute to the prevention of cirrhosis and liver cancer for the patient, and the formation of new patients in terms of public health. Every patient with anti-HCV positivity is advised to be consulted by the infectious disease's experts. Organizing in-service training seminars for physicians of other specialties, and to provide warnings in case of anti-HCV positivity on the hospital automation system is recommended for increasing awareness and to ensure that the patients are followed appropriately.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee with the date of 23.08.2019 and decision number 14/6.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.Ş., C.B., A.T.G., M.M.D., Concept: G.Ş., F.D., Design: G.Ş., F.D., Data Collection or Processing: G.Ş., M.C., O.K., C.B., A.T.G., M.M.D., Analysis or Interpretation: G.Ş., C.B., A.T.G., M.M.D., Literature Search: G.Ş., M.C., O.K., F.D., Writing: G.Ş., F.D.

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