

The Prevalence and Epidemiological Characteristics of Hepatitis B Virus and Hepatitis C Virus Coinfection in Turkey

Türkiye’de Hepatit B Virüs ve Hepatit C Virüs Koenfeksiyonu Prevalansı ve Epidemiyolojik Özellikleri

Bilgehan AYGEN,^a
Mustafa Kemal ÇELEN,^b
İftihar KÖKSAL,^c
Selma TOSUN,^d
Oğuz KARABAY,^e
Tansu YAMAZHAN,^f
Orhan YILDIZ,^g
Celal AYZAZ,^h
Fehmi TABAKⁱ

^aDepartment of Infectious Diseases and Clinical Microbiology,
Erciyes University Faculty of Medicine, Kayseri,
^bDepartment of Infectious Diseases and Clinical Microbiology,
Dicle University Faculty of Medicine, Diyarbakır
^cDepartment of Infectious Diseases and Clinical Microbiology,
Karadeniz Technical University Faculty of Medicine, Trabzon,
^dClinic of Infectious Diseases,
Manisa Public Care Hospital, Manisa,
^eDepartment of Infectious Diseases and Clinical Microbiology,
Sakarya University Faculty of Medicine, Sakarya,
^fDepartment of Infectious Diseases and Clinical Microbiology,
Ege University Faculty of Medicine, İzmir,
^gDepartment of Infectious Diseases and Clinical Microbiology,
Istanbul University Faculty of Cerrahpaşa Medicine, İstanbul,

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Yazışma Adresi/Correspondence:
Bilgehan AYGEN
Erciyes University Faculty of Medicine,
Department of Infectious Diseases and Clinical Microbiology, Kayseri,
TÜRKİYE/TURKEY
baygen@erciyes.edu.tr

ABSTRACT Objective: We aimed to determine prevalence and epidemiological characteristics of cases coinfecting with hepatitis B virus (HBV)/hepatitis C virus (HCV) in Turkey. **Material and Methods:** The data for this study was obtained from Turk-Hepatitis Registry (HEP-NET) Project, which includes real-life cohort of hepatitis patients from 15 centers in Turkey, and is supported by Viral Hepatitis Society. In the project, 10,165 hepatitis cases were evaluated in 10 hospitals. **Results:** According to initial visit results, HBV/HCV coinfection was detected in 99 patients. The ratio was 974/100 000. The mean age of the cases was 40.9±21.7 years, 56.6% of them were males and 43.4% were females. The major risk factors were dental therapy, any surgical procedure, hemodialysis and blood transfusion. The mean alanine aminotransferase (ALT) levels were 70.9±49.1 IU/L in coinfecting patients. In 12% of cases HBeAg was positive. The median HCV RNA level was found 0 IU/mL (minimum: 50-maximum: 2.18x10⁷ IU/mL), and the median HBV DNA level was found 2.50x10² IU/mL (minimum: 12-maximum: 1.70x10⁸ IU/mL). In 8.1% of the patients both HCV RNA and HBV DNA were positive, and in 87.5% of cases HCV infection was dominant. The most important risk factor was hemodialysis (25%) in this group. **Conclusion:** This is the most detailed study which evaluates the prevalence of HBV/HCV coinfection in Turkey. HBV/HCV coinfection prevalence was not higher than HBV or HCV mono-infections. In cases where both HCV RNA and HBV DNA were positive, HCV was predominant.

Key Words: Hepatitis B; hepatitis C; coinfection; epidemiology

ÖZET Amaç: Türkiye’de hepatit B virüs (HBV)/hepatit C virüs (HCV) koenfekte hasta sıklığını ve koenfekte olguların epidemiyolojik özelliklerini araştırmayı amaçladık. **Gereç ve Yöntemler:** Veriler Türk Hepatit Kayıt Çalışması (HEP-NET) Projesi’nden elde edildi. Proje Viral Hepatitle Savaşım Derneği tarafından desteklenmektedir ve Türkiye’de 15 merkezde hepatitli hastaların gerçek yaşam kohortu yapılmaktadır. Proje kapsamında toplam 10 hastaneye ait 10 165 hepatit hastası tarandı. **Bulgular:** Hastaların ilk vizit sonuçları değerlendirildiğinde, 99 hastada HBV/HCV koenfeksiyonu saptandı. Oran 974/100 000 olarak bulundu. Olguların %56,6’sı erkek, %43,4’ü kadın olup, yaş ortalamaları 40,9±21,7 yıl idi. En önemli risk faktörleri diş tedavisi, cerrahi girişim, hemodiyaliz uygulaması ve kan transfüzyonu olarak saptandı. Koenfekte hastalarda alanin aminotransferaz (ALT) değerleri ortalaması 70,9±49,1 IU/L bulundu. Olguların %12’sinde HBeAg pozitifliği vardı. HCV RNA düzeyleri ortancası 0 IU/mL (minimum: 50-maksimum: 2,18x10⁷ IU/mL), ve HBV DNA düzeyleri ortancası 2,50x10² IU/mL (minimum: 12-maksimum: 1,70x10⁸ IU/mL) bulundu. Olguların %8,1’inde hem HCV-RNA hem de HBV-DNA pozitifliği vardı ve bu vakaların %87,5’inde HCV enfeksiyonu baskındı. Bu gruptaki en önemli risk faktörü hemodiyaliz (%25) olarak bulundu. **Sonuç:** Bu çalışma ülkemizde HBV/HCV koenfeksiyon sıklığını araştıran en kapsamlı çalışmadır. HBV/HCV koenfeksiyon oranı HBV veya HCV monoenfeksiyon oranlarından yüksek değildir. HCV RNA ve HBV DNA’nın birlikte pozitif olduğu hastalarda HCV enfeksiyonu baskın bulundu.

Anahtar Kelimeler: Hepatit B; hepatit C; koenfeksiyon; epidemiyoloji

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Hepatitis B virus (HBV) and hepatitis C (HCV) virus infections are among the most common causes of advanced chronic liver disease worldwide. Patients coinfecting with HBV and HCV have faster fibrosis, higher rates of progression, more severe liver disease, and are at markedly increased risk of developing hepatocellular carcinoma (HCC) as compared to those with HBV or HCV mono-infection.¹⁻³ The pathophysiology of HBV/HCV is complex, since different patterns of virological dominance may occur, which can even fluctuate over time.⁴⁻⁸

Although HBV/HCV coinfection is not uncommon, its epidemiology is poorly defined.^{5,9} An estimated 7-20 million individuals are affected worldwide.⁴ According to study reports, approximately 5-7% of HBV-infected patients also were positive for anti-HCV, and 2-10% of chronic hepatitis C (CHC) patients were positive for HBsAg.^{5,10} HBV and HCV coinfection is overwhelmingly common in several high risk populations, including intravenous drug users, patients on hemodialysis, recipients of organ transplantations, and human immunodeficiency virus positive patients.⁵ In endemic areas, however, the incidence of coinfection provides the basis for an appreciable rate of HBV and HCV co-infection in the general population.¹⁰ Dual chronic infection with HBV and HCV is common in areas endemic for either virus. HCV superinfection in patients with chronic HBV infection was the most common clinical features of coinfection in Asia-Pacific countries.⁵

This retrospective, multicenter study aimed to investigate the epidemiological characteristics of coinfecting patients with HBV/HCV in Turkey.

MATERIAL AND METHODS

The data for this study has come from Turk-Hepatitis Registry (HEP-NET) Project. The project includes real-life cohort of hepatitis patients from 15 centers in Turkey, and is supported by Viral Hepatitis Society. In the study, 10,165 hepatitis cases were evaluated in 10 hospitals. This study included patients followed up between 1998-2011 with records kept regularly. The HBV and HCV coin-

fection patients were diagnosed with serum HBsAg, and antibodies to HCV-positive and detectable serum HCV RNA and/or HBV DNA and compensated liver disease. Data were collected using case records from the doctors in charge of the hospitals involved, baseline epidemiological and virological characteristics were obtained by retrospective review of medical records. Demographic data regarding the participants were the year of diagnosis, possible transmission routes of viruses, alanine aminotransferase (ALT) levels, markers of hepatitis, results of HCV RNA and HBV DNA. The epidemiological and virological data of patients coinfecting with HBV and HCV were analyzed.

Laboratory tests were performed at each individual hospital. ALT tests were performed with automatic devices and techniques. Serological markers (anti-HCV, HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc) have been tested with different enzyme immunoassay kits. HBV DNA and HCV RNA have been investigated by using real-time polymerase chain reaction (RT-PCR) with different kits. All the results were converted to IU/mL.

The SPSS (version 16.0) software package was used to perform statistical analysis. The data were expressed as means and standard deviations, or as minimum-maximum and median. Statistical analysis was performed with Mann-Whitney test. P-values less than 0.05 were considered as statistically significant.

Ethical approval was obtained from the ethical committee of the coordinating center (Date: October 04, 2010 and Number: 16341). Local ethical committees were informed. Patients' informed written consents were also obtained.

RESULTS

Of the data evaluated came from 10 centers: nine were academic hospitals, and one was a public care hospital located in five different geographical regions. According to the first visit results, HBV/HCV coinfection was detected in 99 patients. The ratio was 974/100 000. The mean age of the patients was 40.9±21.7 years, and 43.4% were fe-

males. The distribution of coinfecting cases were; 34.3% in Central Anatolian Region, 31.3% in Southeastern Region, 19.2% in Black Sea Region, 10.1% Aegean Region, and 5.1% Marmara Region. The diagnosis was made in 8% during general health control, in 5% during blood donation, in 4% during military service, in 2% during pregnancy. The major risk factors were dental therapy, any surgical procedure, hemodialysis, and blood transfusion. Patients' characteristics are summarized in Table 1.

The mean ALT levels were 70.9 ± 49.1 IU/L. HBeAg was positive in 12% of the patients. Of the patients with coinfection, 43 (43.4%) were HCV

RNA positive, 56 (56.6%) were HBV DNA positive. HCV RNA levels were between $50-2.18 \times 10^7$ IU/mL and the median HCV RNA level was found 0 IU/mL. Of 43 patients, 24 (55.8%) had HCV RNA level below 600 000 IU/mL. HBV DNA levels were between $12-1.70 \times 10^8$ IU/mL and the median HBV DNA level was found 2.50×10^2 IU/mL. Twenty-two of the 56 patients (39.3%) had HBV DNA levels less than 2.000 IU/mL.

In 8.1% (eight patients) of the patients both HCV RNA and HBV DNA were positive and in 87.5% of cases HCV infection was dominant. In HCV RNA and HBV DNA-positive group, three patients had high ALT levels. HCV RNA levels were in the range of $50-2.40 \times 10^6$ (median 3.95×10^5) IU/mL in eight patients. HBV DNA levels were $12-5.19 \times 10^4$ (median 1.31×10^3) IU/mL in these patients. In one patient, HBV DNA level was 12.271 IU/mL with low level of HCV RNA (50 IU/mL). In two of eight cases (25%) the most important risk factor was hemodialysis. Serum HCV RNA levels were compared between patients with and without detectable serum HBV DNA. HCV RNA levels were lower in the patients with detectable HBV DNA (median: 3.95×10^5) compared to the patients without detectable HBV DNA (minimum: 0-maximum: 2.97×10^7 , median: 0). There was a statistically significant difference ($p=0.0059$).

TABLE 1: Characteristics of 99 patients coinfecting with hepatitis B virus/hepatitis C virus.	
The mean age, years*	40.9±21.7
Sex, female/ male n (%)	43 (43.4)/ 56 (56.6)
Distribution of patients n (%)	
Central Anatolian Region	34.3
Southeastern Region	31.3
Black Sea Region	19.2
Aegean Region	10.1
Marmara Region	5.1
Risk factors n (%)	
Surgical procedure+dental therapy	20 (20.2)
Dental therapy	15 (15.2)
Surgical procedure	14 (14.1)
Hemodialysis	6 (6.1)
Blood transfusion	5 (5.1)
Surgical procedure+ blood transfusion	2 (2.0)
Dental therapy+blood transfusion	2 (2.0)
Surgical procedure+dental therapy+blood transfusion	1 (1.0)
Not found	34 (34.3)
Mean ALT level, IU/L*	70.9±49.1
Virological characteristics	
HCV RNA positivity n (%)	43 (43.4%)
Median (minimum-maximum)	0 (50-2.18x10 ⁷)
HCV RNA level, IU/mL	
HBV DNA positivity n (%)	56 (56.6%)
Median	2.50x10 ²
(minimum-maximum)	(12-1.70x10 ⁸)
HBV DNA level, IU/mL	
HBV DNA and HCV RNA positivity n (%)	8 (8.1)

*Mean±standard deviation

ALT: Alanine aminotransferase.

DISCUSSION

Because of the shared modes of transmission, HBV/HCV coinfection is not uncommon in highly endemic areas and among subjects with a high risk parenteral infection.^{5,11} The worldwide prevalence of HBV/HCV coinfection is unknown.^{4,5,9,12} A rate of dual infection in 0.68% of a randomly selected healthy population of over 2200 individuals was found in one Eastern European study.¹³ In patients with chronic hepatitis B (CHB), the rates of HCV co-infection are in the 9 to 30% range, depending on the geographic region.¹⁴ One Italian study found that rates of dual infection increased with age, and was more common in patients over 50 years of age.¹⁵ These numbers may underestimate the true number of patients with both viral infections because no large-scale studies have been performed,

and there is a well-described phenomenon of “serologically silent” occult HBV infection in patients with CHC.¹⁶ Data related to HCV-HBV coinfection are lacking in Turkey. In our study, coinfection ratio was found 974/100 000. These results show that HBV/HCV coinfection prevalence is not higher than HBV or HCV mono-infections.

Frequently co-infected with HBV and HCV are certain high risk patients, such as intravenous drug users, patients on hemodialysis, patients with human immunodeficiency virus infection, and recipients of organ transplants.¹⁷ In the areas of high prevalence of HBV infection, HCV super-infection in individuals with CHB is the most common type of HBV and HCV co-infection.^{5,18} In this study, the risk factors were dental therapy, surgical procedure, hemodialysis and blood transfusion, which may reflect some difference in the epidemiology between other countries. Zhang et al. reported that the clinical characteristics of patients with HBV/HCV coinfection were significantly different among different HCV contamination modes.¹⁹

Epidemiological studies on viral interaction have not been consistent. Some reported no interaction, others reported a sub/supra-additive or a multiplicative interaction.²⁰ Additionally, most, but not all, clinical observations suggested that interference between the two viruses was mostly characterized by an inhibition of HBV replication exerted by HCV. However, longitudinal follow-up studies have demonstrated that the virological patterns in coinfection cases are widely divergent and have dynamic profiles over time.⁵ The case report of profound suppression of CHC after super-infection with HBV and establishment of CHB has been published by Coffin et al.⁷ It is hypothesized that HBV infection precipitated generalized and/or virus-specific cellular immune responses that profoundly suppressed HCV replication and yet failed to inhibit progression to CHB. HBV and HCV can replicate in the same cell without evidence for di-

rect interference in vitro.⁸ In our study, HCV RNA was higher in the patients without detectable serum HBV DNA. HCV-RNA and HBV-DNA were positive in eight patients and HCV infection was dominant in seven of the eight patients. This is especially noticeable in hemodialysis patients, and present finding may be due to the high prevalence of HCV in hemodialysis patients. Lee et al. reported that HCV infection suppressed the serum HBV DNA level in hemodialysis patients and found that HBV/HCV coinfection in comparison with single HBV infection did not cause more severe liver disease or reduce patient survival in hemodialysis patients during a 10-year follow up.²¹ Therefore, the viral interference observed in coinfecting patients is probably due to indirect mechanisms mediated by innate and/or adaptive host immune responses.⁸

In conclusion, this is the most detailed study in Turkey evaluating the prevalence of HBV/HCV coinfection. Our study demonstrates that most patients coinfecting with HBV and HCV had a history of dental therapy, any surgical procedure, hemodialysis, and blood transfusion. HBV/HCV coinfection prevalence is not higher than HBV or HCV mono-infections. In cases where both HCV RNA and HBV DNA were positive, HCV was predominant. This is especially noticeable in hemodialysis patients in our study. Detailed serological and virological evaluations are required for HBV/HCV coinfecting patients. Larger populations must be examined and occult infections must be determined to detect the true prevalence of coinfection.

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