



# Hepatitis A and Hepatitis E Virus Seropositivity in Patients with Hepatitis B Surface Antigen (HBsAg) Positivity

## Hepatit B Yüzey Antijeni (HBsAg) Pozitif Hastalarda Hepatit A ve Hepatit E Virüsü Seropozitifliği

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### Abstract

**Introduction:** In this study, we aimed to determine the anti-HAV IgG and anti-HEV IgG seroprevalence in patients admitted to our clinic with Hepatitis B surface antigen (HBsAg) positivity.

**Material and Method:** Data of 1827 patients followed up on for HBsAg positivity between 2010 and 2019 were obtained retrospectively.

**Results:** The mean age of 1827 HBsAg positive patients was 42.71±14.84; there were 730 (39.96%) female patients and 1097 (60.04%) male. Of the 923 HBsAg positive patients whose anti-HAV IgG was measured, 830(89,9) were detected to be positive, and 93 (10.1%) negative. Anti-HAV IgG negative patients were most often in the 21-30 age range (38.7%). Age medians were significantly different between the groups (p=0.001). HBsAg positive patients who were also positive for anti-HAV IgG tended to be older than anti-HAV IgG negative patients. In contrast, there was no significant difference in gender between anti-HAV IgG negative and positive patients (p=0.674). Of 143 HBsAg positive patients who were tested for anti-HEV-IgG, five were positive (3.5%).

**Conclusion:** It is of interest that we found a lower rate of anti-HAV IgG positivity in young Chronic Hepatitis B patients. When hepatitis B virus is detected, a test for anti-HAV IgG should be requested from patients and if the test result is negative, the patient should be vaccinated. Our study data analysis also revealed a low anti-HEV IgG positivity.

**Keywords:** Hepatitis B virus, hepatitis A virus, hepatitis E virus, coinfection, seroprevalence

### Öz

**Giriş:** Bu çalışmada, Hepatit B yüzey antijeni (HBsAg) pozitifliği ile kliniğimize başvuran hastalarda anti-HAV IgG ve anti-HEV IgG seroprevalansını belirlemeyi amaçladık.

**Gereç ve Yöntem:** 2010-2019 yılları arasında, HBsAg pozitifliği nedeniyle takip edilen 1827 hastanın verileri geriye dönük incelendi.

**Bulgular:** HBsAg pozitif 1827 hastanın yaş ortalaması 42,71±14,84 idi; 730 (%39,96)'u kadın, 1097 (%60,04)'si erkekti. Anti-HAV IgG bakılmış olan 923 HBsAg pozitif hastanın 830'u (%89,9) pozitif, 93 'ü (%10,1) negatif saptandı. Anti-HAV IgG negatif hastalar %38,7 oranıyla en sık 21-30 yaş aralığındaydı. Yaş ortalamaları, gruplar arasında anlamlı farklılık gösterdi (p=0,001). Anti-HAV IgG pozitif hastalar yaş dağılımı bakımından, anti-HAV IgG negatif olan hastalardan daha yaşlı olma eğilimindeydi. Buna karşılık anti-HAV IgG negatif ve pozitif hastalar arasında cinsiyet bakımından anlamlı bir fark yoktu (p=0,674). Anti-HEV IgG için test edilen 143 HBsAg pozitif hastanın 5'i (%3,5) pozitif saptandı.

**Sonuç:** Genç Kronik Hepatit B hastalarında daha düşük anti-HAV IgG pozitifliği bulmamız ilgi çekicidir. Hepatit B virüsü saptandığında, hastalardan anti-HAV IgG testi istenmeli ve test sonucu negatif çıkarsa hasta aşılanmalıdır. Çalışma veri analizimiz, düşük bir anti-HEV IgG pozitifliğini de ortaya çıkardı.

**Anahtar Kelimeler:** Hepatit B virüs, hepatit A virüs, hepatit E virüs, koinfeksiyon, seroprevalans



## INTRODUCTION

Hepatitis A infection is caused by the hepatitis A virus (HAV), a Ribonükleik asid (RNA) virus without an envelope that is the most common cause of acute viral hepatitis all over the world. HAV is transmitted individually, mainly through food and water contaminated with human feces and domestic contamination. The most significant causes of HAV infection's geographical diversity are a lack of compliance with hygiene and cleaning rules, a lack of access to clean water resources, and poor socioeconomic conditions. More importantly, it has been reported in various studies that the HAV vaccine included in some countries' routine vaccination programs affects the frequency of infection. The frequency of HAV infection has recently decreased in many countries around the world, except in underdeveloped and some developing countries. In underdeveloped and developing countries, the disease is more common in the first years of life, and its seroprevalence rate can reach up to 100%. Since encounters with the virus appear late in central endemic areas, acute HAV cases are more common in adolescents and adults. However, the disease has tended to be more severe in adolescents and adults, and hepatitis A outbreaks may also occur.<sup>[1-3]</sup> Since HAV is a single serotype, the disease is experienced once, and Ig Immunglobulin (Ig) G type antibodies occur in the serum throughout an individual's life.<sup>[4]</sup> One of the leading causes of deaths among vaccine-preventable diseases, with over 100,000 deaths per year recorded worldwide, is acute hepatitis A infection with a fulminant course. Previous studies have concluded that individuals over the age of 50 and those with concomitant liver disease are at risk for a fulminant course.<sup>[5]</sup> Our country is a developing country, and it is a central endemic area for HAV infection.<sup>[6]</sup> HAV can spread rapidly to susceptible hosts since the disease progresses without symptoms in 90% of children and 25%-50% of adults.<sup>[5]</sup>

Superinfection with HAV in patients with chronic viral hepatitis has been reported to worsen the prognosis of hepatitis and increase the risk of fulminant hepatitis and death.<sup>[7-9]</sup> In a multicenter study conducted in our country, the anti-HAV Ig G positivity rate was 93.5% in 4793 patients with chronic hepatitis B virus (HBV) infection.<sup>[6]</sup> In another study from Diyarbakır, the anti-HAV IgG positivity rate was found to be 98.6% in patients with chronic HBV infection.<sup>[10]</sup>

Hepatitis E virus (HEV), transmitted mainly by the fecal-oral route, person-to-person contact, and the consumption of contaminated food or water, but also through transfusion and mother-to-fetus transmission as being other transmission routes, is a non-enveloped RNA virus from the herpesviridae family that causes HEV infection. Acute HEV infection, sporadically seen in our country, may rarely become chronic. In immunosuppressed individuals, including those undergoing organ transplantations and pregnant women in the second and third trimesters, the risk of complications and the risk of developing fulminant hepatitis due to HEV infection is high.<sup>[11]</sup>

Reactivation of HBV infection can be considered another form of concurrent viral hepatitis in both immunocompromised and non-immunocompromised patients. In chronic hepatitis B (CHB) patients, superinfection with hepatitis E, especially in patients with pre-existing cirrhosis, can lead to morbidity and mortality.<sup>[12]</sup>

HAV and HEV have similar fecal oral transmission routes and clinical findings, and infections with these viruses in patients with CHB may cause more rapid liver disease progression and increased morbidity and mortality. There are a limited number of studies on HEV, and there are no studies investigating anti-HEV IgG seroprevalence and HEV superinfection in patients with CHB in our country. In this study, we aimed to identify the anti-HAV IgG and anti-HEV IgG seroprevalence in our country's HBsAg positive patients and their contributions to our region's epidemiological data.

## MATERIALS AND METHOD

The study was carried out with the permission of Necmettin Erbakan University Ethics Committee (Date: 03.04.2020, Decision No: 2020/2407). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 1827 patients admitted to our clinic for HBsAg positivity between 2010 and 2019 were included in this retrospective study. Those with anti-HCV, anti-HDV and anti-HIV positivity, and those with hepatocellular cancer (HCC) diagnoses were excluded. The epidemiological information and anti-HAV IgG, anti-HEV IgG, HBeAg, and anti-HBe results were obtained by retrospectively scanning through patient follow-up files and the hospital information management system. Anti-HAV IgG, anti-HEV IgG, and HBsAg tests were analyzed with the chemiluminescence enzyme immunoassay method (Architect, Abbott Laboratories, USA) in the microbiology laboratory.

### Statistical Analysis

The collected data were recorded, and statistical analysis was performed using SPSS software (version 22, SPSS Inc). Descriptive data were given as numbers and percentages. The median (interquartile range (IQR)) represented the descriptive statistics; A chi-square test was applied to compare categorical variables, and a t-test was used to compare numerical variables. A  $p < 0.05$  value was considered statistically significant.

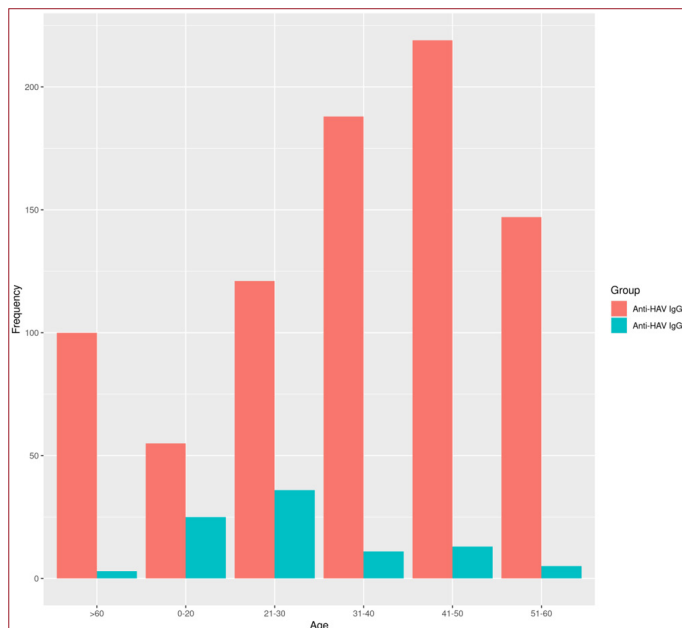
## RESULTS

The mean age of 1827 HBsAg positive patients was  $42.71 \pm 14.84$ , and 1097 were male. Of the HBsAg positive study participants, 1534 (84%) were HBeAg negative, 293 (16%) were HBeAg positive, 323 (17.7%) anti-HBe negative, 1502 (82.3%) were anti-HBe positive. Of the 923 HBsAg positive participants whose anti-HAV IgG levels were measured, 93

(10.1%) tested negative for anti-HAV IgG, while 830 (89.8%) tested positive. Participants with negative anti-HAV IgG test results were predominantly (38.7%) in the 21-30 age range. The distribution by age group of the anti-HAV IgG test results for the HBsAg positive participants is presented in **Table 1** and **Graphic 1**.

**Table 1. Anti-HAV IgG results by age groups in HBsAg positive patients**

| Age distribution | Anti-HAV Ig G negative n (%) | Anti-HAV Ig G positive n (%) | Total | P     |
|------------------|------------------------------|------------------------------|-------|-------|
| 0-20             | 25 (26.9)                    | 55 (6.6)                     | 80    | 0.001 |
| 21-30            | 36 (38.7)                    | 121 (14.6)                   | 157   |       |
| 31-40            | 11 (11.8)                    | 188 (22.7)                   | 199   |       |
| 41-50            | 13 (14)                      | 219 (26.4)                   | 232   |       |
| 51-60            | 5 (5.4)                      | 147 (17.7)                   | 152   |       |
| >60              | 3 (3.2)                      | 100 (12)                     | 103   |       |
| Total            | 93                           | 830                          | 923   |       |



**Graphic 1.** Anti-HAV IgG results by age groups in HBsAg positive patients

The HBsAg positive participants with negative anti-HAV IgG test results, and those with positive anti-HAV IgG test results had a similar gender distribution, with 35 (37.6%) females, and 331 (39.9%) males and 331 (39.9%) females and 499 (60.1%) males, respectively; thus, there were no significant difference between the groups in terms of gender ( $p=0.674$ ). However, there was a significant age difference between the groups ( $p=0.001$ ); with the HBsAg positive participants who tested positive for anti-HAV IgG tending to be older than those who tested negative. There was also a statistically significant difference between HBeAg positivity in anti-HAV IgG negative participants ( $p=0.001$ ) and anti-HBeAg positivity in anti-HAV IgG positive participants ( $p=0.001$ ).

Of the 143 HBsAg positive participants who were tested for anti-HEV IgG, 138 (96.5%) tested negative, and 5 (3.5%) tested

positive. The gender of the anti-HEV IgG negative participants was identified as female in 55 (39.9%) participants and male in 83 (60.1%) participants, and among the anti-HEV IgG positive participants, female in 3 (60%) participants and male in 2 (40%) participants.

Comparison of subjects epidemiological features among anti-HEV IgG negative and positive patients are given in **Table 2**.

**Table 2. Comparison of subjects' epidemiological features among anti-HEV IgG negative and positive patients**

|                    | Anti-HEV IgG negative n=138 (96.5%) | Anti-HEV IgG positive n=5 (3.5%) | P    |
|--------------------|-------------------------------------|----------------------------------|------|
| Age                | 43.46±13.33                         | 48±7.52                          | 0.45 |
| Gender female/male | 55 (39.9), 83 (60.1)                | 3 (60), 2 (40)                   | 0.37 |

## DISCUSSION

Studies show that acute HAV infection is rarely fatal in young adults, but it can be severe in participants with HBV infection and can lead to fatal complications, especially in the elderly.<sup>[13]</sup> In a study conducted in Konya, Turkey, the anti-HAV IgG test results were positive for 506 (94.2%) of the 537 participants, 437 of whom had chronic hepatitis B (CHB).<sup>[3]</sup> In a study conducted in Balıkesir, Turkey 77 (77%) of 100 HBsAg-positive participants were found to be positive for the anti-HAV IgG.<sup>[14]</sup> In a study conducted in Afyonkarahisar, Turkey, anti-HAV-Ig G status was not investigated in 207 (43.1%) of the 480 participants, but was tested in 273 (56.9%) of which 178 (65.2%) were followed up with diagnosis of inactive HBsAg carrier, and 95 (34.8%) with CHB. At the time, ninety-five of the participants were receiving treatment with a diagnosis of CHB. Anti-HAV IgG test results were positive for 257 (94.1%) participants.<sup>[15]</sup> In a study conducted in Kütahya, Turkey, anti-HAV Ig G positivity in HBsAg positive patients was 340/486 (69.9%) between all age groups.<sup>[16]</sup> In a study conducted in Tokat, Turkey, 105 (94.6%) of 111 chronic hepatitis B patients were anti-HAV IgG positive.<sup>[17]</sup> Anti-HAV IgG (+) was detected in 179 (74.9%) of 239 male patients aged 18-30 years with chronic HBV.<sup>[18]</sup> In our study, the anti-HAV IgG test results were positive for 830 (89.9%) of the 923 participants, which is similar to the rates reported in the available national study date. It is also important to consider that, in some provinces of Turkey, the epidemiology pattern of HAV infection is changing, and the disease with severe progress when seen, is now less common due to improved socioeconomic status, health and hygiene conditions in these provinces.<sup>[6]</sup> The Advisory Committee on Immunization Practices (ACIP) recommends HAV vaccine for those with seronegative HAV, infection with HBV, HCV, and those with chronic liver disease due to alcoholic hepatitis.<sup>[19]</sup>

Age and anti-HAV IgG seroprevalence are essential variables that determine the cut off age at which the hepatitis A vaccine can be administered.<sup>[20]</sup> In a study conducted in Diyarbakir, anti-HAV IgG seronegativity of 209 chronic HBV patients was observed at the highest rate with 11.8% in the group under

20 years old, and it was 1.6% in the 20-29 age group. All of the 30 years and older group had anti-HAV IgG positivity.<sup>[10]</sup> In the study conducted in Balıkesir, HAV IgG negativity was found to be 51% under the age of 40 and 5% over the age of 40.<sup>[14]</sup> Alkan Çeviker et al. reported anti-HAV IgG positivity in HBsAg positive patients was 22.7% between the ages of 18-20 years, 48.3% between the ages of 21-30.<sup>[16]</sup> In addition, data generated by another study records seropositivity in 83.2% of the HBsAg positive male population over 20 years old.<sup>[21]</sup> More importantly, Kumbasar et al. reported anti-HAV IgG positivity in 80.5% of their participants under 40 years of age who had chronic hepatitis.<sup>[22]</sup> In the multi-center study conducted by Çelen et al. in Turkey, the HAV seronegativity rates among 4793 HBsAg positive cases were reported as 26.2% for individuals less than 19 years old, 15.5% for individuals in the 20-25 age range, and 12.5% among individuals 26 to 29 years of age.<sup>[6]</sup> In our study, among the HBsAg positive participants, a negative anti-HAV IgG status was most common among the HBsAg positive participants between 21 and 30 years of age, at 38.71%, followed by the 0-20 age range 26.88%; whereas anti-HAV IgG positivity was highest among the 40-50 age group, at 26.4%. This data from our study is in agreement with the findings of other studies in the literature. In Turkey, increased compliance with hygiene and sanitation rules, access to clean water resources, improved socioeconomic conditions, and inclusion of the hepatitis A vaccine in the routine childhood vaccination program in 2012 have caused a decrease in the prevalence of HAV infection among the population.<sup>[5,11]</sup> Our country, routine hepatitis B vaccination implements in children at 0,1<sup>st</sup> and 6<sup>th</sup> months.<sup>[23]</sup> Routine hepatitis A vaccination implements in children at 18<sup>th</sup> and 24<sup>th</sup> months.<sup>[5]</sup> The relationship between gender and HAV seroprevalence in HBsAg positive individuals varies from region to region within Turkey. In a study by Kim et al, there was not difference in the seroprevalence of HAV between the genders.<sup>[24]</sup> In contrast, Sagnelli et al. found the seroprevalence of HAV to be greater among women. This result can be attributed to the fact that the study was conducted in a developing country, and the female participants, most of whom were housewives and had a low sociocultural status, probably had higher levels of exposure to HAV via social and domestic contact than the male participants.<sup>[25]</sup> In the study of Alkan Çeviker et al., anti-HAV IgG positivity in HBsAg positive women was 69.8% and 70.2% in men. There was no statistical difference between the two groups in terms of gender.<sup>[16]</sup> In our study, we found no difference in HAV seropositivity rates between genders.

Hepatitis E, which causes an asymptomatic infection uncommon in children, but more prevalent among men than women, often infects young adults.<sup>[26]</sup> In Turkey, HEV frequency varies from region to region (0-73%), with an overall seroprevalence rate of 6.3%.<sup>[27]</sup> In our study, no comparisons could be made between genders because 3 of the 5 (3.5%) anti-HEV IgG positive participants were female, while the other 2 were male, and a few participants had a positive anti-HEV IgG status.

HEV IgG positivity rate was 6.6% in 424 healthy people in İzmir.<sup>[28]</sup> In a study conducted in 180 healthcare workers in our country, anti-HEV IgG was found positive in 13 (7.2%) individuals.<sup>[29]</sup> It has been reported that HEV exposure is higher in patients with chronic HBV infection than in the general population.<sup>[30]</sup> In recent studies, it has been reported that hepatitis E seroprevalence is still high in Turkey. The national HEV seroprevalence is estimated to be between 7% and 35%.<sup>[31]</sup> In the study of Ozel Yeşilyurt et al., 50 (44.6%) of 112 naive HBV patients were found to be anti-HEV IgG positive.<sup>[32]</sup> In the study of Kayalı et al. in Elazığ, Turkey, anti-HEV IgG was found positive in 7 of 40 chronic HBV patients.<sup>[33]</sup> Bayram et al. in their study in Gaziantep, Turkey, reported that the rate of anti-HEV IgG positivity was 13.7% in chronic HBV patients and 15.7% in healthy individuals, and the difference was not significant.<sup>[34]</sup> These findings are similar to the results obtained in our study, in which 5 (3.5%) of the 143 HBsAg positive participants were positive for HEV IgG, a lower rate than that established for individuals without hepatitis B in Turkey. The fact that quite different HEV seropositivity results have been obtained in studies indicates that different protein forms of HEV It may be caused by the use of different commercial kits in the ELISA (Enzyme Linked ImmunoSorbent Assay) tests where it is used.

In the study of Kayalı et al., no significant difference was found between the genders in terms of HEV seropositivity in chronic HBV, cirrhosis and autoimmune hepatitis groups.<sup>[33]</sup> In our study, there was no difference between genders in terms of HEV seropositivity.

## CONCLUSION

In our country, HAV seropositivity in adults is similar to the rates in the national studies. The findings of our study indicate that a sizable proportion of elderly HBsAg positive individuals have been exposed to HAV. HAV should be screened on at the first visit during which HBsAg is detected; if the anti-HAV IgG test result is negative, the patient should be vaccinated. In our study, the frequency of anti-HEV IgG among HBsAg positive participants was 3.5%, However because there are only a few studies on this subject, more research is required.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Necmettin Erbakan University Ethics Committee (Date: 03.04.2020, Decision No: 2020/2407).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.



**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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