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Zoonotic Hepatitis E Virus Infection: Where Are We and Where Should We Look?

Zoonotik Hepatit E Virüs Enfeksiyonu: Neredeyiz ve Nereye Bakmalıyız?

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ABSTRACT

Zoonotic hepatitis E virus (HEV) causes a worldwide problem. Generally transmitted via infected animals/eating contaminated food. Fully understanding the distinctive biology, transmission routes, and clinical consequences of zoonotic HEV strains is essential for developing efficacious prevention and control tactics. Current knowledge gives prominence to animals, with pigs in particular being recognized as reservoirs, and examines the clinical variances between zoonotic and strictly human HEV genotypes. This analysis further explores recent advances in diagnostics, immunization efforts, and protective measures while identifying gaps in our comprehension, requiring additional research to better address HEV as a public health menace. Furthermore, strategies aiming to reduce potential zoonotic transmission through improved hygiene standards and strict inspection of the food supply chain merit consideration.

Keywords: Hepatitis E virus, zoonotic, diagnosis, epidemiology, prevention, vaccine

ÖZ

Zoonotik hepatit E virüsü (HEV) dünya çapında bir soruna neden olmaktadır. Genellikle enfekte hayvanlar/kirlenmiş gıdaların yenmesi yoluyla bulaşır. Zoonotik HEV türlerinin kendine özgü biyolojisinin, bulaşma yollarının ve klinik sonuçlarının tam olarak anlaşılması, etkili önleme ve kontrol taktikleri geliştirmek için kesinlikle gereklidir. Mevcut bilgiler, başta domuzlar olmak üzere rezervuar görevi gören hayvanları ön plana çıkarmakta ve zoonotik ve tamamen insani HEV genotipleri arasındaki klinik farklılıkları incelemektedir. Bu analiz ayrıca, teşhis, bağışıklama çabaları ve koruyucu önlemlerdeki son gelişmeleri araştırırken, HEV'i bir halk sağlığı tehdidi olarak daha iyi ele almak için ek araştırma gerektiren kavrayışımızdaki boşlukları belirlemektedir. Ayrıca, hijyen standartlarının iyileştirilmesi ve gıda tedarik zincirinin sıkı bir şekilde denetlenmesi yoluyla potansiyel zoonotik bulaşmayı azaltmayı amaçlayan stratejiler de dikkate alınmalıdır.

Anahtar Kelimeler: Hepatit E virüsü, zoonotik, epidemiyoloji, tanı, korunma, aşı

Introduction

Overview of HEV Types and Genotypes

Hepatitis E virus (HEV) is a virus from the *Hepeviridae* family according to the 10th report of the International Committee on Taxonomy of Viruses (ICTV) (1). It has a (+)- chain ribonucleic acid strain various gene size of 7.2-7.4 kb (2), single-stranded, positive-stranded, has measurement between 27 and 34 nanometres in diameter (nm) (3,4,5,6). It was initially recognised as a cause of certain types of hepatitis (non-A, non-B) (7). This virus encompasses both animal-based strains, which can infect humans, and variants restricted to animals, which complicates the epidemiology and transmission dynamics of HEV (3,4,5,6).

According to the 10th ICTV report, HEV consists of two types of genera: *Orthohepevirus* and *Piscihepevirus* (1). *Piscihepevirusincludes* genus exclusive to *Oncorhynchus clarkii* virus, while *Orthohepevirus* includes class of *aves* and *mammalia* HEV isolates. Four different types of *Orthohepevirus* are as follows: A, B, C, and D, and are divided into at least 8 genotypes (1,8,9,10). Genotypes 3 and 4 are the primary cause of zoonotic infections; other strains also show potential (Table 1) (10,11).

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Table 1. Currently classification of HEV

Family	Genera	Species	Genotypes
Hepeviridae	*Orthohepevirus*	A, B, C, D	I, II, **III***, **IV***, V, VI, VII, VIII
	Piscihepevirus		

*: Zoonotic, HEV: Hepatitis E virus

There are genotypes and subtypes of HEV associated with host species and geographic origin (12). Studies have detected an association with clinical outcomes, while others have not observed such an association (13,14).

Genomic analyses indicate that *Hepeviridae* may have arisen from ancient recombination between *Alphatetraviridae* and *Astroviridae* (15). The HEV strains that infect humans are members of the *Orthohepevirus A* species, which ICTV has recently, renamed *Paslahepevirus balayani (P. balayani)* (16). Subtypes 1g, 3k, 3l, 3m, and 8a are now included in the revised list of suggested reference sequences for *P. balayani* subtype classification (17). The ongoing identification of diverse HEV strains suggests that *Hepeviridae* taxonomy will continue to evolve (1).

Zoonotic Transmission and Primary Animal Reservoirs

It is not known exactly which hosts HEV infects, because most infections are asymptomatic and virus replication is low. Because virus release is irregular, detecting HEV-RNA in different host species is difficult and resource-intensive. Furthermore, it is difficult to detect infected individuals, as viral load is usually low. Every strain of HEV has the same serotype, which prevents differentiation of infections with different strains (18).

HEV has potential hosts that can be detected in many animal species such as domestic pigs, wild boars, chickens, mice, rabbits, deer, fish, cattle, sheep, and bats, and the virus is constantly expanding its host range. Other possible hosts are still under investigation, making the spread of HEV more complex (19). Recent findings have revealed that HEV *homologues* are found in fish (20), amphibians (21), moose (22), kestrels (23) and many other organisms, suggesting that the *Hepeviridae* family, like the *Herpesvirales* order, may exhibit a wide range of hosts and that HEV has the ability to cross interspecies barriers (24).

HEV isolates are classified into eight species. Species A includes isolates from humans, pigs, deer, hares, camels, and mongooses. Species B comprises *aves* class HEV isolates from birds. Species C includes isolates from rodent family members (Indian bandicoot rat, Asian musk shrew, and various rodent species), while Species D consists of isolates from bats. Only isolates that infect humans have 8 genotypes and belong to species A. Genotypes 1 and 2 infect only humans, while genotypes 5, 6, 7, and 8 infect wild boar, humans, and camels, specifically *Camelus bactrianus* (8).

HEV Biology and Genomic Characteristics

HEV Genome Structure and Replication

The *mammalia* HEV genome, a single-stranded, positive-sense RNA, is approximately 7200 nucleotides long, while the *aves* HEV genome is approximately 6650 nucleotides long (25). Although animal models and cell transfection are used to study the biology and pathogenesis of HEV, its structure and replication cycle are still difficult to understand because of slow replication, ineffective cell cultures, and unknown receptors (2,6,7,18,21,25,26,27,28,29,30,31,32,33). Though its molecular specifics are unclear, the uncoating process is associated with polysaccharide-binding sites (26).

The HEV genome includes functional regions such as the methyltransferase Y domain papain-like cysteine protease enzymatic, RNA helicase, phosphoprotein [open reading frame 3 (ORF3)], capsid (ORF2), and RNA-dependent RNA polymerase. It has a 5′ non-coding region, 5′ and 3′ untranslated regions, and three ORFs (ORF1, ORF2, ORF3) (Figure 1) (33). ORF1 encodes a polyprotein for replication, ORF2 encodes a capsid protein, and ORF3 encodes a protein involved in virion morphogenesis. HEV-3 strains are divided into 13 subtypes. The genome is 7.3 kb, and HEV virions are non-enveloped in feces, and semi-enveloped in blood. Two virus-like particle types exist: T=1 (270 Å) and T=3 (320-340 Å). The capsid protein exists in two forms, ORF2S and ORF2C, with four cis-regulatory elements crucial for replication (2,5,6,7,8,16,18).

Researchers on HEV have found that there is a conserved receptor binding motif in the capsid protein (26), a potential binding site in the M domain (27), and interactions with heparin sulphate proteoglycans (28). It was also suggested that a 55 kDa protein may play a role as an entry receptor, but it was emphasized that this hypothesis requires further confirmation (29). It has been suggested that HSC70 and Grp78 may play a role in intracellular transport processes rather than receptor functions (30).

HEV enters cells through a clathrin- and dynamin-2-dependent pathway, utilizing different routes for enveloped (quasi-enveloped) and non-enveloped virions. This process involves the small GTPases Rab5 and Rab7. Although HSP90 inhibitors block the intracellular transport of the virus, they do not interfere with its entry into the host cell (32). Semi-enveloped HEV (eHEV) virions enter cells via clathrin-mediated endocytosis and are also known to require Rab5 and Rab7 GTPases. Figure 2 presents a model of cell entry of naked and semi-eHEV virions (33).

Hepatocytes also allow eHEV particles to be released into the circulation from the cellular surface into the blood. Therefore, eHEV can be detected in blood and urine, while non-eHEV (naked HEV) can only be found in bile and feces (33,34).

The replication process starts with viral RNA producing a negative sense intermediate, which is used as a template to produce both positive sense genomic RNA and subgenomic bicistronic mRNA (35). Viral RNA replication proceeds slowly and peaks 8 days after transfection of reporting genes such as green fluorescent protein or luciferase (36).

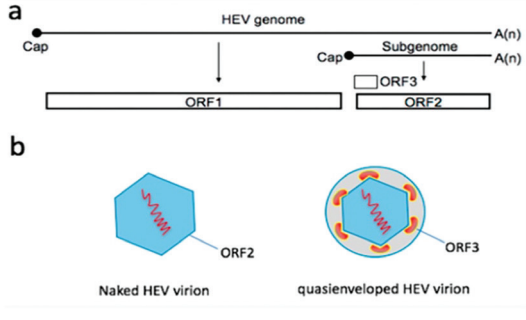

Figure 1. The HEV genome, its encoded proteins (a), and two types of virions (b)

HEV: Hepatitis E virus, ORF: Open reading frame

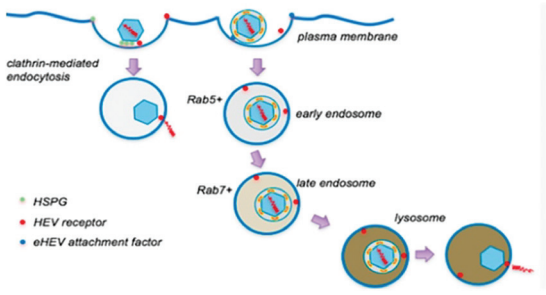

Figure 2. Model for cellular entry of naked and quasi-enveloped HEV virions

HEV: Hepatitis E virus, eHEV: Enveloped HEV, HSPG: Heparan sulfate proteoglycan

A recent study suggests that the eHEV envelope likely originates from the trans-Golgi network (TGN) and is derived from HEV intracellular membranes. The study emphasizes the role of TGN in forming the envelope of HEV particles and the dynamic processes of TGN membranes in virus discharge and bloodstream passage (4). Another study found that HEV genotypes 1 and 3 successfully replicated in primary intestinal cell cultures. HEV RNA and ORF2-specific antigens were detected in a chronic infection patient's intestinal crypts, indicating that HEV proliferates in the intestines and replicates before passing to hepatocytes (37).

Differences Between Zoonotic and Human-restricted Strains

The genetic dissimilarities between zoonotic and human-restricted strains of HEV center around genetic diversity, evolutionary adaptations, and host interactions. Zoonotic strains like genotype 3 and genotype 4 exhibit greater genetic diversity owing to their ability to infect multiple animal species, leading to swift evolutionary changes and intricate genome architectures. They also demonstrate notable variation in structural proteins such as ORF2, allowing them to adapt to different types of hosts and settings. Comparatively, human-restricted strains like genotype 1 and genotype 2 are more genetically stable and primarily infect humans, resulting in less genetic fluctuation and fewer mutations. They are more genetically stable and evolve within a single host species, which reduces their flexibility (2,3,8,9,12).

Research has revealed that before the identification of genotypes of the wild boar and camel origins (HEV-5 to HEV-8), the ancestors of all *Orthohepevirus A* species were enzootic (38).

Over the past decade, exploration into HEV's cross-species transmission has made progress, though questions remain. ORF1 is a key determinant, but further investigation is needed to recognize precise domains. Comprehending HEV's interactions with host cells is crucial for understanding its targeting and infection, and decoding these interactions will help in understanding the full range of HEV cross-species transmission mechanisms (12).

Zoonotic Transmission and Pathogenesis of HEV: Host Tropism and Adaptations Enabling Cross-species Transmission

Modern HEV strains, which emerged around 6800 years ago due to pig domestication and agricultural intensification (39), while *Orthohepevirus A*, which infects rabbits, camels, and swine, originated in Asia around 4500-6800 years ago (40).

The HEV genome is diverse across different genotypes, often linked to specific host species. Genetic recombination in HEV genomes contributes to their genetic diversity and facilitates cross-species transmission. Factors influencing HEV's ability to spread from animals to humans include: viral determinants like ORF1, host-specific factors like cellular receptors and immune responses, and alterations in translation efficiency and viral genome packaging. These factors contribute to HEV's ability to infect multiple species (40,41,42,43,44). Underlying mechanisms for cross-species HEV infection are unclear, with specific cellular receptors and virus entry mechanisms being poorly understood (44).

HEV has evolved several adaptations to facilitate its zoonotic transmission. These include genetic diversity, host range, and species-specific modifications (12). One study suggested that HEV ancestors may have evolved from animal hosts to humans (38), while another research report states that *Orthohepevirus A*'s first host was humans and then evolved into cross-species and human-exclusive genotypes (40). HEV has evolved mechanisms to evade immune responses in various hosts, allowing it to infect a wide variety of animals (12). In addition to the divergence of enzootic and human-limited genotypes, the evolutionary history of *Orthohepevirus A* also includes the divergence of genotypes that infected camels during camel domestication. The divergence of HEV-3ra coincided with rabbit domestication (40).

A study found a bias in HEV-1's ORF2 protein production in deer cells, which could be corrected by introducing a short 5' RNA sequence from HEV-3. This suggests that translation efficiency can vary significantly depending on the host strain, potentially restricting the viral species' host range. The study underscores the complexity of interactions between host and virus and provides insights into how host-specific factors shape HEV's zoonotic potential (41).

A study in Singapore analyzed viral populations from 15 chronic HEV patients to identify lineage and points of interest for mutation. In this study, 21 viral RNA samples were examined from a single hospital between 2012 and 2017. Phylogenetic analysis identified the whole sequences spanning the HEV-3a subclass, indicating a unique local ancestry (42).

Recent studies have identified genetically distinct HEV variants from various animal species, identified in specific isolates from specific animals. Recombination events have been observed in both animal reservoirs and human patients. Chronic HEV infection in immunocompromised individuals creates a human host carrying genes of virus strains, suggesting potential for adaptation and host-virus interactions (43). Exosome-released HEV particles are shielded from neutralizing antibodies, potentially facilitating HEV spread (4). Natural selection is a crucial process for virus fitness in specific environments (45). Transmission with frequent cross-species contact may emerge as parallel evolution due to adaptation to new host environments (46). HEV's large host range may be due to evolutionary conservation of host factors, but further investigation of HEV's strategies to evade distinct host immune responses is needed (44).

The exact method of transmission between species in HEV remains unclear. Knowledge of the host and viral factors involved has advanced, with the majority of the research to date focused on HEV ORFs and evolutionary events (12).

Epidemiology

Global Epidemiology of Zoonotic HEV Strains

HEV has established itself globally as the primary factor for acute hepatitis in many areas, with the majority of infections going unnoticed or asymptomatic, and as the fifth recognized cause of human viral hepatitis (47). Historically thought to occur only in resource-poor regions, HEV is now recognized as predominantly zoonotic in nature, endemic even in developed countries. Genotype 3 (and genotype 4) has especially garnered attention given our evolved understanding of its ubiquity and position as a dominant source of community-acquired hepatitis across Europe (48).

Approximately 20 million people fall ill from HEV each year worldwide. Though not all experience symptoms, over 70,000 die as a result of infection. Outbreaks have plagued refugee camps and regions with inadequate sanitation infrastructure. Though sporadic cases, also surface outside of epidemics, countries from Africa to Central/South America, through temperate East Asia, and into the Middle East witness the virus's effect (49,50). Most recent World Health Organization data indicate HEV led to over 44,000 deaths in 2015 alone, constituting 3.3% of viral hepatitis mortality rate globally (50). Genotypes 1 and 2 have periodically sparked large outbreaks across parts of Asia, Africa, and Mexico, linked to heavy rain and the subsequent contamination of water supplies (50,51,52,53). According to the study by Li et al. (53), Figure 3 shows the distribution of HEV genotypes globally.

HEV infections are an increasingly grave public health issue, particularly in developing regions where close contact with livestock like pigs, goats, sheep, and cattle in conjunction with traditional meat consumption habits and subpar hygiene exacerbate transmission risks. Multifarious determinants including agricultural techniques, meat handling protocols, and inadequate preventive health infrastructure compound the infection risks. To stymie the spread, thorough cooking, improved sanitation, and regulated animal agriculture and hygienic practices are indispensable (51,52,53,54,55).

HEV is rampant in less developed nations with deficient clean water access and sanitation (51). It has surfaced in persistently affected areas like Asia, the Middle East, Africa, and even in parts of Central America, which have been categorized as developing regions (52). A meta-analysis of 419 studies showed that more than 12% of people worldwide have encountered the virus. At-risk populations include raw meat eaters, soil handlers, blood donors, travelers to endemic areas, canine companions, rustics, and poorly educated groups. The study implies nearly 939 million individuals have had HEV (53).

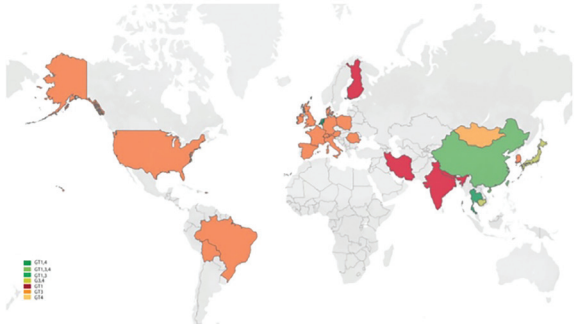

Figure 3. The global distribution of HEV genotypes
HEV: Hepatitis E virus

A meta-analysis of HEV seroprevalence in industrialized countries found that rates fluctuate from 5% to 50%, depending on location and demography. While certain divergences may relate to serological testing techniques, current understanding of transmission avenues fails to thoroughly clarify these dissimilarities. The work emphasizes pronounced inconsistencies, notably in research utilizing the Wantai HEV-IgG ELISA screening (54).

A meta-analysis of 432 studies from 2003 to 2015 found that HEV seroprevalence in Europe is between 0.6% and 52.5%, increasing with age but not gender. Rates varied by test type, with higher rates in individuals in contact with swine and wildlife. Geographical region, test type, and exposure status also influenced seroprevalence. France had the highest rates, while Italy had the lowest (55).

A meta-analysis of HEV infection seroprevalence in Middle Eastern countries revealed a total of 21.3%, with Egypt having the highest rate at 35%. Pregnant women had the highest rates at 47.9%, while kidney transplant patients had a lower rate at 30.8% (56).

Information on anti-HEV seroprevalence in Türkiye is limited. A 2018 meta-analysis in Türkiye found that HEV prevalence ranged from 0 to 12.4%, with lower rates in children. While the incidence is 7-8% in pregnant women, it is 13% and 35% in patients with chronic hepatitis B, C, renal failure and agricultural workers, respectively. HEV seroprevalence among those migrating from Türkiye to Europe was determined to be 10.3% in Italy and 33.4% in the Netherlands. This study emphasized that the studies were not reflecting the entire population and excluded immunocompromised patients and solid organ recipients, suggesting that HEV was endemic in Türkiye (57). In a review study conducted in Türkiye, high rates of HEV seroprevalence in hemodialysis patients and low rates in children were reported, especially in the regions of Eastern Anatolia and Southeastern Anatolia. However, considering the epidemiologic characteristics of HEV infection, HEV seroprevalence varies according to age, location and underlying special risk group status (58).

In a meta-analysis examining the prevalence of HEV IgG antibody in pregnant women, seroprevalence was found to be 16.51% according to data from 15 studies. The highest prevalence, 61.29%, was found in Sudan, and the lowest prevalence, 3.41% was found in Italy. High heterogeneity was observed among the studies, and the results show that HEV seroprevalence varies according to geographical regions (59).

A study on HEV's seroprevalence in pigs and the environment highlights its potential for transmission through water, food, and humans. The high prevalence in domestic animals, like pigs, suggests that the virus can spread in the environment and meat supply chains. Detection in water sources and animal products increases infection risk, highlighting the need for further research in animal markets (60).

Transmission Routes of HEV

HEV is primarily transmitted via ingestion of food or water that has come into contact with and been contaminated by the feces of infected individuals or animals (fecal-oral route). Typical routes of transmission include drinking untested water sources, eating undercooked meat (particularly pork) products, and lacking proper hygiene practices (49,52,60,61,62). Although HEV3 and HEV4 are usually transmitted zoonotically, these viral variants have still been found polluting untreated wastewater, pig manure storage tanks, and surrounding river waterways (63).

HEV also has a zoonotic transmission route where it can be passed from animals (especially pigs, deer, and other livestock) to humans through consumption of infected meat (60). Additionally, bloodborne transmission can occur through blood transfusions or organ transplants from infected donors (51). HEV can also be spread via contaminated medical equipment, though this is rare. Lastly, there is a possibility of environmental transmission through contact with contaminated surfaces or soil, but this route is less frequently reported (62). Vertical transmission can happen during pregnancy, leading to complications for both the mother and fetuses (64).

HEV can also transmit zoonotically, with humans becoming ill after consuming inadequately cooked meat from infected pigs, deer, and livestock. Bloodborne spread through tainted blood donations or organ transplants is another potential path of transmission (51). Rarely, the virus might spread through contaminated medical equipment. It's also possible, yet less reported, to contract HEV by touching surfaces contaminated by infected excrement or soil (62). During pregnancy, vertical transmission in the womb can endanger both expectant mothers and their fetuses.

HEV3 and HEV4 have been found in several animal species, including domestic animals, wild boars, and sika deer, and are common in domestic pigs worldwide. Pigs aged three to five months have the highest excretion of HEV. These animals can transmit HEV to humans. Although HEV3 and HEV4 infection remain asymptomatic, the virus is retained in herds thanks to the high amount of excreted virus in the faeces of infected animals (65).

Scientists have identified HEV3 and HEV4 within numerous animal populations as well, such as domesticated pigs and boars, sika deer, and even household pets. Pigs between three and five months of age have been found to carry the highest viral loads in their feces. These swine can pass HEV on to humans who handle or consume them. While asymptomatic in pigs, the virus persists in herds because of immense quantities excreted by infected swine.

Clinical Manifestations of Zoonotic HEV Infection

Symptomatology and Complications in Zoonotic HEV Infection

Infection with HEV poses significant risk to pregnant women, infants, the elderly, those with immunocompromised systems, individuals with chronic liver conditions, and people who work closely with host animals of HEV (61,66,67). HEV infections can result in various clinical manifestations, including acute and self-limiting hepatitis, acute-on-chronic liver disease, chronic hepatitis, cirrhosis, and liver failure (67).

Chronic HEV infection can develop in immunocompromised patients. The host immune response may mediate liver damage caused by HEV, and its clinical manifestation may vary, especially in high-risk groups (61). Zoonotic and non-zoonotic HEV infections share common symptoms (61,66,67). Zoonotic HEV (genotypes 3 and 4) is more likely to cause chronic infection, especially in immunocompromised individuals, and is associated with extrahepatic complications such as neurological disorders, glomerulonephritis, and autoimmune responses. In contrast, non-zoonotic HEV (genotypes 1 and 2) are generally self-limiting in healthy individuals but pose a higher risk of severe outcomes in pregnant women, including acute liver failure (ALF), stillbirth, and preterm delivery, especially in the third trimester. While zoonotic HEV can lead to chronic hepatitis and cirrhosis in susceptible populations, non-zoonotic HEV is more likely to cause acute infection with a better prognosis in most individuals, except in pregnancy (49,50,67).

Zoonotic HEV (genotypes 3 and 4), which are usually spread by undercooked pork or animal products, are linked to extrahepatic complications like neurological disorders, glomerulonephritis, and autoimmune reactions. It is also more likely to cause chronic infection, particularly in immunocompromised individuals. Non-zoonotic HEV (genotypes 1 and 2), on the other hand, is mainly waterborne and spreads through contaminated water in unsanitary areas. While certain conditions are generally self-limiting in healthy individuals, pregnant women are at a higher risk of serious complications, such as ALF, stillbirth, and preterm delivery, particularly during the third trimester. With the exception of pregnancy, non-zoonotic HEV is more likely to produce acute infection with a better prognosis in most people, compared to zoonotic HEV, but zoonotic HEV can induce chronic hepatitis and cirrhosis in vulnerable populations.

Acute Hepatitis

Acute HEV infection typically manifests with a prodromal phase lasting around one week. It possesses an incubation period averaging six weeks, though it can extend from two to nine weeks (49). It often induces mild symptoms such as malaise, fever, body aches, nausea and vomiting prior to progressing to dark urine and jaundice. Occasionally, acute HEV infection accounts for only five to thirty percent of overall HEV cases. Other common symptoms include abdominal pain, loss of appetite, joint pain, and itchy skin (11,49,67).

The convalescent phase resolves icteric symptoms, with HEV1 causing more severe acute hepatitis presentations than HEV2. Older men are susceptible to severe infections from HEV3 and HEV4, while patients with chronic liver disease can develop acute-on-chronic liver failure (ACLF) (67).

Pregnant women and immunocompromised individuals has critical time window for diagnosis and management, which crucial for improving patient outcomes (11,49,67). These women, especially in their second and third trimesters, face high risk of symptomatic disease and ALF from HEV1, leading to mortality rates as high as 25% (68,69,70). In the third trimester, HEV1 can endanger mothers through eclampsia, hemorrhaging, and liver failure. Babies are vulnerable to transmission during birth or breastfeeding, known as vertical transmission (71).

Newborns face severe risks due to maternal-fetal transmission of HEV, often leading to clinical symptoms like hypoglycemia, hepatitis, and neonatal death (70). A recent study investigating risk factors associated with vertical transmission of HEV found that 46.09% of HEV-IgM-positive mothers passed the virus to their fetuses. Among 29.41% of newborns, delivered by mothers with ALF tested, are positive for HEV-RNA.

The research highlighted that viral load was a salient predictor of the transmission of the infection from mother to child, along with hemoglobin and folate levels. Researchers developed a novel risk evaluation system incorporating such elements from these indicators to more precisely foresee the likelihood of vertical transmission. This model reinforced that a higher viral burden plays a pivotal role in impacting whether HEV transfers to the fetus (64).

Chronic Hepatitis

Although HEV generally emerges as an acute infection, it is able to induce chronic HEV in immunocompromised patients (such as those receiving organ transplants or those with human immunodeficiency virus). Hepatocellular carcinoma (liver cancer), cirrhosis, and progressive liver damage can all be brought on by a persistent infection. Antiviral therapy and ongoing monitoring are necessary for chronic infections because chronic infections can result in serious, long-term liver damage (11,49,67).

Zoonotic HEV (genotypes 3 and 4) infections, spread primarily via undercooked pork, have been tied to several extrahepatic manifestations including neurological issues, glomerulonephritis, and autoimmune responses. Moreover, it often results in chronic infection, particularly in immunocompromised individuals. Non-zoonotic HEV (genotypes 1 and 2) is mainly waterborne and is transmitted through contaminated water in unsanitary areas. Generally, a stronger immune system in healthy individuals can prevail without complications, but pregnant women are at a higher risk of serious complications, such as ALF, stillbirth, and preterm delivery, particularly during the third trimester. Non-zoonotic HEV often causes an acute infection with a favorable prognosis for disease (with the exception of pregnant women), but zoonotic HEV can cause chronic hepatitis and cirrhosis in susceptible groups (49,50,61,67).

Hepatic Fibrosis and Cirrhosis

HEV infection has been shown to expedite the progression of liver fibrosis, inevitably leading to cirrhosis in individuals with a chronic case, especially those with pre-existing liver conditions (such as existing chronic liver disease).

Individuals with pre-existing liver disease may experience further hepatic decompensation from HEV superinfection, while recipients of solid organ transplants and those with severe immunosuppression may experience asymptomatic acute HEV infection (49). Cirrhosis can raise the risk of complications including hepatocellular cancer and liver failure over time (61,66,67).

However, studies cannot provide sufficient evidence for a conclusive inference when different studies are examined. A study found higher anti-HEV IgG and HEV-RNA positivity rates in cryptogenic cirrhosis patients compared to healthy controls. However, a positive correlation was observed between HEV-RNA levels and liver enzymes (AST and ALT), suggesting HEV infection may contribute to liver damage in these patients. This suggests a possible association between HEV and cryptogenic cirrhosis, but further research is required to confirm this association (72).

Extrahepatic Manifestations

HEV infection can cause neurological, renal, pancreatic, and hematological complications, complicating diagnosis due to mild liver function tests (67,73). Neurological issues include polyradiculopathy, Guillain-Barre syndrome, Bell's palsy, ataxia, and mental confusion. Renal issues include nephritis and a specific type of glomerulonephritis. Hemolytic anemia has been linked to HEV infection in immunocompromised individuals, and rare cases can cause pancreatitis (67,74).

While previous analyses had examined HEV's interactions with human-derived monocytes and macrophages, a new investigation revealed that monocytes, macrophages, and bone marrow-derived macrophages from humans exhibit tolerance to HEV infection. These immune cells, crucial for defense mechanisms, can be reservoirs for persistent infections, especially in individuals with compromised immunity. This persistence could lead to chronic infection and complicate patient management, especially in patients with immunodeficiencies or immunosuppressive treatments. The life cycle of HEV in human bone marrow-derived macrophages could be linked to the development of hematological conditions that manifest as extrahepatic symptoms, such as anemia and thrombocytopenia. However, there is a significant gap in understanding the full spectrum of extrahepatic manifestations associated with HEV, especially in immunocompromised patients. Further research is needed to clarify the mechanisms by which HEV affects various organ systems and contributes to non-liver-related symptoms (75).

Co-infection with Other Viruses

Infections with other hepatotropic viruses (as hepatitis B or hepatitis C) can coexist with zoonotic HEV infections, particularly in immunocompromised people. In this case, co-infection makes diagnosis and treatment more difficult, which results in severe conditions such as liver disease (76,77).

Autoimmune Phenomena

HEV infection can cause autoimmune reactions, particularly in people with less than ideal immunity. These reactions might manifest as rheumatic symptoms like arthritis and myalgia (pain in the muscles) or autoimmune hepatitis, in which the immune system unintentionally targets liver cells (78).

Diagnosis of HEV Infection

Both diagnostic and epidemiologic uses have led to the development of serological and nucleic acid testing (NAT) for the detection of HEV. The identification of HEV antigen, HEV-RNA, and serum antibodies against HEV [immunoglobulin A (IgA), IgM, and IgG] is necessary for the laboratory diagnosis of HEV infection (48,79).

Anti-HEV IgG antibodies can persist for over ten years, indicating distant exposure, but anti-HEV IgM antibodies can be found during the acute stage of the illness, and can continue for four to five months, indicating recent exposure. Therefore, the

presence of anti-HEV IgM, HEV antigen, and HEV-RNA, is used to diagnose acute infection, but anti-HEV IgG is the primary basis for epidemiological studies (79).

Acute HEV is diagnosed by detecting HEV IgM in serum; HEV-RNA in serum or stool specimens confirms the serologic diagnosis. Long-term, serial detection suggests chronic HEV infection. The United States of America Food and Drug Administration does not approve diagnostic tests for (specific condition or purpose).

HEV infection, but some establishments provide screening services.

The diagnostic laboratory within the Centers for Disease Control and Prevention's Viral Hepatitis Diagnostic Reference Laboratory division can offer testing assistance to identify HEV-specific antibodies (IgM and IgG) in patient samples and can provide an assay to detect HEV-RNA in blood and fecal samples (49).

Anti-HEV antibodies are frequently undetectable in immunocompromised individuals with chronic HEV, and NATs are the only accurate diagnostic method in these situations. When HEV-RNA is detected for three months or more, it is considered a chronic case of HEV. Viral load testing is utilized in these chronic instances to detect recurrent infections, and assess how well patients respond to changes in immunosuppressive medication or antiviral therapy (48).

In summary, the current European Association for the Study of the Liver guide recommends using a comb for the diagnosis of acute HEV infection (48).

The convalescent phase resolves icteric symptoms, with HEV1 and HEV2 causing more severe acute hepatitis presentations. HEV3 and HEV4 may cause severe infections in older men and ACLF in chronic liver disease patients (67).

Pregnant women and immunocompromised individuals are at risk for severe outcomes, and early diagnosis and timely management are crucial for improving patient outcomes (11,49,67). Pregnant women are at a high risk of developing symptomatic disease and ALF, leading to, mortality rates of 15-25% in specific trimesters, for those who develop these conditions (68,69,70). Acute HEV1 infections, particularly during the third trimester, can cause maternal morbidity and up to 20% maternal mortality due to eclampsia, hemorrhagic complications, and liver failure (69). Vertical transmission refers to the transfer of a virus from parent to child during childbirth or through breastfeeding (71). The application of serology and NAT tests diagnoses HEV infection, while the application of NAT tests specifically diagnoses chronic HEV infection (48).

Treatment

HEV infection usually has spontaneous viral clearance without treatment. No set approach is required for acute HEV infection; there is no approved treatment for chronic HEV infection. There is no vaccine approved by the (United States) Food and Drug Administration (66). Ribavirin therapy for severe acute HEV infection has very few available case reports. Within a few days of starting ribavirin medication, liver functions returned to normal, and HEV-RNA was no longer detected. There have been documented cases of ribavirin therapy for HEV genotype 1 and HEV genotype 3 infections. In one instance, liver synthetic function quickly improved (80). Individual cases of ALF that were later shown to be caused by HEV infection have been treated with corticosteroids. In these instances, steroid treatment was linked to better liver function metrics (48). But currently, there isn't enough data to support corticosteroid therapy for individuals with ALF brought on by HEV infection (81).

Risks for Public Health

HEV causes significant human infection in European Union/European Economic Area countries, with over 21,000 reported acute cases and 28 fatalities over the past decade, which shows a tenfold increase in reported cases. The majority of these cases (80%) have been from France, Germany, and the United Kingdom. However, as HEV infections are easy to miss and surveillance practices vary, the actual number of cases is likely higher than reported cases. Food-borne transmission, primarily through pigs and wild boars, is considered a major route of HEV infection in Europe. Both outbreaks and sporadic cases have occurred in immune-competent individuals, especially in those with high-risk conditions such as pre-existing liver conditions, immunosuppressive diseases, or those undergoing immunosuppressive treatments (82).

Preventive Measures and Vaccination Strategies

HEV is primarily transmitted through exposure to contaminated food and environmental factors. However, the propagation rate of HEV through these transmission routes can vary depending on factors such as the virus genotype, environmental conditions, hygiene practices, and the food consumed (83).

Waterborne transmission is the most common way for genotypes 1 and 2 for large outbreaks. The determination of zoonotic strains with the ability to traverse cross-species lines has expanded the host range and raised public health concerns due to its larger impact area. Every animal species is a possible host for HEV, and contact or consumption of host animals pose risks for infection, especially swine (19).

Development and Current Status of HEV Vaccines

Vaccine development for HEV in Europe is limited, with HEV-239 only being available in China for 10 years. Challenges in vaccine development include differences in genotype distribution, transmission routes, risk groups, and immune responses in vulnerable groups. This time, possible vaccine types focus on enhancing the immune system by stimulating proteins to induce protective antibody responses. The HEV-239 trial aimed to prevent acute symptomatic infections, but it is unclear if immunocompromised individuals have worse outcomes. Development of passive immunization or monoclonal antibody therapy, which has a neutralizing effect, is promising. Created vaccines should show clear effectiveness across all variations and maintain a strong safety standard (84).

Future Directions and Research Priorities

Future research on HEV should focus on improving epidemiological surveillance, developing diagnostic tools, vaccines, and therapeutics to control and prevent the spread of this disease. Key areas of surveillance include creating global networks to track HEV outbreaks, identifying asymptomatic infections, and studying HEV prevalence in animal populations. Rapid, affordable, and easy-

to-use diagnostic tools are essential for early detection. Portable genomic sequencing technologies can enable widespread viral monitor, track mutations, and understand HEV's evolution. Vaccine research should focus on universal vaccines, improve accessibility, and explore monoclonal antibodies. Host-based therapeutic approaches targeting immune responses or cellular mechanisms involved in HEV replication could complement antiviral therapies for chronic infections. Research into HEV's life cycle will help develop personalized treatments and prevent HEV-related liver cancer.

Conclusion

Zoonotic and non-zoonotic HEV infections are prevalent in different regions without discriminating the economic classifications and transmitted by various agents.

Zoonotic HEV is primarily spread from animals, particularly pigs, and can cause mild illness in healthy individuals with an healthy immune system but can lead to chronic liver damage in immunocompromised patients. Non-zoonotic HEV is generally acute and self-limiting but can cause severe complications, especially in pregnant women. Both types can cause extrahepatic manifestations, but zoonotic HEV is more likely to lead to chronic conditions.

While knowledge regarding HEV epidemiology and genetics has expanded in recent decades, surveillance shortcomings, diagnostic ambiguities, and vaccination barriers remain. Moving forward, prioritizing the differentiation of zoonotic from strictly human genotypes, enhancing diagnostic precision, and innovating preventive inoculations should be emphasized. A cohesive and integrated approach combining epidemiology, molecular biology, and vaccine development will be crucial for dealing with the complex nature of HEV.

In this disease, which does not discriminate between economic conditions, developed countries can take the lead and establish an information exchange structure with easy access to digital methods for worldwide monitoring and standardized reporting. This will create pivotal and ideal conditions for mitigating HEV's impact and improving global public health.

Footnotes

Authorship Contributions

Concept: M.A., Design: M.A., Literature Search: S.A., İ.E., M.A., Writing: S.A., M.A.

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Research Article

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Investigation of the Prevalence of HBV, HCV and HIV in Patients Receiving Hemodialysis Treatment for Chronic Renal Failure

Kronik Böbrek Yetmezliği Nedeniyle Hemodiyaliz Tedavisi Uygulanan Hastalarda HBV, HCV ve HIV Sıklığının Araştırılması

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ABSTRACT

Objectives: Patients on hemodialysis (HD) are more vulnerable to infections than the general population due to immunosuppression caused by chronic renal failure. Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) transmitted by blood are the most important causes of morbidity and mortality in these patients. The aim of this study is to investigate the prevalence of HBV, HCV and HIV in chronic renal failure patients undergoing HD treatment over a four-year period.

Materials and Methods: This study analyzed 3,799 patient records of persons receiving HD at Meram Medical Faculty and Konya City Hospitals from April 1, 2020, to December 31, 2023. Serum samples from all patients were analyzed for HB surface antigen (HBsAg), anti-HBs, anti-HCV, and anti-HIV markers. The serological parameters were assessed using the Architect I200 SR (Abbott, USA) or the Cobas 8000 immunoassay analyzer (Roche, Mannheim, Germany).

Results: After exclusion of duplicate data, 463 patients were eligible for the study. Of the patients, 52.4% were male, and 47.6% were female. The mean age was 54.5±16.1 years. All patients tested negative for anti-HIV. Seventeen patients (3.7%) were positive for anti-HCV, 11 patients (2.3%) were positive for HbsAg, and 423 patients (91.9%) were positive for anti-HBs.

Conclusion: Our results regarding the seroprevalence of HbsAg, anti-HCV, and anti-HIV in HD patients were consistent with existing literature from Türkiye. Conversely, we observed an

ÖZ

Amaç: Hemodiyaliz (HD) tedavisi uygulanan hastalar, kronik böbrek yetmezliği nedeniyle bağışıklıkları baskılandığı için enfeksiyonlara karşı normal popülasyona göre daha duyarlıdır. Kan yoluyla bulaşan hepatit B virüsü (HBV), hepatit C virüsü (HCV) ve insan immün yetmezlik virüsü (HIV) bu hastalarda en önemli morbidite ve mortalite nedenlerindendir. Bu çalışmanın amacı HD tedavisi gören kronik böbrek yetmezliği nedeniyle HD tedavisi alan hastalarda HBV, HCV ve HIV sıklığının incelenmesidir.

Gereç ve Yöntemler: Çalışmada 01.04.2020-31.12.2023 tarihleri arasında Meram Tıp Fakültesi ve Konya Şehir Hastanelerinde HD tedavisi gören 3.799 hasta kaydı değerlendirildi. Tüm hastaların serum örneklerinde hepatit B yüzey antijeni (HBsAg), anti-HBs, anti-HCV ve anti-HIV parametreleri araştırıldı. İlgili parametreler Architect I200 SR (Abbott, ABD) veya Cobas 8000 immünoanaliz analizör (Roche, Mannheim, Almanya) cihazları kullanılarak incelendi.

Bulgular: Tekrar veriler çıkarıldıktan sonra çalışmaya dahil edilen 463 hastanın yaş ortalaması 54,5±16 yıl olup, %52,4'ü erkekti. Serolojik belirteçler incelendiğinde hastaların tamamında anti-HIV negatif bulundu. Anti-HCV 17 (%3,7) hastada; HBsAg 11 (%2,3) hastada pozitif olarak saptanırken, anti-HBs ise 423 hastada (%91,9) hastada pozitif olarak belirlendi.

Sonuç: Çalışmamızda HD hastalarındaki HBsAg, anti-HCV, anti-HIV pozitiflik oranlarında, ülkemizde yapılmış olan çalışmalara benzer veriler elde edildi. Anti-HBs pozitifliği ise daha yüksek saptandı.

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elevated prevalence of anti-HBs positivity among HD patients. The vaccination procedures administered to dialysis patients receiving treatment in tertiary hospitals in Konya were deemed highly effective. We emphasize that those at risk for HBV infection must receive vaccination without exception, and that infection control protocols in dialysis units should adhere to established guidelines.
Keywords: Chronic renal failure, hemodialysis, HBV, HCV, HIV

Sonuç olarak, Konya ilinde bulunan üçüncü basamak hastanelerde tedavi gören diyaliz hastalarında uygulanan aşılama politikalarının başarılı olduğu belirlendi. Hepatit B'ye karşı duyarlı olan hastaların mutlaka aşılanması ve diyaliz ünitelerinde uygulanan enfeksiyon kontrol önlemlerinin standartlara uygun şekilde yürütülmesi gerektiği kanaatindeyiz.
Anahtar Kelimeler: Kronik böbrek yetmezliği, hemodiyaliz, HBV, HCV, HIV

Introduction

Hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) are significant public health concerns affecting millions of people worldwide. In 2022, it was reported that HBV affected 1.1 million people, while HCV infected 244,000 individuals. Without effective measures, it is estimated that viral hepatitis could cause 1.14 million deaths by 2034 (1,2). HIV, on the other hand, was responsible for 630,000 deaths in 2022, and the annual incidence of HIV exceeds 1.5 million (3). It is estimated that 80% of individuals infected with viral hepatitis and HIV are unaware of their condition and therefore lack access to treatment (3). HCV infection is a serious health problem that can progress to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. Although there is currently no effective vaccine, HCV can be treated with highly effective antiviral agents, which can reduce complications. However, because HCV infection is often asymptomatic, it can easily go undiagnosed (4).

Chronic kidney disease (CKD), which impairs the kidneys' metabolic and endocrine functions, is a major health concern as it can lead to severe fluid and electrolyte imbalances due to decreased glomerular filtration rates (5). Hemodialysis (HD), which is used to improve life expectancy and quality in CKD patients, weakens the patients' cellular immune system, making them more susceptible to blood-borne viral infections (5). Factors such as percutaneous interventions, blood transfusions, patient age, dialysis duration, and the contamination of HD machines and other equipment increase the risk of HBV, HCV, and HIV transmission among HD patients (6,7). The World Health Organization and the Turkish Society of Nephrology (TSN) recommend vaccinating patients diagnosed with CKD against HBV, implementing infection control measures to prevent the transmission of HBV, HCV, and HIV in HD units, and routinely screening blood products for these pathogens (8). As a result of the implemented strategies, the prevalence of HBV and HCV in HD units has gradually decreased. For instance, with the initiation of HBV vaccination programs in the United States, HBV incidence among HD patients has decreased by 95% (9). This study aims to examine the seroprevalence of HBV, HCV, and HIV among CKD patients undergoing HD in the Konya region.

Materials and Methods

In this study, patient records of 3,799 individuals receiving HD treatment at Meram Medical Faculty and Konya City Hospitals between April 1, 2020, and December 31, 2023, were retrospectively reviewed. After removing duplicate records, 463 patients were included in the study.

Statistical Analysis

Serum samples from all patients were tested for hepatit B surface antigen (HBsAg), anti-HBs, anti-HCV, and anti-HIV parameters. These parameters were analyzed using chemiluminescent immunoassay on the Architect I2000 SR (Abbott, USA) or electrochemiluminescence on the Cobas 8000 immunoassay analyzer (Roche, Mannheim, Germany). HCV ribonucleic acid (RNA) levels were detected using a commercial kit (HCV-RNA QS-RGQ Kit, Hilden, Germany) through real-time polymerase chain reaction (PCR) analysis.

The obtained data were evaluated using descriptive statistical tests, percentage calculations, and mean ± standard deviation.

The protocol was reviewed and approved by Necmettin Erbakan University Drug and Non-Medical Device Research Ethics Committee (date: 16.06.2023, decision number: 2023/4385).

Results

The mean age of the 463 patients in the study was 54.5±16.1 years, with 52.4% being male. Upon the assessment of the serological markers, anti-HIV was found to be negative in all cases. Anti-HCV was found to be positive in 17 patients (3.7%), HBsAg in 11 patients (2.3%), and Anti-HBs in 423 patients (91.4%). HCV-RNA was undetectable in the plasma of 17 anti-HCV positive patients using the real-time PCR method. The mean anti-HCV value was 54.1±28.2 cut-off index (COI) [minimum (min): 0.935, maximum (max): 99.5]; the mean HBsAg value was 2,375.2±1,826.6 COI (min: 33, max: 7,531); and the mean anti-HBs value was 396.0±27 IU/mL (min: 10.7, max: 99.5), as represented in Table 1.

We observed that the serological tests were routinely performed every three months. Among the 423 anti-HBs-positive HD patients, 18.4% (78/423) were identified as seronegative at least once during the study duration. For these patients, the following situation was revealed when the study timeline was extended both forward and backward. Even though the patients had received prior vaccinations, they gradually lost their antibody titers and developed an anti-HBs negative status. It took a mean of 8.1 months for the anti-HBs titer to decline by 50%, and 32.1 months for it to decline to less than 10 IU/mL. Both HBsAg and anti-HBc were negative in those patients. Among those 78 patients, 24.4% (19/78) developed anti-HBs titers of <100 IU/mL after completing HBV vaccination, a condition defined as that of a low-responder. Non-responders to immunization were identified in 17 of the HD patients (3.8%).

Table 1. Seroprevalence of hepatitis markers in hemodialysis patients

	Percentage of seropositivity (n)	Mean value of serum levels	Mean age	Gender
HBsAg	%2.3 (11/463)	2,375.2±1,826.6 COI	54.5±16.1	52.4% (male) 47.6% (female)
Anti-HCV	%3.7 (17/463)	54.1±28.2 COI		
Anti-HBS	%91.4 (423/463)	396±27 IU/mL		
Anti-HIV	Not detected	-		

HBsAg: Hepatitis B surface antigen, Anti-HCV: Hepatitis C antibody, Anti-HBs: Hepatitis B surface antibody, Anti-HIV: Antibody against human immunodeficiency virus, COI: Cut-off index

Discussion

The prevalence of HBsAg positivity in dialysis patients correlates with the endemicity in the general population. Notwithstanding the availability of effective vaccinations since 1982, HBV infection remains widespread in numerous countries. Türkiye is classified as a medium-risk endemic area for HBV. Numerous studies indicate that the HBsAg positive rate among HD patients in Türkiye ranges from 3.6% to 8.7% (10,11,12,13,14). A systematic analysis of global research revealed HBsAg positivity rates among HD patients of 1% in the United States, 5.9% in Italy, 12% in Brazil, and between 1.3% and 14.6% in Asia Pacific nations (15). The HBsAg positive rate among HD patients in Türkiye was reported by the TSN as 3.8% in 2016 and 2.57% in 2019 (16). In our investigation, the HBsAg positivity rate was slightly lower than the national data reported by TSN. Individuals having an anti-HBs titer of ≥10 mIU/mL and a negative anti-HBc status are deemed to be immune against HBV via vaccination (17). Patients who are negative for anti-HBs, anti-HBc, and HBsAg and have not previously been exposed to the HBV are at risk of HBV infection during HD. HBV vaccinations must be promptly delivered to these patients (17). Research conducted in Türkiye indicates that the anti-HBs positivity ranges from 33.5% to 64% (18). Research in the Konya region found that the anti-HBs positivity rate among HD patients was 11.2% (19). We found that the anti-HBs positivity rate among HD patients in the Konya region was significantly higher than those reported in other local surveys (19). Strict adherence to HD patient follow-up requirements may be the cause of the high antibody positivity rate. We observed that serological tests were routinely performed every three months on HD patients. The patients whose antibody titers started to wane received the booster dose or vaccination in a timely manner. Another reason may be a meticulous analysis of the records we performed. We carefully avoided duplicate data. Furthermore, during the course of the three-year study period, we found that 18.4% (78/423) of HD patients who had been positive for anti-HBs developed seronegative status. The response of HD patients to vaccination varies depending on nutritional status and immunological factors (20). It has been reported that the general population and HD patients have inadequate seroconversion rates of 5-10% and 20%, respectively (20). An anti-HBs titer greater than 10 IU/mL is considered to indicate seroconversion. Indeed, an anti-HBs titer greater than 100 IU/mL is recommended. On the other hand, a low response is indicated if the anti-HBs titer is less than 100 IU/mL (20). We observed that 24.4% of HD patients had anti-HBs titers of less than 100 IU/mL five weeks after completion of the HBV immunization, while 3.8% were found to be non-responders.

The HBV vaccine's durability is not well established. While the general population and HD patients are known to experience a reduction in anti-HBs titer over time, patients on renal replacement therapy experience this decline much more frequently and more quickly (20). The majority of HD patients have undetectable anti-HBs titers at the end of the third year of vaccination (20). In our study, it took a mean of 8.1 months for the anti-HBs titer to decline by 50%, and 32.1 months for it to decline to less than 10 IU/mL. Furthermore, antibody titers in anti-HBs-positive HD patients should be assessed at regular intervals to evaluate potential declines in immune response and ascertain the necessity for a booster dose of the HBV vaccination (anti-HBs ≤10 mIU/mL) (20).

Nosocomial transmission constitutes a significant risk factor for HBV infection in HD patients. The preparation of medications for intravenous administration in the HD setting has been demonstrated to elevate the transmission risk of HBV infection (21). Although it has been demonstrated that HBV-DNA crosses the dialysis membrane during high-flux dialysis, the infectiousness of dialysate and ultrafiltrate remains an issue of debate. The Centers for Disease Control and Prevention states that dialyzers obtained from HBsAg positive patients must not be reused, and dialysis equipment should be segregated. HBsAg screening tests should be conducted every three months to identify new HBV infections in HD patients. Consequently, the dialysis units for these patients must be isolated, and specific infection control protocols should be implemented to mitigate the risk of HBV transmission. Patients diagnosed with chronic HBV infection should be evaluated for HBeAg, HBV-DNA levels, and the progression of cirrhosis. Despite the low rate of occult HBV infection in HD patients, those who are HBsAg negative and HBV-DNA positive must be dialyzed apart from those who are HBsAg positive to mitigate the risk of nosocomial transmission (21).

Despite the lower rate of HCV infection compared to HBV in Türkiye, it continues to be of importance among specific patient groups due to its severity and the absence of a vaccine. HCV infection is particularly critical due to its potential for nosocomial transmission among dialysis patients (22). The frequency and duration of dialysis, screening through antibody detection tests prior to blood transfusion and transplantation, and intravenous drug use are factors that increase the risk of HCV transmission (23). The anti-HCV positivity rate among HD patients in Türkiye ranges from 4.1% to 28% (24,25,26,27,28). The global anti-HCV positivity rate among HD patients ranges from 4% to 59% (29). The TSN reported an anti-HCV positivity rate of 5.2% in HD patients in 2016 (30). Our study revealed an anti-HCV positivity rate of 3.7% among

HD patients in Konya, which is slightly lower than the rate reported by the TSN.

The data concerning the rates of HIV infection in HD patients are limited. Reports show that the prevalence of anti-HIV antibodies in HD patients in Türkiye is 0.1% (30). HIV infection can be prevented by strict adherence to standard infection control protocols in dialysis facilities. Isolation of dialysis machines or patients is not advised. HIV transmission during HD has been documented in Argentina, Egypt, and Colombia (31,32,33). We found that anti-HIV antibodies were negative in all HD cases. Research conducted in various countries has shown similar findings (19).

To prevent viral hepatitis and HIV transmission in HD patients, it is essential to screen blood products for HBsAg and HBV core antibody (anti-HBc), anti-HCV, and anti-HIV; vaccinate staff and susceptible patients; implement infection-control strategies in dialysis units; use erythropoiesis-stimulating agents to decrease transfusion requirements; isolate dialysis machines for patients with viral hepatitis; and prevent shared use of equipment and medications among patients. Nevertheless, vaccination efforts and prevention measures implemented in HD units, healthcare staff, and patients remain at elevated risk of blood-borne viral agents (34).

In our study, the mean anti-HCV level was determined to be 54.1±28.2 (COI), the mean HBsAg level was 2,375.2±1,826.6 (COI), and the mean anti-HBs level was 396±27 mIU/mL. Our results defy the widespread knowledge that false positive results for HIV and HCV tests are common in HD patients. We did not observe false positives for anti-HIV. Additionally, in our study, low-titer anti-HCV positivity was very rare, and repetitive tests confirmed these results as negative.

Conclusion

Strict implementation of infection control measures, the separation of dialysis machines for patients with viral hepatitis, and the correct application and expansion of vaccination policies are essential to prevent viral transmission in HD patients. Serological screening tests should be regularly monitored. Moreover, HD patients susceptible to HBV should be vaccinated, and appropriate precautions should be implemented by monitoring anti-HBs levels post-vaccination.

Ethics

Ethics Committee Approval: The protocol was reviewed and approved by Necmettin Erbakan University Drug and Non-Medical Device Research Ethics Committee (date: 16.06.2023, decision number: 2023/4385).

Informed Consent: Informed consent was not obtained since it was a retrospective study.

Footnotes

Authorship Contributions

Concept: A.R.U., B.E., B.F., M.Ö., Design: A.R.U., B.E., B.F., M.Ö., Data Collection or Processing: A.R.U., B.E., B.F., M.Ö., Analysis or Interpretation: A.R.U., B.E., B.F., M.Ö., Literature Search: A.R.U., B.E., B.F., M.Ö., Writing: A.R.U., B.E., B.F., M.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research Article

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Genotype Distribution of Hepatitis C Virus in Patients with Chronic Hepatitis C in Muğla, Türkiye (2019-2024)

Kronik Hepatit C'li Hastalarda Hepatit C'nin Genotip Dağılımı, Muğla, Türkiye (2019-2024)

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ABSTRACT

Objectives: Hepatitis C virus (HCV) continues to be an increasingly significant public health concern due to its substantial impact on morbidity and mortality. This study aims to determine the dynamic genotype (GT) distribution of HCV among HCV infections admitted to Muğla Training and Research Hospital and to evaluate the relationship between HCV GTs and factors such as gender and age.

Materials and Methods: A total of 230 patients with chronic HCV were included in the study between January 2019 and October 2024. Quantitative HCV-RNA polymerase chain reaction (PCR) tests were performed using the Rotor-Gene Q real-time PCR system, and HCV genotyping was conducted with the PyroMark Q24 pyrosequencing system.

Results: Among the 220 patients analyzed for HCV GTs, 69.5% were male, and 30.5% were female. The most prevalent GT was GT1, observed in 66.4% of cases. In females, the most common GT was 1b (58.2%), while in males, GT3a was the most frequent (35.9%). Of the patients, 90.9% (200) were Turkish, while 9.1% (20) were foreign nationals. The most common GT was GT1b, with frequencies of 34.0% and 70.0% respectively. On a yearly basis, GT1b was detected at the highest rates in 2021, 2022, 2023, and 2024. In contrast, GT1a was most common in 2019, and GT3a was predominant in 2020. Regarding age groups, the highest prevalence was observed in the 18-30 age range (30.9%; 68 cases), while the lowest was in individuals under 18 years, with only one case.

Conclusion: In our study, among patients tested for HCV GTs, GT1 was the most common GT, with a prevalence of 66.4%. This finding is consistent with many studies worldwide. The GT distribution was found to be associated with the patients' gender. The GT distribution was statistically significantly higher in the 18-30 age group among all age groups.

Keywords: Hepatitis C virus, hepatitis C virus genotypes, chronic hepatitis C, hepatitis C virus subtypes

ÖZ

Amaç: Hepatit C virüsü (HCV), morbidite ve mortalite üzerindeki önemli etkisi nedeniyle giderek artan bir halk sağlığı sorunu olmaya devam etmektedir. Bu çalışmanın amacı, Muğla Eğitim ve Araştırma Hastanesi'ne başvuran HCV enfeksiyonlu olguların HCV'nin dinamik genotip (GT) dağılımını belirlemek ve HCV GT'si ile cinsiyet ve yaş gibi faktörler arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntemler: Ocak 2019 ile Ekim 2024 tarihleri arasında 230 kronik HCV'li hasta çalışmaya dahil edildi. Kantitatif HCV-RNA polimeraz zincir reaksiyonu (PCR) testleri, Rotor-Gene Q gerçek zamanlı PCR cihazında ve HCV GT'lendirme, PyroMark Q24 pyrosekans cihazında yapıldı.

Bulgular: HCV GT'leri araştırılan 220 hastanın, %69,55'i erkek ve %30,5'i kadındı, en yaygın GT %66,4 ile GT1 idi. Kadınlarda, %58,2 ile GT1b, erkeklerde ise %35,9 ile GT3a idi. Hastaların %90,9 (200)'u Türk, %9,1 (20)'i ise yabancı idi, en sık görülen GT sırasıyla, %34,0 ve %70,0 ile GT1b idi. Yıllara göre; 2021, 2022, 2023 ve 2024 yıllarında GT1b, 2019'da GT1a ve 2020'de ise GT3a en yüksek oranda saptanmıştır. Yaş gruplarına göre; en yüksek %30,9 (68) ile 18-30 yaş arasında, en düşük ise 1 olgu ile 18 yaş altında görüldü.

Sonuç: Çalışmamızda HCV GT'leri araştırılan hastada, %66,4 ile GT1 en yaygın görülen GT'ydi, bu bulgu, dünya genelindeki birçok çalışmayla paralellik göstermektedir. GT dağılımının hastaların cinsiyetiyle ilişkili olduğunu göstermiştir. Yaş gruplarına arasında GT dağılımları 18-30 yaş arasında istatistiksel olarak anlamlı ölçüde yüksek idi.

Anahtar Kelimeler: Hepatit C virüsü, hepatit C virüsü genotipleri, kronik hepatit C, hepatit C virüsü alt tipleri

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Introduction

Hepatitis C virus (HCV) is responsible for a significant proportion of chronic liver diseases worldwide (1). Due to its substantial impact on morbidity and mortality, HCV continues to be a significant public health concern (2). Unlike hepatitis A and B, there is currently no vaccine available to prevent HCV infection (3). It is estimated that HCV accounts for 27% of cirrhosis cases and 25% of hepatocellular carcinoma cases globally (1). HCV can be detected in blood and body fluids, with transmission primarily occurring through contact with infected blood or blood products. In developed countries, the most common route of transmission is needle sharing among people who inject drugs. Perinatal transmission from mother to child and sexual transmission among men who have sex with men have also been documented (4). The World Health Organization (WHO) has set a goal to eliminate HCV infection by 2030, which includes "a 90% reduction in new chronic HCV cases, a 65% reduction in HCV-related deaths, and treatment for 80% of eligible individuals with chronic HCV infection" (5).

HCV is an enveloped (E), single-stranded, positive-sense RNA virus belonging to the *Hepacivirus* genus of the *Flaviviridae* family (6). The HCV genome contains both highly conserved and highly variable regions. The 5' untranslated region, core, E1, and non-structural protein 5B regions are relatively well-conserved and are used for classification purposes. In contrast, the E2 glycoprotein region is the most variable part of the genome (7). HCV exhibits significant genetic diversity due to the high mutation rate of its viral polymerase and the high turnover of the virus (8). Based on phylogenetic and sequence analyses of the entire viral genome, seven genotypes (GTs) (1a+1b, 2, 3, 4, 5, 6, and 7) have been documented. HCV strains show extensive genetic diversity, with nucleotide regions differing by approximately 35%. Each GT is further subdivided into 67 confirmed and 21 provisional subtypes, with strains from the same family differing by less than 15% in nucleotide regions (9).

The distribution of HCV GTs varies across different geographical regions worldwide. GT1 is prevalent in North America, South America, Western and Northern Europe, accounting for 46% of all HCV cases. GT3 is common in South Asia, Australia, and parts of Western Europe, representing 30% of global HCV cases (10). GT2 is found predominantly in West Africa and South America, while GT4 is prevalent in Central and North Africa (10). GT5 is primarily located in the Middle East and North Africa but has also been reported in South Africa. GT6 is mostly distributed across Southern China and Southeast Asia (5). GT7 has been reported in Central Africa, having been isolated from patients in the Democratic Republic of Congo (9). In studies conducted on the general population in Türkiye, GT1 accounts for 76-93% of HCV cases, GT3 for 3.7-6.7%, GT2 for 1.5-2.2%, and GT4 for 1.1-9.8% (11). The global distribution of HCV genetic variations is likely influenced by increasing international travel, migration between countries, and historical events (7).

The dominant treatment for HCV infection previously consisted of pegylated interferon-α combined with the nucleotide analog ribavirin. Recently, the development of direct-acting antivirals (DAAs) has enabled near-complete eradication of HCV in infected individuals. However, the high cost of DAAs, the presence of undiagnosed patients, and the emergence and spread of resistant mutants pose significant challenges to the elimination of HCV (6). Currently, the choice of DAA regimen, treatment duration, and sustained virological response remains dependent on the HCV GT and subtype (7). As the effects of pangenotypic treatments on different GTs are not yet fully understood, determining the HCV GT before treatment remains crucial.

This study aims to identify the dynamic GT distribution of HCV in cases of HCV infection presenting to Muğla Training and Research Hospital and to evaluate the relationship between HCV GT and factors such as age and gender.

Materials and Methods

This study included 230 HCV-RNA-positive patients, who underwent HCV GT testing in the Molecular Laboratory of the Muğla Training and Research Hospital between January 2019 and October 2024. Ethical approval was obtained from the Muğla Sıtkı Koçman University Medical Sciences Ethics Committee (approval number: 177, date: 23.12.2024).

Quantitative HCV-RNA Analysis

HCV-RNA in plasma samples was determined using quantitative real-time reverse transcription polymerase chain reaction (RT-PCR). Viral nucleic acid extraction was performed using the "QIAsymphony DSP Virus/Pathogen Midi Kit" (Qiagen, Catalog No: 937055, Hilden, Germany) with the QIAsymphony SP/AS device (Qiagen, Catalog No: 9001297, Hilden, Germany). Quantitative HCV-RNA PCR tests were conducted with the Arthus HCV QS-RGQ PCR Kit (Qiagen, Catalog No: 4518366, Hilden, Germany) using the Rotor-Gene Q real-time PCR system (Qiagen, Catalog No: 9001580, Hilden, Germany). The test's dynamic range was 50 IU/mL to $1x10^7$ IU/mL, and the linear range was $1.77x10^6$ IU/mL to $2.50x10^7$ IU/mL.

HCV genotyping of the study population (GTs: 1a, 1b, 2a, 2b, 3a, 3b, 3k, 4a, 4d, 5a, 6, and 7a) was performed using the QIAGEN OneStep RT-PCR Kit (Qiagen, Catalog No: 210210 or 210212, Hilden, Germany) on the Qiagen PyroMark Q24 Pyrosequencing System (Qiagen, Hilden, Germany).

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 22.0 (Armonk, NY, USA). The normality of variable distributions was assessed through visual methods (histograms and probability plots) and the Kolmogorov-Smirnov test. Quantitative variables were compared using the Mann-Whitney U test, while qualitative variables were analyzed using Pearson's chi-square test. Correlation coefficients and statistical significance between variables were calculated using Spearman's rank correlation coefficient test. Results with a p-value of less than 0.05 were considered statistically significant.

Results

This study included 220 chronic HCV patients whose HCV GTs were investigated using real-time PCR. The mean age of the 220 participants was 42.61±17.09 years, with 30.45% being female and 9.1% being foreign nationals.

Among the 220 patients analyzed, GT1 was the most prevalent GT, observed in 66.4% of cases, followed by GT3 in 30.9%, GT4 in 1.8%, and GT2 in 0.9% (Figure 1). Among chronic HCV patients with GT1, subtype 1b was identified in 37.3%, and subtype 1a was identified in 29.1%. For GT2, only subtype 2a was detected in 0.9% of cases, with no other subtypes identified. Among GT3 patients, subtype 3a was present in 30.9% and subtype 3b in 0.5%. For GT4, only subtype 4a was detected in 1.8% of cases, with no other subtypes identified. GTs 5, 6, and 7 were not observed in the study population. Additionally, no mixed-GT infections were detected. The distribution of HCV GTs based on demographic and virological characteristics is presented in Table 1.

Of the patients tested for HCV GTs, 69.55% (153) were male, and 30.5% (67) were female. The proportion of males was statistically significant higher than that of females (p=0.001). The most common GTs in females were GT1b (58.2%) and GT1a (19.4%), whereas in males, GT3a (35.9%) and GT1a (33.3%) were more prevalent. The mean age of patients within the GT groups was highest in GT1b, with a mean of 52.74±17.87 years. The median age for each GT group is shown in Table 1.

Among the patients tested, 90.9% (200) were Turkish nationals, while 9.1% (20) were foreign nationals. No statistically significant difference was found between Turkish and foreign patients (p=0.068). The most common GTs among Turkish patients were GT1b (34.0%) and GT3a (32.0%), while GT1b was predominant in foreign nationals (70.0%).

When evaluating GT distribution over the years, GT1b was found at the highest rates in 2021, 2022, 2023, and 2024, while GT1a was most common in 2019, and GT3a was most prevalent in 2020. No statistically significant difference in GT distribution across years was observed (p=0.215) (Table 1).

HCV GTs were most frequently observed in the 18-30 age group (30.9%, n=68), with the lowest occurrence in individuals under 18 years old (1 case). The most common GTs by age group were GT1b in 18-30 years, GT3a in 31-40 years, GT3a in 41-50 years, and GT1b in 51-60 years, and GT1b in individuals over years. When comparing GT distributions among age groups, the prevalence in the 18-30 age group was statistically significantly higher than in other age groups (p=0.001) (Figure 2).

Table 1. Demographic and laboratory data of the study population

	Total (n)	Genotype 1a, n (%)	Genotype 1b, n (%)	Genotype 2a, n (%)	Genotype 3a, n (%)	Genotype 3b, n (%)	Genotype 4a, n (%)	p-value
Number	220	64 (29.1)	82 (37.3)	2 (0.9)	67 (30.5)	1 (0.5)	4 (1.8)	
Age, mean	42.61±17.09	37.33±15.40	52.74±17.87	36.50±17.68	35.54±11.49	27±0.0	44.75±8.62	
Sex								
Female	67	13 (19.4)	39 (58.2)	1 (1.5)	12 (17.9)	0 (0.0)	2 (3.0)	
Male	153	51 (33.3)	43 (28.1)	1 (0.7)	55 (35.9)	1 (0.7)	2 (1.3)	0.001
Nationality								
Turkish	200	61 (30.5)	68 (34.0)	2 (1.0)	64 (32.0)	1 (0.5)	4 (2.0)	
Foreigner	20	3 (15.0)	14 (70.0)	0 (0.0)	3 (15.0)	0 (0.0)	0 (0.0)	0.068
Years								
2019	43	18 (41.9)	10 (23.3)	1 (2.3)	13 (30.2)	0 (0.0)	1 (2.3)	0.215
2020	42	13 (31.0)	10 (23.8)	0 (0.0)	17 (40.5)	0 (0.0)	2 (4.8)	
2021	41	7 (17.1)	20 (48.8)	0 (0.0)	13 (31.7)	0 (0.0)	1 (2.4)	
2022	29	9 (31.0)	12 (41.4)	0 (0.0)	8 (27.6)	0 (0.0)	0 (0.0)	
2023	29	11 (37.9)	13 (44.8)	0 (0.0)	5 (17.2)	0 (0.0)	0 (0.0)	
2024	36	6 (16.7)	17 (47.2)	1 (2.8)	11 (30.6)	1 (2.8)	0 (0.0)	

Discussion

HCV GTs exhibit varying prevalence across different regions of the world. The distribution of HCV GTs differs by geographic areas, populations, and even specific risk groups. Globally, GT1 accounts for 44% of HCV infections and 60% of infections in high- and middle-income countries. GT3 constitutes 25% of all HCV infections, GT4 accounts for 15%; while GTs 5, 7, and 8 represent less than 1% of global HCV infections (12). Effective control of HCV infections depends on determining GT distribution, as it is integral to predicting treatment response and selecting the appropriate DAA regimen and its duration. Changes in GT prevalence pose challenges in the development of vaccines and therapeutics (10).

According to WHO guidelines, pan-GT treatment regimens are preferred for individuals with chronic HCV. However, GT-specific treatments are recommended in countries where certain viral GTs

are more prevalent (13). GT1 is the most common globally and in developed countries. It responds well to second-generation DAAs, achieving viral eradication rates of over 90% (7).

Studies investigating GT distribution in chronic HCV patients worldwide show consistent regional variations. For instance, Pimenov et al. (13) reported GT1 dominance in Russia (53.6%), followed by GT3 (35.4%) and GT2 (7.8%). Similarly, Yang et al. (14) identified GT1 as the most prevalent in China (58.2%), with GT2 (18.4%) and GT3 (11.4%) being the second and third most common, respectively. In Brazil, Pereira et al. (15) found GT1 (46.98%), including subtypes 1a (14.1%) and 1b (15.7%), as the most frequent, followed by GT3a (13.0%), GT3 (7.1%), and GT2 (1.2%). Petruzziello et al. (16) reported that GT1b remained dominant across three study periods in Italy (51.8% in 2006-2008, 48.3% in 2009-2011, and 54.4% in 2012-2014). In Ethiopia, Hundie et al. (17) found GT4 to be the most prevalent (76.1%), followed by GT2 (13%) and GT1 (8.7%).

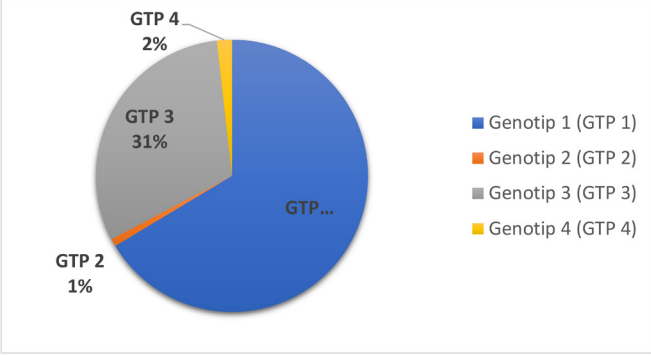


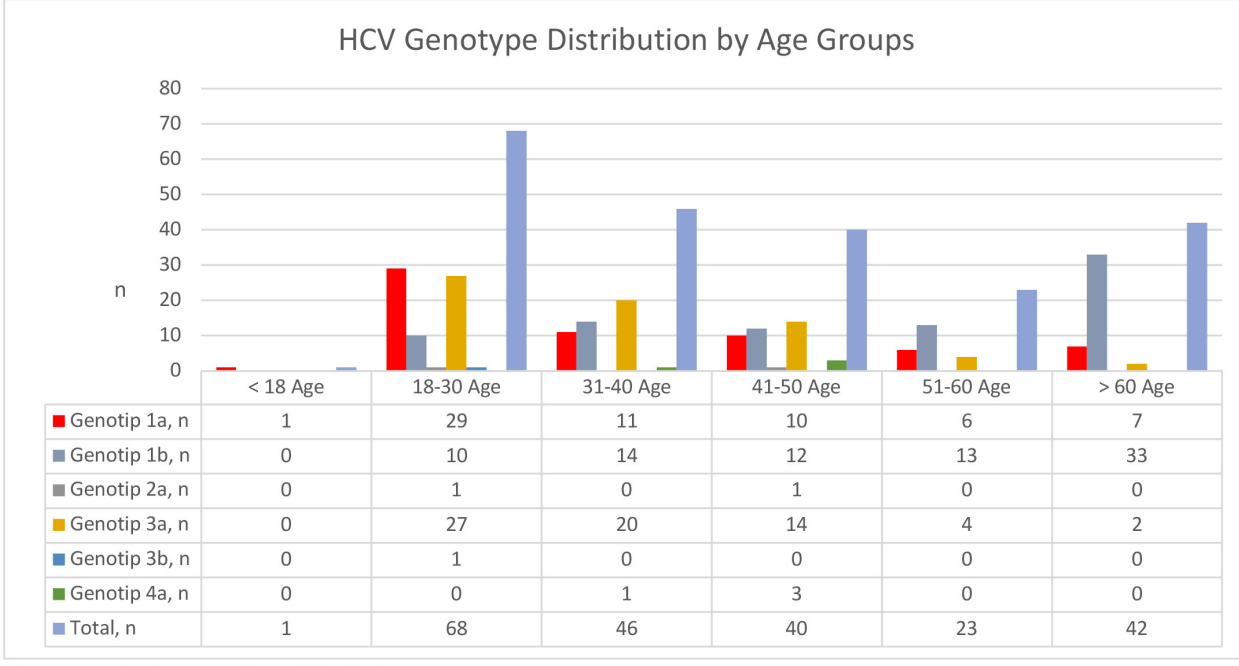
Figure 1. Distribution of hepatitis C virus genotypes in the study population

In Türkiye, GT1 has been reported as the leading cause of HCV infections, with prevalence ranging from 51.7% to 97.1% (7). Specific studies in Türkiye have demonstrated similar trends. For example, Cırıt et al. (18) found GT1 to constitute 51.5% of infections in Gaziantep, followed by GT3 (21.4%) and GT4 (20%). Bulut et al. (19) reported GT1 as the most frequent in İstanbul (81.3%), followed by GT3 (8.8%) and GT2 (3.4%). Selek et al. (20) identified GT1b in 67.0% of cases, GT3 in 16.0%, GT1a in 14.2%, and GT2 in 2.8%. Kirdar et al. (21) observed GT1 as the most prevalent in Aydın (90.2%), followed by GT3 (5.9%), GT2 (2.1%), and GT4 (1.4%). Karabulut et al. (7) found GT1 to dominate (82.5%), followed by GT3 (10.7%), GT2 (4.6%), and GT4 (2.2%).

In line with other national studies, our study identified GT1 as the most common GT (66.4%), followed by GT3 (30.9%), GT4 (1.8%), and GT2 (0.9%). The prevalence of the most common subtype 1b, in Türkiye has been reported to range between 56.5% and 100% (7). In our study, among chronic HCV patients with GT1, subtype 1b was found in 37.3% and subtype 1a in 29.1%. For GT2, only subtype 2a was identified (0.9%). Among GT3 patients, subtype 3a was observed in 30.9% and subtype 3b was observed in 0.5%. For GT4, only subtype 4a was identified (1.8%).

Our findings reveal both similarities and notable differences compared to previous global and national studies on chronic HCV. GT1 remains the most commonly detected GT in Turkish patients, aligning with global studies, particularly in developed countries and Türkiye, where GT1 prevalence exceeds 50%.

Social events causing changes in society, such as war and migration, along with increased population mobility and various transmission routes, significantly influence the epidemiology of infections. In Europe, GT3 is the second most common GT, especially prevalent among intravenous drug users. The prevalence of GT3 in Türkiye varies substantially. In our study, GT3 ranked



	< 18 Age	18-30 Age	31-40 Age	41-50 Age	51-60 Age	> 60 Age
Genotip 1a, n	1	29	11	10	6	7
Genotip 1b, n	0	10	14	12	13	33
Genotip 2a, n	0	1	0	1	0	0
Genotip 3a, n	0	27	20	14	4	2
Genotip 3b, n	0	1	0	0	0	0
Genotip 4a, n	0	0	1	3	0	0
Total, n	1	68	46	40	23	42

Figure 2. Distribution of hepatitis C virus genotype by age groups

second after GT1, accounting for 30.9% of cases. Muğla, a tourist city with intense tourism activity, experiences substantial human circulation and migration, which may explain the differences in HCV GTs observed in this region. In our study, subtype 1b was identified in 37.3% of cases, consistent with the high prevalence reported by Karabulut et al. (7). The predominance of subtype 1b among GT1 cases in Türkiye, compared to other countries, suggests that GT-specific treatment approaches, particularly for subtype 1b, may be effective given its favorable response to therapy.

This study revealed a significant association between GT distribution and patient sex. Among patients with identified HCV GTs, 69.5% were male, and 30.5% were female. The proportion of males was statistically significantly higher than females (p=0.001). Various epidemiological studies suggest that men may engage in higher-risk sexual behaviors, leading to a higher prevalence of HCV among men. Subtypes 1b and 1a were more common among women, whereas subtype 3a and subtype 1a were more common among men. Research by Pimenov et al. (13) in Russia showed that GT1 and GT3 were the most prevalent GTs among both men and women. Yang et al. (14) in China identified GT1 and GT2 as the most common GTs in both sexes. In Georgia, Baliashvili et al. (4) reported that GT3 and GT1b were predominant in men, while GT1b and GT2 were most common in women. Studies conducted in Türkiye also support these findings: Cırıt et al. (18) in Gaziantep found that GT1 and GT4 were more prevalent among women, whereas GT1 and GT3 were more common among men. Bulut et al. (19) reported higher rates of subtype 1a and GT3 among men, with subtype 1b more prevalent among women. Karabulut et al. (7) found that GT1 and GT2 were more common in women, while GT3 and GT4 were more frequent in men. Variations in transmission routes, particularly sexual transmission and intravenous drug use, may influence the distribution of HCV GTs. Specific GTs may have distinct transmission tendencies, varying according to geographical and epidemiological factors. For example, men may exhibit more risk behaviors in certain regions, while women might have lower-risk transmission routes. Sexual transmission may account for the higher prevalence of certain GTs, such as GT1. Additionally, differences in intravenous drug use rates between men and women may lead to a higher prevalence of certain GTs among men. GT3a, for instance, is more frequently observed among intravenous drug users due to its association with the use of contaminated needles.

Among the patients whose HCV GT was investigated, 90.9% were Turkish citizens, while 9.1% were foreign nationals. No statistically significant difference was found between Turkish and foreign patients. The most common GTs among Turkish patients were GT1b (34.0%) and GT3a (32.0%), whereas GT1b was predominant among foreign patients (70.0%). This similarity may be attributed to the fact that foreign patients in Muğla are primarily long-term residents rather than transient visitors.

When evaluating GT distribution by year, GT1b was detected at the highest rates in 2021, 2022, 2023, and 2024, while GT1a was predominant in 2019, and GT3a was the most common in 2020. No statistically significant difference was observed in GT distribution across the years. The continued predominance of GT1b in recent years is consistent with previous studies indicating that GT1b remains the dominant strain in Türkiye and many other regions. The transient increase in GT1a in 2019 and GT3a in 2020 may reflect localized outbreaks, demographic shifts in the tested patient population, or changes in injection drug use patterns, which are often associated with GT3a. However, the absence of a statistically significant difference over the years suggests that these fluctuations may result from random variation rather than a true epidemiological shift. Given that Muğla is a province in Türkiye with high levels of tourism, the continuous influx of people may contribute to ongoing changes in HCV GT distributions.

HCV GTs were most commonly observed in the 18-30 age group (30.9%) and least common in individuals under 18 years old (one case). Comparisons of GT distribution across age groups revealed that the 18-30 age group exhibited statistically significant higher rates than other age groups. The most frequently observed GTs by age group were subtype 1b in the 18-30 age group, GT3a in the 31-40 and 41-50 age groups, and subtype 1b in the 51-60 and over-60 age groups. In Georgia, Baliashvili et al. (4) found that HCV GTs were most prevalent in the 40-49 age group, with GT3 being the most frequently identified GT. Hundie et al. (17) in Ethiopia observed the highest rates in the 31-40 age group, with GT4 being the most prevalent GT. Bulut et al. (19) reported the highest prevalence in the 61-70 age group, with subtype 1b as the dominant GT. Differences in GT distribution across age groups may be linked to transmission routes, immune system responses, treatment outcomes, and genetic factors. Transmission routes for HCV have evolved over time. During the 1980s and 1990s, transmission through blood transfusions and medical interventions played a significant role in HCV spread, with GT1 and GT2 being more common. However, since the late 1990s, younger populations have shown higher prevalence rates of GTs like 3a, associated with changes in transmission routes such as intravenous drug use and sexual transmission. In younger individuals, behaviors such as intravenous drug use and sexual transmission may increase the frequency of specific GTs, while older individuals may exhibit different GTs due to historical transmission routes and weakened immune systems. HCV GT distributions can vary among age groups, influenced by historical transmission patterns, risk behaviors, and advancements in healthcare services. GT1b has long remained the dominant strain in Türkiye and many other regions. Older individuals may have been infected during periods when GT1b was the most prevalent. Insufficient infection control measures may have facilitated the transmission of this GT due to past medical procedures, blood transfusions, and the absence of widespread screening and antiviral treatments. Before the implementation of stricter sterilization and blood safety regulations, hospital-acquired (nosocomial) infections played a significant role in HCV transmission. The association of GT1b with iatrogenic (medical intervention-related) transmission in healthcare settings may explain its higher prevalence among older individuals. Genotypic differences among age groups necessitate the individualization of treatment strategies. Older patients should be carefully managed due to fibrosis risk, comorbidities, and potential drug interactions. On the other hand, public health interventions are crucial for younger patients to prevent reinfection. Understanding these variations can contribute to the development of personalized treatment approaches, ultimately improving patient outcomes.

Study Limitations

The limitations of this study include its retrospective design, which prevented the evaluation of transmission routes and risk groups among the patients. Additionally, the GT distribution was based solely on patient data requested by clinicians, which may have influenced the proportional representation in our findings.

Conclusion

HCV infection remains a global public health concern. Achieving the WHO's plan to eliminate HCV as a public health threat by 2030 requires comprehensive characterization of HCV prevalence and GT distribution. In our study, among the patients whose HCV GTs were investigated, GT1 was the most common GT (66.4%), followed by GT3 (30.9%), GT4 (1.8%), and GT2 (0.9%). Differences in treatment responses may exist between HCV GTs. GT information is crucial for determining the most effective drug combinations to achieve optimal treatment outcomes. Understanding the distribution of HCV GTs can aid in epidemiological studies, in identifying transmission pathways, and in developing public health strategies. GT data remain a critical factor for the development of new treatment options and for exploring more effective therapies targeted at specific GTs.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Muğla Sıtkı Koçman University Medical Sciences Ethics Committee (approval number: 177, date: 23.12.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.K., A.A., Design: M.K., A.A., Data Collection or Processing: M.K., A.A., Analysis or Interpretation: M.K., Literature Search: M.K., Writing: M.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research Article

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Evaluation of Hepatitis C Virus Genotype and Viremia Prevalence in a Tertiary Care Hospital in Ankara, Türkiye

Ankara'da Üçüncü Basamak Bir Hastanede Hepatit C Virüs Genotip ve Viremi Prevalansının Değerlendirilmesi

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ABSTRACT

Objectives: According to 2023 the World Health Organization data, around 50 million people globally have chronic hepatitis C virus (HCV) infections, presenting an ongoing public health challenge. This study aimed to evaluate HCV prevalence, viremia rates, and genotype (GT) distribution among HCV-positive cases in Ankara.

Materials and Methods: In this study, anti-HCV results from 308,309 patients were evaluated. Anti-HCV tests were analyzed using the Cobas 8000 system, and quantitative HCV ribonucleic acid polymerase chain reaction (PCR) tests were performed on the Cobas 8800 real-time PCR system. A commercial PCR-based Bosphore HCV genotyping kit v5 was used to determine HCV GTs.

Results: The anti-HCV prevalence was 0.38%, HCV viremia prevalence was 0.04%, and the viremia rate was 11.1% (131/1,179). The viremia rate was 6.4% in 2022, 12% in 2023, and 10.9% in 2024 (p=0.25). The highest HCV viremia prevalence was in those aged 70 and above (0.07%), while the highest HCV viremia rate (16.7%) occurred in the 0-29 age group (both p<0.001). Among foreign patients, the anti-HCV prevalence, HCV viremia prevalence, and viremia rate were 2.3%, 0.4%, and 18.8%, respectively, whereas in Turkish citizens, these rates were 0.3%, 0.03%, and 10%, (p<0.001, p<0.001, p=0.008, respectively). The most common GT was GT1 (55.7%).

Conclusion: This study has demonstrated that HCV prevalence and viremia rates are lower compared to global data. GT1 has been identified as the predominant GT. The higher viremia rates observed in the young population and foreign individuals highlight the importance of early diagnosis and screening programs in these groups.

Keywords: Hepatitis C virus, viremia, genotype, PCR, prevalence

ÖZ

Amaç: 2023 Dünya Sağlık Örgütü verilerine göre dünya genelinde yaklaşık 50 milyon insan kronik hepatit C virüsü (HCV) enfeksiyonu ile mücadele etmekte, bu da süregelen bir halk sağlığı sorunu teşkil etmektedir. Bu çalışma, Ankara'daki HCV-pozitif olgular arasında HCV prevalansı, viremi oranları ve genotip (GT) dağılımını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntemler: Bu çalışmada, 308.309 hastadan alınan anti-HCV sonuçları değerlendirilmiştir. Anti-HCV testleri Cobas 8000 sistemi ile analiz edilmiş ve kantitatif HCV ribonükleik asit polimeraz zincir reaksiyonu (PCR) testleri Cobas 8800 gerçek zamanlı PCR sistemi ile gerçekleştirilmiştir. HCV GT'lerini belirlemek için ticari bir PCR temelli Bosphore HCV genotyping kit v5 kullanılmıştır.

Bulgular: Anti-HCV prevalansı %0,38, HCV viremi prevalansı %0,04 ve viremi oranı %11,1 olarak bulunmuştur. Viremi oranı 2022'de %6,4'ten 2023'te %12'ye ve 2024'te %10,9'a yükselmiştir (p=0,25). En yüksek HCV viremi prevalansı 70 yaş ve üzeri grupta (%0,07) görülürken, en yüksek viremi oranı %16,7 ile 0-29 yaş grubunda tespit edilmiştir (her ikisi de p<0,001). Yabancı hastalarda anti-HCV prevalansı, HCV viremi prevalansı ve viremi oranı sırasıyla %2,3, %0,4 ve %18,8 iken, Türk vatandaşlarında bu oranlar sırasıyla %0,3, %0,03 ve %10 olarak bulunmuştur (sırasıyla p<0,001, p<0,001, p=0,008). En yaygın GT, GT1 (%55,7) olmuştur.

Sonuç: Bu çalışma, HCV prevalansı ve viremi oranlarının küresel verilere kıyasla daha düşük olduğunu ortaya koymuştur. Genç nüfus ve yabancılar arasında daha yüksek viremi oranları, bu gruplarda erken tanı ve tarama programlarının önemini vurgulamaktadır. Pangenotipik tedavilerin yaygın kullanımına rağmen, GT1'in baskın olmaya devam etmesi, bu tedavilerin GT dağılımı üzerinde önemli bir etki yaratmadığını göstermektedir.

Anahtar Kelimeler: Hepatit C virüsü, viremi, genotip, PCR, prevalans

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Introduction

Hepatitis C virus (HCV) is a single-stranded, enveloped RNA virus belonging to the *Hepacivirus* genus of the *Flaviviridae* family (1). According to 2023 data from the World Health Organization (WHO), approximately 50 million people worldwide are estimated to be chronically infected with HCV, with around 1.5 million new infections reported annually. Chronic HCV infection remains a significant global public health issue (2). In Türkiye, data from 2018 indicate that approximately 250,000 to 500,000 individuals over the age of 18 are infected with HCV (3).

HCV transmission occurs through multiple potential routes, with blood transfusion and intravenous drug use being the most common. Additionally, factors such as orodental procedures, piercings, tattoos, sharing of shaving equipment, sexual contact, and perinatal transmission: increase the risk of infection (4,5).

In the clinical course of individuals infected with HCV, it is known that 15-45% of cases spontaneously clear the infection within six months due to an effective immune response while 55-85% of cases progress to chronic hepatitis. In untreated cases, approximately 80% of patients with chronic infection are at high risk of developing severe complications such as liver fibrosis, cirrhosis, and hepatocellular carcinoma (6,7).

The HCV genome exhibits high genetic diversity due to the absence of error-correcting mechanisms in RNA-dependent RNA polymerase and the virus's rapid replication capacity. As a result of genetic differences, eight distinct genotypes (GTs) and 93 different subtypes of HCV have been identified (8). While the distribution of GTs varies by geographic region, GT1 and 3 are the most common worldwide. Additionally, GT2 is predominant in West Africa and South America, and GT4 and 6 are prevalent in some regions of North Africa and East/Southeast Asia (9). In Türkiye, GT1 is known to be the dominant GT. However, Türkiye's position as a crossroads between Europe and Asia, coupled with increasing migration in recent years, is thought to contribute to changes in the GT distribution (10,11).

Despite the availability of pangenotypic direct-acting antiviral (DAA) treatments, determining the HCV, GT still plays an important role in optimizing treatment duration and response rates. Therefore, GT determination remains clinically valuable in treatment planning (12).

The diagnosis of HCV infection primarily involves HCV antibody testing, HCV core antigen testing, HCV RNA detection, and genotyping. Initially, an antibody test is used to detect antibodies against HCV. In cases where HCV antibodies are reactive, a quantitative real-time polymerase chain reaction (PCR) test is performed to confirm active infection by detecting HCV-RNA. The HCV core antigen test can also be used to identify active infection. Genotyping of HCV is typically carried out using PCR-based methods, sequencing, and hybridization-based tests (10,13).

In this study, we aimed to determine the prevalence of HCV, HCV viremia, and the GT distribution of HCV-positive cases in a tertiary care hospital in Ankara, the second-largest city in Türkiye by population.

Materials and Methods

Study Design

This study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval number: 2024-805, dated: 28.08.2024). In this retrospective, single-center, cross-sectional study, patients from all age groups who underwent anti-HCV testing between November 2022 and July 2024 at University of Health Sciences Türkiye, Ankara Etlik City Hospital were evaluated. A total of 308,309 patients were included in the study. Demographic data (age, gender, ethnicity) and laboratory results (anti-HCV, HCV-RNA, HCV GTs) were obtained from the hospital's information management system. Patients without accessible HCV test results (anti-HCV, HCV-RNA, or HCV GT) were excluded from the study. Taking repeated test results into account, only the first sample from patients who were anti-HCV reactive, who underwent multiple tests, was included in the analysis. Patients who were anti-HCV reactive but did not undergo HCV-RNA testing were excluded from the study.

To evaluate changes in HCV prevalence and GT distributions, patients were divided into four age groups: 0-29 years, 30-49 years, 50-69 years, and 70 years and older.

HCV Antibody Analysis

Anti-HCV testing was performed using the Roche Elecsys anti-HCV test kit (Roche Diagnostics GmbH, Mannheim, Germany). This test kit is based on the electrochemiluminescence immunoassay method for detecting antibodies against HCV. A reference value of anti-HCV signal/cut-off ratio ≥1.0 was considered indicative of a reactive test result.

Quantitative HCV-RNA Analysis

HCV-RNA analysis in plasma samples was performed using the fully automated extraction and PCR amplification processes of the Cobas® 8800 system (Roche Diagnostics GmbH, Mannheim, Germany), which integrates all analysis steps into a single device. The limit of detection for the test was set at 15 international units (IU)/mL, and the lower limit of quantification was also 15 IU/mL.

HCV Genotyping

HCV genotyping in the study population was performed using the commercial PCR-based Bosphore HCV genotyping kit v5 (Anatolia Geneworks, Türkiye). This kit targets the NS5B region to detect the six major HCV GTs and their most common subtypes (GTs1, 2, 3, 4, 5, 6 and subtypes 1a, 1b). The results were evaluated according to the manufacturer's instructions.

Statistical Analysis

All statistical analyses were conducted using Statistical Package for the Social Sciences version 27.0 software (International Business Machines Corporation). The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables that did not follow a normal distribution were expressed as the median (interquartile range) and minimum-maximum values; comparisons between two groups were made using the Mann-Whitney U test while the Kruskal-Wallis test was

used for comparisons between more than two groups. Categorical data were presented as frequencies and percentages, and the chi-square test or Fisher's exact test, where appropriate, was used to assess the relationship between groups. A p-value of <0.05 was considered statistically significant.

Results

Anti-HCV Antibody Positivity and HCV Viremia Rates

Anti-HCV antibody positivity was detected in 1,179 of 308,309 patients, with a prevalence of 0.38% [95% confidence interval (CI): 0.36-0.40]. The prevalence of viremic HCV infection in the entire tested patient population was calculated as 0.04% (131 out of 308,309 patients) (95% CI: 0.04-0.05). The HCV viremia rate was 11.1% (131/1,179) (95% CI: 9.37-13.05).

Significant differences in anti-HCV and HCV viremia prevalence were observed across different age groups. Anti-HCV prevalence increased with age; the lowest prevalence was observed in the 0-29 age group at 0.2% (192/97,155), while the highest was found in the 70 and older group at 0.8% (339/39,840) (p<0.001). Similarly, the prevalence of HCV viremia was lowest, at 0.03%, in the 0-29 age group (32/97,155) and the 50-69 age group (28/86,645) while it was highest in the 70 and older group (32/39,840) (p<0.001). The highest viremia rate was detected in the 0-29 age group at 16.7% (32/192), while the lowest was in the 50-69 age group at 7.1% (28/392) (p<0.001).

An analysis by year revealed that anti-HCV prevalence was highest in 2022 (0.5%) and showed a gradual decline in subsequent years, reaching its lowest level in 2024 (0.3%) (p<0.001). The prevalence of HCV viremia remained stable, in the years 2022 (0.03%), 2023 (0.04%), and 2024 (0.03%) (p=0.12). The HCV viremia rate was lowest in 2022 (6.4%) and peaked in 2023 (12%) before decreasing in 2024 (10.9%), although this change was not statistically significant (p=0.25) (Table 1).

In terms of ethnicity, anti-HCV prevalence, HCV viremia prevalence, and the viremia rate were found to be 2.3% (139/6,159), 0.4% (26/6,159), and 18.8% (26/139) in foreign nationals, while these rates were 0.3% (1,040/302,150), 0.03% (105/302,150), and 10% (105/1,040), respectively, in Turkish citizens. These differences were statistically significant (p<0.001, p<0.001, p=0.008, respectively).

HCV Genotype Prevalence

Among 70 HCV patients in the study, the most frequently detected GT was GT1, observed in 55.7% of cases. Among GT1 subtypes, GT1b was the most common at 30%. GT3 was identified in 28.6% of cases, while both GT2 and GT4 were found in 7.1% of cases. GT5 was rarely isolated in one patient (1.4%).

Distribution of HCV Genetype by Gender

GT1 was the most common GT in both male (55.8%) and female (55.6%) patients. GT1a was more prevalent in males (39.5%), while GT1b was more frequent in females (51.9%) (p<0.001) (Table 2).

Distribution of HCV Genetype by Ethnicity

Among patients with GT analysis, 78.6% (55/70) were of Turkish nationality. GT1 was the most frequently detected GT in both Turkish (58.2%) and foreign patients (46.7%) (p=0.186). After GT1, the most common GTs in Turkish patients were GT3 (27.3%) and GT2 (9.1%), while in foreign patients, GT3 (33.3%) and GT4 (13.3%) were the most common. Additionally, GT1b was more frequently detected in the Turkish population, whereas

Table 1. Prevalence of anti-HCV and HCV viremia, and viremia rates from 2022 to 2024

	Anti-HCV prevalence				
Years	**Total, n**	**Anti-HCV reactive, n**	**%**	**95% CI**	**p-value**
2022	26,382	125	0.47	0.39-0.56	0.002
2023	170,701	679	0.39	0.37-0.43	
2024	110,015	375	0.34	0.31-0.38	
Total	308,309	1,179	0.38	0.36-0.40	
	HCV viremia prevalence				
	Total, n	**HCV-RNA positive, n**	**%**	**95% CI**	
2022	26,382	8	0.03	0.01-0.06	0.240
2023	170,701	82	0.04	0.04-0.06	
2024	110,015	41	0.03	0.03-0.05	
Total	308,309	131	0.04	0.04-0.05	
	HCV viremia rate				
	Total*, n	**HCV-RNA positive, n**	**%**	**95% CI**	
2022	125	8	6.4	2.80-12.22	0.177
2023	679	82	12	9.72-14.77	
2024	375	41	10.9	7.96-14.54	
Total	1,179	131	11.1	9.37-13.05	

*Patients who underwent HCV-RNA testing. HCV: Hepatitis C virus; RNA: Ribonucleic acid, CI: Confidence interval

Table 2. Demographic and laboratory characteristics of patients based on HCV GT

	HCV GT							
	GT1	GT1a	GT1b	GT2	GT3	GT4	GT5	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
n=70	39 (55.7)	18 (25.7)	21 (30)	5 (7.1)	20 (28.6)	5 (7.1)	1 (1.4)	
Gender								
Male	24 (55.8)	17 (39.5)	7 (16.3)	4 (9.3)	12 (27.9)	2 (4.7)	1 (2.3)	<0.001
Female	15 (55.6)	1 (3.7)	14 (51.9)	1 (3.7)	8 (29.6)	3 (11.1)	0 (0)	
Etnicity								
Turkish	32 (58.2)	14 (25.5)	18(32.7)	5 (9.1)	15 (27.3)	3 (5.5)	0 (0)	0.273
Foreign nationals	7 (46.7)	4 (26.7)	3 (20)	0 (0)	5 (33.3)	2 (13.3)	1 (6.7)	
Age*	42	28	58	28	31	31	-	<0.001
IQR	28-61	23-32	42-66	24-58	26-44	24-51	-	
Age range	11-84	16-67	11-84	24-86	19-64	22-54	-	
HCV-RNA†	5.7	5.5	6.0	7.1	5.8	6.3	-	0.063
IQR (25-75)	4.7-6.7	4.4-6.4	5.0-6.7	6.8-7.4	4.6-6.8	5.0-7.0	-	
Range	0.7-7.6	0.7-7.0	2.7-7.5	6.7-7.4	0.7-7.1	5.0-7.0	-	

HCV: Hepatitis C virus, GT: Genotype, IQR: Interquartile range, *: Median, †: log_{10} IU/mL, IU: International unit

GT1a was more common among foreign patients (p=0.280). No mixed HCV GT infections were detected in the study population (Table 2).

Distribution of HCV Genetype by Age Groups

The median age of patients infected with GT1b was 58 years, while patients infected with GT1a were younger, with a median age of 28 years. The median age for those infected with GT3 was determined to be 31 years. The age differences between GTs were statistically significant (p<0.001). GT1a was the most common GT in the 0-29 age group (44%). GT3 was most prevalent in the 30-49 age group (40%), while GT1b was the most frequently detected GT in the 50-69 age group (66.7%) and the 70 years and older group (80%). GT5 was only identified in the 30-49 age group (4%) (p=0.001) (Figure 1).

Viral Load Relationship with HCV Genetype

The median HCV-RNA viral load levels (log_{10}, IU/mL) were highest in patients infected with GT2 at 7.1, although no statistically significant difference in HCV-RNA levels was found between GTs (p=0.063). The demographic and clinical characteristics of patients by HCV GTs are presented in Table 2.

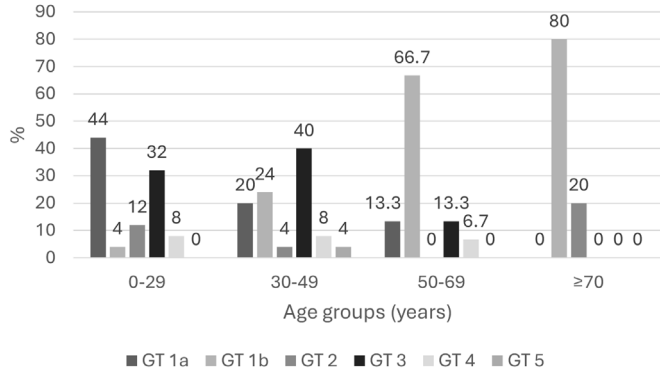

Figure 1. Distribution of HCV genotypes by age group
HCV: Hepatitis C virus

Discussion

HCV remains one of the leading causes of chronic liver disease worldwide, responsible for approximately 400,000 deaths annually. The WHOs Global Health Sector Strategy, launched in 2016, aims to reduce HCV transmission by 90% and HCV-related deaths by 65%, with the ultimate goal of eliminating the virus by 2030. Achieving these targets depends on the widespread use of DAA therapies and increased HCV awareness (14,15,16). Understanding the prevalence of HCV viremia and rates of infection is crucial for assessing disease burden and guiding treatment strategies. Consequently, studies estimating disease burden are necessary for developing national strategies. In this study, we examined HCV viremia prevalence, viremia rates, and HCV GT distribution at a tertiary care hospital, comparing the findings with data from the literature.

It is important to note that anti-HCV positive individuals do not always have an active infection; thus, the prevalence of HCV viremia is a more specific marker for active infection. Globally, the distribution of HCV infection varies by geographic region. Countries with the highest anti-HCV antibody prevalence include Gabon (4.3%) and Pakistan (4.1%), while nations such as Saudi Arabia, Spain, and the Netherlands report prevalence rates below 0.1% (17). In rural areas, these rates can vary significantly; for instance, in rural Taiwan, prevalence rates as high as 16.7% have been reported (18). A recent study identified the highest HCV prevalence in Egypt (6.3%), followed by the Democratic Republic of Congo (4.3%). Among developed countries, notable findings include a prevalence exceeding 2% in Estonia and Italy (19). In Türkiye, studies on anti-HCV prevalence have reported rates ranging from 0.27% to 2.76% (4,17,20,21). In our study, the anti-HCV prevalence was found to be

0.38%, which falls at the lower end of this range when compared to other studies in Türkiye and globally. This discrepancy may be attributed to the demographic characteristics of the region and population studied.

The prevalence of viremic HCV infection in this study was 0.04%. Globally, a significant decrease in HCV viremia prevalence has been observed over the years. A meta-analysis covering the period from 2015 to 2020 showed substantial changes in global HCV infection prevalence and viremia rates due to treatment efforts. In 2015, the global prevalence of viremia was 0.9%, which decreased to 0.7% in 2020, with the number of viremic infections dropping from 63.6 million to 56.8 million. In 2020, HCV prevalence was highest in Eastern Europe (2.9%) and Central Asia (2.6%). The highest number of viremic infections occurred in South Asia (14.5 million) and East Asia (10 million). In Türkiye, no significant change in viremic HCV prevalence was noted between 2015 and 2020, with the rate remaining at 0.3%. In regions such as Western Europe and North America, HCV prevalence has fallen below 0.1% (16). Another study reported a global viremic HCV prevalence of approximately 1.1%. Regionally, the highest viremia rate was found in sub-Saharan Africa (4.1%), while the lowest was in Western Europe (0.6%) (22). In Türkiye, viremic HCV prevalence has been reported to range from 0.3% to 2.05% (4,20). In this study, the prevalence of viremic HCV infection was 0.04%, significantly lower than the global and national averages. Differences in viremic HCV prevalence in Türkiye may be attributed to regional and demographic variations, as well as the characteristics of the study population, diagnostic methods, and access to healthcare.

The age-related HCV antibody prevalence was highest among those aged 70 and over (0.8%) and lowest among individuals under 29 (0.2%). Studies conducted in Türkiye have confirmed that HCV antibody prevalence increases with age. This rise is likely associated with older individuals who became infected during periods when blood transfusions and medical procedures posed a higher risk of transmission, particularly in the 1970s and 1980s. Additionally, advancements in medical practices in recent years may explain this trend (4). On the other hand, Chlibek et al. (23) found the highest HCV antibody prevalence in the 30-44 age group in the general population, while Suntur et al. (21) reported elevated anti-HCV prevalence in patients aged 18-29. Both studies suggested that the higher prevalence in these age groups may be linked to intravenous drug use (21,23). These data indicate that intravenous drug use plays a significant role in HCV transmission, particularly among younger populations, and that efforts to reduce this behavior are critical for controlling the spread of the infection.

Globally, HCV viremia rates show significant regional variations; for instance, viremia rates as low as 43% have been observed in Central Asia, while rates in South Asia have risen as high as 81% (22,24). Two studies conducted in Türkiye reported viremia rates of 21.3% and 33.17% (10,20). In this study, the HCV viremia rate was significantly lower at 11.1% compared to rates reported in both studies. Several factors may explain the lower viremia rates observed in our study. First, limited HCV-RNA testing among anti-HCV positive individuals may result in underreporting of true viremia rates. Additionally, widespread screening and treatment programs in Türkiye, as well as the increasing use of DAA therapies, may contribute to the decline in viremia rates.

Although HCV GT testing is no longer as crucial in determining treatment as it once was, it remains important in some cases. The first-generation DAA therapies had varying efficacy depending on the HCV GT, making GT determination critical in treatment selection. However, with the development of pan-genotypic DAAs that are effective against nearly all HCV GTs, routine GT testing is no longer necessary. Nevertheless, in certain cases, genotyping is still relevant (25,26). Studies investigating global HCV GT distribution have shown that GT1 is the most common GT at 49.1%, followed by GT3 at 17.9% and GT4 at 16.8% (24). Research conducted in the Middle East and North Africa has reported that GT1 is prevalent in the region. Countries such as Morocco, Algeria, Bahrain, and Libya show higher frequencies of GT2, while GT3 is more common in Afghanistan and Pakistan, and GT4 is dominant in Egypt, Iraq, Qatar, Palestine, and Syria (9). Studies on HCV GT distribution in Türkiye have also shown that GT1 is the most common GT, with GT1b being the most prevalent subtype (10,15,20). In this study, GT1 was identified as the most prevalent GT. While GT1a was dominant in the 0-29 age group, GT1b was the predominant subtype in other age groups. These findings suggest that despite the widespread use of pan-genotypic DAAs, there has been no significant change in HCV GT distribution. However, as pan-genotypic DAAs have been reported to achieve high success rates across all GTs, it is still unclear whether GT distribution will shift over time.

Study Limitations

The fact that the data belong to a single center is one of the limitations of this study.

Conclusion

This study has demonstrated that HCV prevalence and viremia rates are lower compared to those found in global data and that GT1 is identified as the predominant GT. The detection of higher viremia rates among the young population and foreign individuals highlights the necessity of early diagnosis and screening programs in these groups.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee (approval number: 2024-805, dated: 28.08.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.F.K., A.B., Design: M.F.K., G.K., A.B., Data Collection or Processing: M.F.K., G.K., A.B., Analysis or Interpretation: M.F.K., A.B., Literature Search: M.F.K., A.B., Writing: M.F.K., A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Research Article

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Evaluation of Exposure to HAV and Vaccination Status of Chronic HBV Cases - A Nationwide Multicenter Study

Kronik HBV Olgularında HAV Maruziyeti ve Aşılanma Durumunun Değerlendirilmesi - Ülke Çapında Çok Merkezli Bir Çalışma

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ABSTRACT

Objectives: Patients diagnosed with chronic hepatitis B virus (HBV) should be tested for hepatitis A virus (HAV) and vaccinated if they are seronegative. However, this test is often neglected. This study aims to investigate the status of HAV testing in chronic HBV patients.

ÖZ

Amaç: Kronik hepatit B virüs (HBV) tanısı alan hastaların hepatit A virüsü (HAV) açısından tetkik edilmesi ve seronegatif olanların aşılanması gereklidir. Ancak bu tetkik genellikle ihmal edilmektedir. Bu çalışmada kronik HBV hastalarına HAV açısından tetkik yapılma durumunun araştırılması amaçlanmıştır.

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Materials and Methods: A multicenter study is being conducted by the Viral Hepatitis Combat Association with 16 centers across the country, including patients who have been receiving treatment for chronic HBV for at least 14 years. The anti-HAV immunoglobulin G (IgG) testing and vaccination status of the patients in this study were evaluated retrospectively. The patients' data recorded in a web-based program were transferred to an Excel form, and the necessary analyses were performed. Statistical analysis was performed using SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Categorical measurements were summarized as numbers and percentages, continuous measurements as mean and standard deviation, and chi-square or Fisher's exact test statistics were used to compare categorical variables.

Results: The study group included 2966 individuals, 1832 of whom were male (61.8%) and 1134 of whom were female (38.2%). Of these patients, 1819 individuals (61.3%) were tested for anti-HAV IgG, while 1147 individuals (38.7%) were not. Of the 1819 individuals tested for anti-HAV IgG, 1688 (92.8%) were seropositive, and 131 (7.2%) were seronegative. It was determined that seropositivity increased significantly with age, and seronegativity was 23% among those aged 18-26 and 21% among those aged 27-33 (p=0.00001). According to the obtained data, HAV seronegativity was detected in one-fourth of individuals younger than 26 years and one-fifth of individuals aged 27-33. At 40 and above, seronegativity decreases significantly, falling to 5% and below.

Conclusion: Due to the changes observed in HAV epidemiology in our country in recent years, HAV seronegativity is high in young adults. According to our study data, anti-HAV IgG should be tested once in all chronic HBV patients, especially patients under the age of 35, and vaccination of seronegative individuals should not be neglected.

Keywords: Chronic HBV, HAV, vaccination, seroprevalence

Gereç ve Yöntemler: Viral Hepatitle Savaşım Derneği tarafından ülke genelinde toplam 16 merkezin katıldığı ve en az 14 yıldır kronik HBV tanısıyla tedavi görmekte olan hastaların dahil edildiği çok merkezli bir çalışma yürütülmektedir. Bu çalışmadaki hastalara anti-HAV immünoglobulin G (IgG) bakılma ve aşılanma durumları retrospektif olarak değerlendirilmiştir. Web tabanlı bir programa kaydedilen hastaların verileri Excel formuna aktarılarak gerekli analizler yapılmıştır. İstatistiksel analizler SPSS for Windows, sürüm 22.0 (IBM Corp., Armonk, NY, ABD) kullanılarak gerçekleştirildi. Kategorik ölçümler sayı ve yüzde olarak, sürekli ölçümlerde ortalama ve standart sapma olarak özetlenmiş, kategorik değişkenlerin karşılaştırılmasında ki-kare test ya da Fisher'ın kesin testi istatistiği kullanılmıştır.

Bulgular: Çalışma grubunda 1832'si erkek (%61,8), 1134'ü kadın (%38,2) olmak üzere toplam 2966 kişi yer almaktadır. Bu hastalardan 1819 kişiye (%61,3) anti-HAV IgG bakılmış, 1147 kişiye ise (%38,7) bakılmamıştır. Anti-HAV IgG bakılan 1819 kişiden 1688'i (%92,8) seropozitif, 131 kişi ise (%7,2) seronegatif olarak saptanmıştır. Yaşla birlikte seropozitifliğin belirgin şekilde arttığı ve 18-26 yaş arasında seronegatifliğin %23, 27-33 yaş arasında da %21 olduğu saptanmıştır (p=0,00001). Elde edilen verilere göre 26 yaştan genç bireylerin dörtte birinde, 27-33 yaş arası bireylerin de beşte birinde HAV seronegatifliği saptanmıştır. Kırk yaş ve üzerinde seronegatiflik anlamlı şekilde azalmakta, %5 ve altına inmektedir.

Sonuç: Ülkemizde son yıllarda HAV epidemiyolojisinde gözlenen değişim nedeniyle genç erişkinlerde HAV seronegatifliği yüksek saptanmaktadır. Çalışma verilerimize göre özellikle 35 yaş altındaki hastalar öncelikli olmak üzere tüm kronik HBV hastalarına bir kere anti-HAV IgG bakılması ve seronagatif bireylerin aşılanması ihmal edilmemelidir.

Anahtar Kelimeler: Kronik HBV, HAV, aşılama, seroprevalans

Introduction

Hepatitis A virus (HAV) infection continues to be the most common type of viral hepatitis in the world. The agent is an RNA virus in the *Hepatovirus* genus of the *Picornaviridae* family and is very resistant to environmental conditions and can survive for months under suitable conditions. The only natural host of the HAV is humans; it has six genotypes (I-VI) and a single serotype. When the disease is contracted, it is usually self-limiting in individuals with a healthy immune system, and only supportive treatment is often sufficient. Acute HAV infection does not become chronic, but acute liver failure can be seen in less than 1% of people over the age of 40 or those with underlying diseases (1,2,3,4,5,6).

Highly effective and reliable vaccines have been used to protect against HAV infection for years (2). In its 2022 update on the HAV vaccine (HAV position paper), the World Health Organization recommended that vaccination against the HAV should be included in national vaccination schedules for individuals ≥12 months of age if indicated based on the following conditions (7). These conditions include an increasing trend over time for acute HAV disease, including severe disease in older children, adolescents, or adults; a change in endemicity from high to moderate; and cost-effectiveness issues. This update also emphasizes that, with changing epidemiology, vaccination coverage may be expanded to adults in high-risk settings, the elderly, men who have sex with men, and other special populations such as homeless persons (6,7).

Materials and Methods

Method

A multicenter study is being conducted by the Viral Hepatitis Combat Association with 16 centers across the country, including patients who have been receiving treatment for chronic hepatitis B virus (HBV) for at least 14 years. The study plan includes patients who started treatment in 2010 and later and who received treatment for at least 12 months, and the data of the patients up to the end of 2024 were evaluated. The anti-HAV immunoglobulin G (IgG) testing and vaccination status of the patients in this study were evaluated retrospectively. The patients' data recorded in a web-based program were transferred to an Excel form, and the necessary analyses were performed.

Statistical Analysis

Statistical evaluation was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Categorical measurements were summarized as numbers and percentages, continuous measurements as mean and standard deviation, and the chi-square test or Fisher' exact test statistics were used to compare categorical variables.

Our institution has received ethical approval from the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: A-83, date: 06.07.2021).

Results

The study group included 2966 people, 1832 of whom were male (61.8%) and 1134 of whom were female (38.2%). Of these patients, 1819 (61.3%) were tested for anti-HAV IgG, while 1147 (38.7%) were not. Of the 1819 people who were tested for anti-HAV IgG, 1688 (92.8%) were seropositive, and 131 (7.2%) were seronegative (Table 1). Of the 2966 patients included in the study, 1819 (61.3%) underwent serological screening for HAV, while 1147 (38.7%) were not. Of the 1819 patients screened for HAV, 1141 (62.7%) were male and 678 (37.3%) were female. Of the 1147 patients not screened, 691 (60.2%) were male and 456 (39.8%) were female. No statistically significant difference was found between genders in terms of HAV screening (p=0.17323).

It was determined that 32 of the 1688 people with known HAV results and seropositivity were immune to the vaccine, and 1656 were naturally infected and became immune.

When the distribution of anti-HAV IgG positivity was examined according to gender, 639 (23.7%) of 1688 HAV-positive individuals were female, and 1049 (62.2%) were male; 31 (23.7%) of 131 HAV-negative individuals were female, and 100 (76.3%) were male; the study group was predominantly composed of male patients.

There was no association between HAV testing in chronic HBV patients and gender (p=0.17323), and HAV IgG positivity was observed to be higher in both genders (p=0.001634) (Table 1).

When HAV positivity was evaluated according to age groups, it was determined that seropositivity increased significantly with age, and seronegativity was 23% between the ages of 18-26 and 21% between the ages of 27-33 (p=0.00001) (Table 2). According to the data obtained, HAV seronegativity was detected in one-fourth of individuals younger than 26 and one-fifth between the ages of 27-33. Seronegativity decreases significantly at age 40 and above, falling to 5% and below (Table 2).

When the relationship between HAV testing and the year of diagnosis was evaluated, the HAV testing rate was higher in those with an older year of diagnosis (Table 3).

When the relationship between HAV testing and the geographical region where the patients live was examined, it was determined that the highest rate of testing was done in people living in the Aegean region (82%), followed by the Marmara region (75%). The lowest testing rates were in the Eastern Anatolia (26.5%) and Southeastern Anatolia (26.5%) regions. It was also determined that the number of people vaccinated for HAV was higher in those living in the Aegean and Marmara regions (Figure 1).

Table 1. Anti-HAV IgG result by gender

Gender	HAV IgG pozitive	HAV IgG negative	Total
Male	1049 (91.3%)	100 (8.7%)	1149
Woman	639 (95.4%)	31 (4.6%)	670
Total	1688	131	1819

The row percentage was taken. *p=0.001634
HAV: Hepatitis A virus, IgG: Immunoglobulin G

Discussion

In recent years, it has been observed that there has been a significant change in the epidemiology of HAV in the world and in our country due to both infrastructure improvements and national vaccination programs. In a review examining the trends reported in the literature between 2000 and 2021 in the epidemiology of HAV in the Western Pacific Region, it was reported that many countries moved from high endemicity to low endemicity, the administration of HAV vaccination in children shifted the susceptibility to the disease to the elderly population, and while seroprevalence among children decreased in most countries, almost 100% seropositivity was observed in middle adulthood (8).

To determine the current epidemiological characteristics of HAV in European countries, a systematic literature review was conducted on articles published on HAV in 11 European countries (Denmark, France, Germany, Greece, Hungary, Italy, the Netherlands, Spain, Sweden, Switzerland and the United Kingdom) in the last twenty years, and PubMed and Embase data were used between January 1, 2001 and April 14, 2021. According to this assessment, acute HAV cases have decreased in Europe since 1990. Still, there are differences from country to country, and routine vaccination also varies from country to country (9).

Table 2. Anti-HAV IgG positivity by age groups

Age groups	Ages	Anti-HAV IgG positive	Anti-HAV IgG negative	Total
After 2000	24	10 (77%)	3 (23%)	13
1999-1998	25-26	10 (77%)	3 (23%)	13
1997-1991	27-33	124 (79.5%)	32 (20.5%)	156
1990-1985	34-39	190 (84%)	36 (16%)	226
1984-1974	40-50	508 (94.6%)	29 (5.4%)	537
1973-1963	51-61	517 (96.8%)	17 (3.2%)	534
1962-1952	62-72	260 (9.6%)	10 (3.4%)	270
1951-1941	73-83	61 (98.4%)	1 (1.6%)	62
1940+	84+	8 (100%)	0	8
Total		1688 (92.7%)	131 (7.2%)	1819

*Percentage of rows, p=0.001
HAV: Hepatitis A virus, IgG: Immunoglobulin G

Table 3. The relationship between the year of diagnosis and anti-HAV IgG detection of chronic HBV patients

Year of diagnosis	HAV screening (+)	HAV screening (-)	Total
2020 and beyond	96 (62%)	61 (38%)	157
2019-2015	554 (56%)	436 (44%)	990
2014-2010	808 (67%)	400 (33%)	1212
2009-2001	271 (61%)	172 (39%)	443
2000 and earlier	82 (77%)	24 (23%)	106

*p<0.001
HAV: Hepatitis A virus, IgG: Immunoglobulin G, HBV: Hepatitis B virus

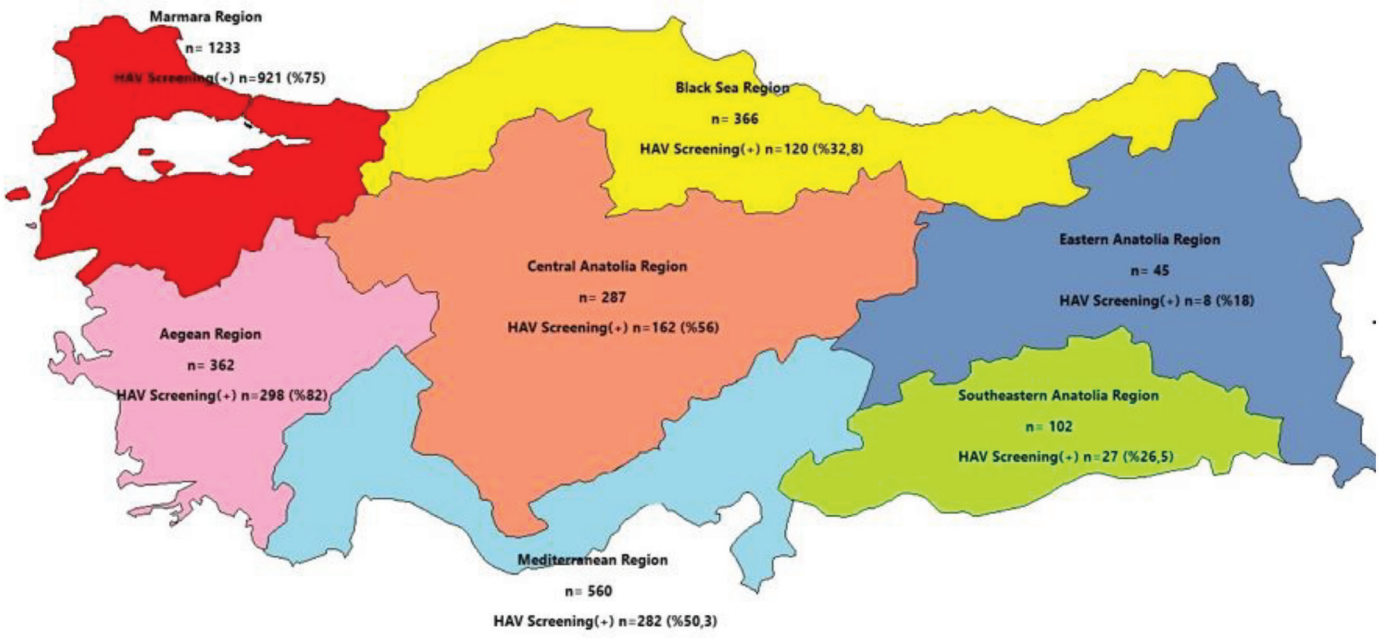

Figure 1. The relationship between HAV examination and the geographical region (n=2955)
HAV: Hepatitis A virus

A recent review, including our country's data, examined publications on HAV epidemiology before and after implementing the childhood HAV vaccination program in Türkiye and reported a significant change in the age of first HAV exposure (10). A meta-analysis recently published in our country scanned studies on HAV published between January 1, 2000, and December 31, 2023, that met the inclusion criteria. Data were obtained from all geographical regions of Türkiye, and the overall prevalence of HAV in the population was 53% (11). Another systematic meta-analysis conducted to evaluate age-specific HAV seroprevalence rates in Türkiye between 2000 and 2023 included 57 articles. HAV seroprevalence was found to be 90.90% in the >35 age group, and the overall seroprevalence estimated using a random effects model was reported as 64.5% (12).

It is known that acute HAV infection progresses more severely in individuals with immunosuppressive conditions or chronic liver disease and that the prognosis is worse when acute hepatitis is added to chronic hepatitis, especially in the presence of damaged livers (7,13).

In a study examining HAV outbreaks seen in the last 20 years in the European region, deaths were reported from five countries (Spain, Denmark, Germany, Hungary, and Italy) during the outbreaks seen in the last 20 years. The case fatality rate was determined to be between 0.05% and 0.26% (14). This analysis also examined the underlying conditions in the fatal cases. These conditions were defined as preexisting liver diseases (such as HBV or HBC infection), HIV infection, renal failure, diabetes, intravenous drug use, pulmonary neoplasia, and pulmonary edema; 70% of the deceased were reported to be ≥60 years of age.

In the United States of America, 33 outbreaks and 37,553 acute HAV cases were seen between 2016 and 2020; 56% of the cases that could be reached were drug addicts, 14% were homeless, 61% of the cases were hospitalized, and 380 people died (15). When the histories of the deceased were examined, it was determined that they had past or current HBV (5%) or HCV (30%) infection. In the large HAV outbreak in Shanghai, China, in 1988, 310,746 cases were seen, and a total of 47 deaths (0.015%) occurred (16). Mortality rates were 0.05% (15/27.346) vs 0.009% (25/283.400) in patients with and without HBV infection, respectively, with a 5.6-fold higher mortality rate in patients with chronic HBV infection than in those without. In this study, Cooksley (16) reported that HBV-infected patients with elevated alanine aminotransferase levels and elevated HBV-DNA levels were at higher risk of liver failure following HAV superinfection. As seen in many similar studies, acute HAV infection in individuals with underlying chronic liver disease can progress severely and even lead to death.

International guidelines also include vaccination of seronegative chronic HBV and HCV patients (17). In our country, vaccination of seronegative individuals in the risk group (including chronic HBV and HCV patients) has been provided free of charge by the Ministry of Health for many years. In addition, the national HAV vaccination was started in October 2012 to be applied to babies aged 18-24 months, and all babies born in March 2011 and later are vaccinated. In connection with this, a very significant decrease in acute HAV infection is observed, especially in children and adolescents (18). Chronic HBV and HCV patients are always included as a risk group regarding HAV vaccination in the hepatitis prevention programs of the Ministry of Health (19). However, many studies conducted worldwide have shown that the HAV screening and vaccination rates of patients with chronic liver disease are not at the desired level. A gastroenterology clinic in the United States of America determined that 50% of 141 chronic liver disease patients with an average age of 54 who were followed up between 2014 and 2015 were vaccinated against HAV, and 46% were vaccinated against

HBV (20). In Iran, when blood was taken from a total of 403 chronic HBV patients between 2016 and 2017 and anti-HAV IgG was tested, it was reported that 379 (94%) were seropositive. None of them had been vaccinated against HAV (21). The average age of the participants in this study was 29 in seronegative individuals and 42 in seropositive individuals. Since the age groups with the highest HAV seronegativity are under 25 and between 25-35 years, it was commented that it would be appropriate to test for HAV in patients younger than 35 years. In a study conducted in Korea between 2008-2010, anti-HAV IgG results were evaluated in chronic HBV and HCV patients and healthy community members, and it was determined that the seroprevalence was similar to the general population (52.5% in the community, 49% in chronic hepatitis patients). In this study, seronegativity was high in those aged 35 and under. Therefore, it was recommended that chronic hepatitis patients in these age groups be tested and vaccinated (22). In another study from Korea, the prevalence of HAV IgG was determined as 86.6% in 986 patients, 714 of whom were male, over 40 years of age (average age 50) with chronic liver disease between 2008-2009 (80% in chronic HBV, 87% in chronic HCV; 93.8% in HBV-related cirrhosis, 100% in HCV-related cirrhosis). As a result, it was reported that most people over 40 years of age had encountered HAV; the distribution by age groups was as follows: in their 20's (6.67%), in their 30's (50.86%), in their 40's (92.29%), in their 50's (97.77%), and over 60's (100%) (23). In Konya, a province located in a medium-high endemic region in terms of HAV seropositivity in our country, HAV seropositivity was examined in chronic HBV and HCV patients between 2011-2014 and was found to be 97.5% in chronic HBV patients and 93.6% in chronic HCV patients (average 94%). Independent risk factors were determined as being younger than 40 and living in a rural area (24). In another study conducted in our country between 2009-2013, a total of 673 chronic HBV patients, 354 male and 319 female, aged between 17-78, were included, and HAV IgG positivity was found to be 34% in those younger than 20 years of age, 79% in those aged between 20-29 years, and 100% in those aged 35 and over (25).

Our study determined that 1819 (61.3%) out of 2966 patients were tested for anti-HAV IgG, and 1147 (38.7%) were not. Our results are similar to other studies in our country, and the rate of chronic HBV in which HAV was not tested is as high as 40%. In our study, 1688 (92.8%) out of 1819 patients tested for anti-HAV IgG were seropositive, and 131 (7.2%) were seronegative. However, since almost half of the patients were not tested for HAV, it was impossible to learn the HAV exposure/vaccination status of these patients. However, according to the available data, one in four patients younger than 27 years of age (born in 1998 and after) were seronegative for HAV. This rate drops to one in five in the 27-33 age group (born between 1997-1991) and 16% in the 34-39 age group (born between 1990-1985). HAV seronegativity decreases significantly in those born at or above 40 (1984 and before), falling below 5%. According to these results, the probability of detecting HAV seronegativity is high in chronic HBV patients under the age of 40 and especially under the age of 30; therefore, testing should not be neglected, especially in these age groups. Although HAV seropositivity increases with age, it is striking that there are seronegative patients even at older ages, although their numbers are very low. Therefore, the idea is to test all chronic HBV patients for anti-HAV IgG once in their lifetime. Since our country was a medium-high endemic region in terms of HAV epidemiology in the past years, the general approach of physicians was that adults had already contracted HAV infection naturally, and therefore, there was no need for testing. However, this change in HAV epidemiology should not be ignored today.

When the relationship between anti-HAV IgG testing and the year of diagnosis was evaluated as expected, the HAV testing rate was higher in those with an older year of diagnosis. This result was thought to be related to the fact that patients had visited different hospitals/physicians over the years, and the possibility of having anti-HAV IgG tested at any time increased.

When the relationship between anti-HAV IgG testing and the geographical region where the patients lived was examined, it was determined that the highest rate of testing was done in patients living in the Aegean region (82%), followed by patients residing in the Marmara region (75%) (Figure 1). The lowest rates were in the Eastern Anatolia (26.5%) and Southeastern Anatolia (26.5%) regions. This may be because the majority of patients are numerically higher in these regions, and physicians in these regions show more interest in the subject. It has been determined that the number of people vaccinated for HAV is higher in those living in the Aegean and Marmara regions.

When the relationship between the anti-HAV IgG test and the geographical region where the patients were born is examined, the highest test rates were found in those born in the Aegean (79%), abroad (77%), Marmara (73%), Central Anatolia (68%), Eastern Anatolia (64%), Southeastern Anatolia (58%), Mediterranean (51%) and Black Sea (49%) regions, respectively.

A pleasing situation observed in the study data is that the majority of chronic HBV patients in the study group were born in 1997 and above (25-27 years of age and above), and the highest number of patients were in the 34-39 age group (birth years between 27-50 years of age). Chronic HBV patients born after the national vaccination program started in 1998 constituted only 1.4% (26/1819) of the study group. This situation is thought to be closely related to the national HBV vaccination program started in our country in 1998; thus, it was observed that the rate of chronic HBV in individuals born after the vaccination program decreased statistically significantly ($p<0.00001$) (Table 3).

Study Limitations

The study's limitation is that some data were difficult to access due to the retrospective collection of data. However, it is thought that the data may reflect the approaches of physicians who follow chronic HBV patients throughout the country, and it is anticipated that these data may create awareness among physicians who follow chronic HBV cases.

Conclusion

As a result, the number of chronic HBV cases among young people is gradually decreasing as a result of national vaccination programs in our country, and there is also a positive change in HAV epidemiology. Since childhood HAV vaccination has been started in our country since 2011, we are likely to encounter HAV seronegative individuals for approximately one more decade.

Considering the severe course of acute HAV infection in individuals with chronic hepatitis, all chronic HBV patients, regardless of their age, should be tested for HAV once, and seronegative individuals should not be neglected to be vaccinated.

Ethics

Ethics Committee Approval: Our institution has received ethical approval from the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine (approval number: A-83, date: 06.07.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.T., F.T., R.G., Design: S.T., F.T., R.G., Data Collection or Processing: S.T., A.B., E.Y.Z., M.A., E.T., E.P., M.O.T., T.T., D.Y.S., Y.Ö., U.B., İ.E.Y., O.K., A.Ö., H.D.Ö., F.T., M.N.T., S.A., B.K., S.K., A.S.Ö., L.N.A., R.G., Analysis or Interpretation: S.T., F.T., R.G., Literature Search: S.T., Writing: S.T.

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Research Article

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Risk of HBV Reactivation During Immunosuppressive Therapy in Psoriasis: A Retrospective Analysis

Psoriasis Hastalarında İmmünosüpresif Tedavi Süresince HBV Reaktivasyonu Riski: Retrospektif Bir Değerlendirme

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ABSTRACT

Objectives: This study aimed to evaluate the risk of hepatitis B virus (HBV) reactivation in patients with a history of resolved HBV infection or isolated anti-HB core immunoglobulin G positivity who received systemic immunosuppressive therapy for psoriasis.

Materials and Methods: A retrospective analysis was conducted on patients ≥18 years old with psoriasis who received systemic immunosuppressive therapy (≥3 months), including methotrexate (MTX), apremilast, cyclosporine, and various biologic agents [tumor necrosis factor-alpha, interleukin (IL)-17, IL-23, IL-12/23 inhibitors] between January 2018 and March 2025. Patients with baseline HBV-DNA positivity, human immunodeficiency virus/hepatitis C virus co-infection, or incomplete data were excluded. HBV reactivation was defined as either HB surface antigen (HBsAg) seroconversion or detectable HBV-DNA. Patients were classified into three risk groups based on serological status and immunosuppressive regimen. Anti-HBs levels were categorized (<10 IU/L, 10-99 IU/L, and ≥100 IU/L), and risk factors were analyzed using Fisher's exact test and logistic regression.

Results: Among 1200 patients screened, 138 eligible individuals were included (63.0% male; mean age 56.9±11.8 years). Seven patients (5.0%) experienced HBV reactivation during immunosuppressive therapy, with no cases of acute hepatitis. Reactivation occurred significantly more often in HBsAg-positive and anti-HBs-negative individuals (p=0.008 and p=0.018, respectively). No reactivation was observed in patients with anti-HBs ≥10 IU/L (p<0.001). Logistic regression showed a trend toward higher reactivation risk with HBsAg positivity (odds ratio:

ÖZ

Amaç: Bu çalışmada, geçirilmiş hepatit B virüsü (HBV) veya izole HB çekirdek antijenine karşı gelişmiş immünoglobulin G antikor pozitifliği olan ve sedef hastalığı nedeniyle sistemik immünosüpresif tedavi alan hastalarda HBV reaktivasyon riski değerlendirildi.

Gereç ve Yöntemler: Ocak 2018-Mart 2025 tarihleri arasında, 18 yaş ve üzerindeki psoriazis hastaları retrospektif olarak incelendi. En az üç aydır sistemik immünosüpresif tedavi metotreksat (MTX), apremilast, siklosporin veya biyolojik ajanlar [tümör nekroz faktörü (TNF)-alfa, interlökin (IL)-17, IL-23, IL-12/23 inhibitörü] alan hastalar dahil edildi. Başlangıçta HBV-DNA pozitif olanlar, insan bağışıklık yetmezlik virüsü/hepatit C virüsü ko-enfeksiyonu bulunanlar ve eksik kayıtlı hastalar çalışma dışı bırakıldı. HBV reaktivasyonu, hepatit B yüzey antijeni (HBsAg) serokonversiyonu veya ölçülebilir düzeyde HBV-DNA tespiti olarak tanımlandı. Hastalar serolojik profilleri ve tedavi rejimlerine göre üç risk grubuna ayrıldı. Anti-HBs düzeyleri (<10 IU/L, 10-99 IU/L ve ≥100 IU/L), ayrı ayrı değerlendirildi. Risk faktörleri Fisher'ın kesin testi ve lojistik regresyon analizi ile incelendi.

Bulgular: Taramaya alınan 1200 hastadan 138'i çalışmaya dahil edildi (%63,0 erkek; ortalama yaş 56,9±11,8 yıl). Yedi hastada (%5,0) HBV reaktivasyonu saptandı; hiçbirinde aktif hepatit gelişmedi. Reaktivasyon, HBsAg pozitif ve anti-HBs negatif hastalarda anlamlı olarak daha yüksekti (p=0,008 ve p=0,018). Anti-HBs ≥10 IU/L olan hiçbir hastada reaktivasyon izlenmedi (p<0,001). Lojistik regresyonda HBsAg pozitifliği anlamlılığa yakın risk faktörü olarak izlendi (olasılık oranı: 8,60; p=0,062). Düşük

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8.60; p=0.062). MTX, despite being classified as low risk, was associated with reactivation in HBsAg-positive patients.

Conclusion: HBV reactivation is strongly associated with HBsAg positivity and low or absent anti-HBs levels. Pre-treatment serological screening and close monitoring, especially in anti-HBs-negative individuals, are essential for safe immunosuppressive therapy in psoriasis.

Keywords: Hepatitis B reactivation, psoriasis, immunosuppressive therapy

riskli kabul edilen MTX, HBsAg pozitif bireylerde reaktivasyonla ilişkiliydi.

Sonuç: HBV reaktivasyonu, HBsAg pozitifliği ve düşük/negatif anti-HBs düzeyleriyle güçlü şekilde ilişkilidir. Tedavi öncesi serolojik tarama ve özellikle anti-HBs negatif hastalarda yakın izlem, psoriazis tedavisinde güvenli immünosüpresyon için gereklidir.

Anahtar Kelimeler: Hepatit B reaktivasyonu, psoriazis, immünosüpresif tedavi

Introduction

Psoriasis vulgaris is a chronic inflammatory skin disease characterized by erythematous and scaly plaques. Treatment options for psoriasis vulgaris include conventional therapies such as methotrexate (MTX), cyclosporine, acitretin, and apremilast, as well as biologic agents targeting specific cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-12/23, IL-17, and IL-23 (1). These agents exert their effects by modulating distinct pathways within the immune system. However, their use in patients infected with hepatitis B virus (HBV) may trigger viral reactivation (2). HBV reactivation can result in serious hepatic complications and may compromise the safety of systemic treatment in affected individuals.

Anti-HB core (anti-HBc) positivity indicates prior exposure to HBV and represents a potential risk for reactivation. In HBsAg-negative individuals, occult HBV infection is characterized by the presence of low-level HBV-DNA in the liver, and occasionally in serum ($<10^3$ copies/mL), despite the absence of detectable surface antigen (3). Approximately 20% of patients with natural immunity exhibit isolated anti-HBc immunoglobulin G (IgG) positivity, a serologic profile that may mask ongoing viral persistence, thereby complicating recognition of reactivation risk (4). Thus, comprehensive serological and virological evaluation is critical prior to initiating immunosuppressive therapy.

This study aimed to assess the frequency of HBV reactivation and the contributing risk factors among psoriasis patients receiving immunosuppressive therapy.

Although the risk of HBV reactivation with certain high-risk immunosuppressive therapies is well known, limited data are available on HBV reactivation risk in psoriasis patients receiving a broader spectrum of systemic treatments, particularly those considered low risk, such as MTX or apremilast. Therefore, this study aimed to fill this gap by systematically evaluating reactivation rates across commonly used agents.

Materials and Methods

Patients aged 18 years or older who were diagnosed with psoriasis vulgaris and followed at the Department of Dermatology, University of Health Sciences Türkiye, Ankara Etlik City Hospital, between January 2018 and March 2025 were retrospectively evaluated. Although HBV reactivation is most commonly observed following the discontinuation of immunosuppressive therapy, cases of reactivation as early as the third month after initiation of treatment have been reported in the literature, characterized by rising HBV-DNA levels. (5,6,7). Therefore, patients who had been receiving systemic immunosuppressive agents for at least three months, including MTX, apremilast, cyclosporine, or biologics such as TNF-α inhibitors, IL-17 receptor blockers, IL-17A inhibitors, anti-IL-12/23, and anti-IL-23 agents, were included. Demographic, clinical, and laboratory data were obtained from the hospital information system.

Eligible patients had negative HBV-DNA at baseline and either isolated anti-HBc IgG positivity or a natural immunity profile (anti-HBc IgG and anti-HBs positive). Accordingly, all 138 patients included in the study had undetectable HBV-DNA at baseline. HBV reactivation risk was classified as high (≥10%), moderate (1-10%), or low (<1%) depending on serologic status and the immunosuppressive agent used (5,8,9). Patients were grouped accordingly into three risk categories. Their immunologic profiles and therapeutic regimens are detailed in Table 1.

According to the available medical records, patients had undergone liver function testing (alanine aminotransferase and aspartate aminotransferase) approximately every three months to monitor for signs of active hepatitis. In cases where elevated liver enzymes were noted, HBsAg and HBV-DNA levels were subsequently assessed (5). HBV reactivation was defined as HBsAg seroconversion or detectable HBV-DNA in serum (10).

Table 1. HBV reactivation risk groups

Group	HBsAg status	Anti-HBc status	Agents used	Risk level	Explanation
Group 1	Negative or positive	Positive	Methotrexate, apremilast, cyclosporine	Low risk	Considered low risk for HBV reactivation.
Group 2	Negative	Positive	TNF-α inhibitors, IL-17R blockers, IL-17A inhibitors, anti-IL-12/23, anti-IL-23	Moderate risk	Considered moderate risk for HBV reactivation.
Group 3	Positive	Positive	TNF-α inhibitors, IL-17R blockers, IL-17A inhibitors, anti-IL-12/23, anti-IL-23	High risk	Received HBV prophylaxis according to current guidelines.

HBsAG: Hepatitis B surface antigen, Anti-HBc: Anti-hepatitis B core, HBV: Hepatitis B virus, TNF: Tumor necrosis factor, IL: Interleukin

Anti-HBs titers were stratified as <10 IU/L, 10-99 IU/L, and ≥100 IU/L, and their association with HBV reactivation was analyzed. Potential effects of age and sex were also evaluated. Patients with HBV-DNA positivity at baseline, human immunodeficiency virus/hepatitis C virus co-infection, liver failure, other significant liver disease, use of non-immunosuppressive systemic agents (e.g., acitretin), combination immunosuppressive therapy, or incomplete records were excluded.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics v15.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess the distribution of continuous variables. The Mann-Whitney U test was used for non-normally distributed variables, and associations between categorical variables were analyzed using Fisher's exact test. A multivariate logistic regression analysis was conducted to evaluate independent predictors of HBV reactivation, including age, sex, HBsAg status, anti-HBs titer, immunosuppressive drug type, and treatment duration. A p-value of <0.05 was considered statistically significant.

The study was approved by the Scientific Research Evaluation and Ethics Committee of the University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025-0290, date: 26.03.2025) and conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

Results

Among 1,200 psoriasis patients retrospectively reviewed, 200 had serological evidence of past HBV infection (anti-HBc IgG positive). After excluding 62 patients due to detectable HBV-DNA or lack of immunosuppressive therapy, 138 patients were included in the final analysis (Figure 1). Baseline HBV-DNA levels were undetectable in all included patients. Detailed information regarding patients' HBsAg and anti-HBs status, as well as prior systemic immunosuppressive therapies—including those administered to patients who developed HBV reactivation—is summarized in Table 2.

Of the 138 patients included in the study, 87 (63.0%) were male and 51 (37.0%) were female, with a mean age of 56.9±11.8 years (range: 28-80 years). The mean duration of treatment

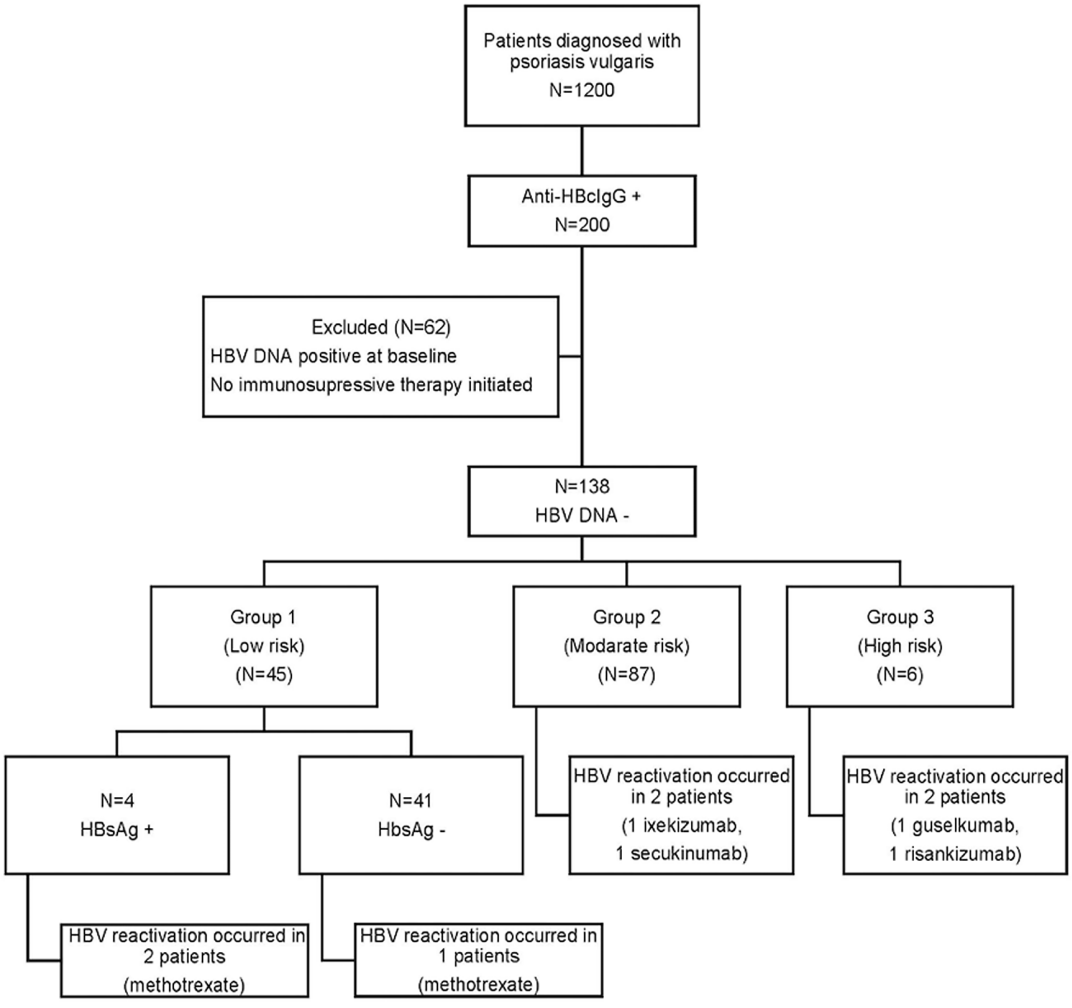

Figure 1. Flow diagram illustrating the characteristics and distribution of the study population
HBV: Hepatitis B virus, HBsAG: Hepatitis B surface antigen

was 21.3±18.9 months (range: 3-108 months). Details regarding treatment agents and durations are provided in Table 3.

Group 1 consisted of 45 patients: 42 on MTX, one on cyclosporine, and two on apremilast. Group 2 included 87 patients, with the most commonly used agent being ixekizumab (n=22), followed by secukinumab (n=18), risankizumab (n=16), ustekinumab (n=12), guselkumab (n=11), adalimumab (n=5), certolizumab (n=2), and bimekizumab (n=1). In group 3, there were six patients who received concurrent antiviral prophylaxis alongside immunosuppressive therapy: two were treated with secukinumab, two with guselkumab, one with risankizumab, and one with ixekizumab.

HBV reactivation occurred in two of the four HBsAg-positive patients in group 1 and in one of the 41 HBsAg-negative patients. In group 2, reactivation was observed in two patients (one on ixekizumab and one on secukinumab), both of whom were HBsAg-negative. In group 3, reactivation developed in two patients (33.3%; 95% confidence interval: 4.3-77.7), both of whom were receiving IL-23 inhibitors (one guselkumab, one risankizumab).

Table 2. Baseline virologic status and treatment history of included patients

Variable	**n (%)**
Number of patients included	138
Baseline HBV-DNA level	Undetectable in all patients
HBsAg status	Positive: 10 (7.2%) Negative: 128 (92.8%)
Anti-HBs status	<10 IU/L: 37 (26.8%) 10-99 IU/L: 31 (22.5%) ≥100 IU/L: 70 (50.7%)
Anti-HBc IgG positivity	138 (100%)
Prior systemic immunosuppressive therapy • Methotrexate • Cyclosporine • Apremilast • Biologics • TNF-alpha inhibitors • IL-17 inhibitors • IL-23 nhibitors • IL-12/23 inhibitors	Yes: 92 (66.7%) No: 46 (33.3%) 88 (63.8%) 40 (29.0%) 5 (3.6%) 4 (2.9%) 3 (2.2%) 1 (0.7%) 0 (0%)
Prior systemic immunosuppressive therapies administered to patients exhibiting reactivation • None • Methotrexate • Adalimumab • Cyclosporine	7 3 (42.9%) 4 (57.1%) 1 (14.3%) 3 (42.9%)

HBV: Hepatitis B virus, TNF: Tumor necrosis factor, IL: Interleukin, HBsAG: Hepatitis B surface antigen, Anti-HBc: Anti-hepatitis B core, Anti-HBs: Anti-hepatitis B surface, IgG: Immunoglobulin G

Table 3. Immunosuppressive agents used in the study population and duration of use

Drug	**Total number (%) (n=138)**	**Mean duration (months) ± SD (min-max)**
Methotrexate	42 (30.4%)	15.95±15.98 (3-80)
Cyclosporine	1 (0.7%)	6.0±0.0 (6-6)
Apremilast	2 (1.4%)	4.5±1.5 (3-6)
Adalimumab	5 (3.6%)	52.2±20.2 (15-72)
Bimekizumab	1 (0.7%)	3.0±0.0 (3-3)
Guselkumab	13 (9.4%)	22.5±19.88 (3-82)
Ixekizumab	23 (16.7%)	20.9±12.34 (6-60)
Risankizumab	17 (12.3%)	14.5±7.31 (6-30)
Secukinumab	20 (14.5%)	24.1±14.6 (6-60)
Certolizumab	2 (1.4%)	30.00±6.00 (24-36)
Ustekinumab	12 (8.7%)	35.75±31.62 (3-108)

SD: Standard deviation, min: Minimum, max: Maximum

Table 4. Characteristics of patients with HBV reactivation and distribution by risk group

Patient no	Age	Sex	Immunosuppressive agent	Risk group	HBsAg status	Anti-HBs status	Time to reactivation (months)	Prophylactic agent used	Development of hepatitis
1	80	M	Methotrexate	Group 1	-	-	10	-	-
2	72	M	Methotrexate	Group 1	+	-	12	-	-
3	65	M	Methotrexate	Group 1	+	-	15	-	-
4	59	M	Secukinumab	Group 2	-	-	6	-	-
5	45	M	Ixekizumab	Group 2	-	-	30	-	-
6	72	F	Risankizumab	Group 3	+	-	6	Entecavir	-
7	39	M	Guselkumab	Group 3	+	-	12	Tenofovir	-

F: Famale, M: Male, HBsAG: Hepatitis B surface, Anti-HBs: Anti-hepatitis B surface, HBV: Hepatitis B virus

Statistical analysis revealed a significant association between reactivation and serological markers (HBsAg and anti-HBs). In group 1, Fisher's exact test showed that anti-HBs-negative individuals had a significantly higher reactivation rate than those who were positive (30% vs. 0%, p=0.008). Reactivation was also significantly more frequent in HBsAg-positive individuals (50% vs. 2.4%, p=0.018). Notably, all cases of reactivation occurred in anti-HBs-negative patients, especially among those who were both HBsAg-positive and anti-HBs-negative; this serological combination was associated with the highest risk.

In group 2, where all 87 patients were HBsAg-negative, reactivation was significantly more common among anti-HBs-negative individuals compared to anti-HBs-positive ones (10.5% vs. 0%, p=0.046). No reactivation was observed in the 68 anti-HBs-positive patients. In group 3, all six patients were both HBsAg-positive and anti-HBs-negative; two developed reactivation (33.3%). Since all patients had the same serological profile, statistical testing could not be performed; however, this profile again appeared to confer high risk.

HBV reactivation occurred exclusively in patients with anti-HBs levels <10 IU/mL. No reactivation was observed among anti-HBs-positive patients (≥10 IU/mL), and this finding was statistically significant (p<0.001, Fisher's exact test).

Overall, seven patients (5.0%) developed HBV reactivation during immunosuppressive therapy, with a mean time to reactivation of 15 months. Antiviral treatment was initiated in these patients, and no cases of clinical hepatitis were observed (Table 4).

There was no statistically significant difference in reactivation rates among different treatment agents (p=0.435). In logistic regression analysis, age, treatment duration, and risk group were not independently associated with reactivation. Additionally, MTX was associated with a 1.33-fold higher odds of HBV reactivation compared to biologic agents, although this difference did not reach statistical significance (p=0.70).

However, HBsAg positivity approached statistical significance [odds ratio (OR): 8.60, p=0.062]. Pairwise comparison using Fisher's exact test showed that HBsAg-positive patients had an approximately 28-fold higher risk of reactivation compared to HBsAg-negative patients (OR: 27.78; p=0.00045), supporting HBsAg positivity as a strong and independent risk factor.

Discussion

HBV infection manifests across a broad clinical spectrum, ranging from acute infection to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. This course is determined by both viral characteristics and the host immune response (11). As of 2022, approximately 254 million individuals globally were living with chronic HBV infection, underscoring its status as a major public health concern (12). The reported prevalence of HBV infection in patients with psoriasis ranges from 0.45% to 5.6% (13,14), and the risk of HBV reactivation in this population varies according to the immunosuppressive regimen and individual serological profile (13).

Although MTX is generally regarded as low risk for HBV reactivation and may be used with close monitoring in the absence of antiviral prophylaxis (9,13), several studies have reported increased risk among HBsAg-positive individuals. One such study in patients with psoriasis identified a reactivation rate of 28.6% in HBsAg-positive MTX users (15). In our study, 2 of 4 HBsAg-positive patients on MTX experienced reactivation (50%), along with 1 of 41 HBsAg-negative patients (2.4%), confirming HBsAg positivity as a strong predictive factor. While current guidelines categorize MTX use as low risk irrespective of HBsAg status, our findings challenge this approach and suggest a need to re-evaluate the risk stratification, especially in the presence of HBsAg positivity. Notably, MTX showed a reactivation rate comparable to or even higher than certain biologics. Although the observed OR did not reach statistical significance, this trend suggests that MTX may not be inherently low risk, particularly in anti-HBs-negative individuals. These findings underscore the importance of nuanced risk assessment and support the need for larger, comparative studies to better guide clinical decision-making and future HBV management strategies.

TNF-α inhibitors are the most extensively studied biologics in terms of HBV reactivation risk (3). Guidelines recommend antiviral prophylaxis in HBsAg-positive patients, with reactivation rates reported between 14% and 63% in the absence of prophylaxis (6). For HBsAg-negative/anti-HBc-positive individuals, the risk is lower (3-5%), and regular monitoring is generally considered sufficient (16). In our cohort, no reactivation was observed among anti-TNF users who were HBsAg-negative.

Studies evaluating ustekinumab, an IL-12/23 inhibitor, report reactivation in 25% of HBsAg-positive and 2.6% of occult HBV-

infected individuals; however, none developed severe hepatitis or liver failure (17). In our study, all patients receiving ustekinumab were HBsAg-negative, and no reactivation occurred, supporting its relative safety in patients with resolved HBV infection.

IL-17 inhibitors (ixekizumab, secukinumab, bimekizumab) are considered low-risk agents (18,19,20). However, in our cohort, reactivation occurred in two patients (20%) with isolated anti-HBc IgG positivity, while no cases were observed among patients with natural immunity. This highlights the protective role of anti-HBs positivity against HBV reactivation.

Although data on IL-23 inhibitors are limited, current evidence suggests a low risk of reactivation (21). In our study, no reactivation was observed in HBsAg-negative patients receiving IL-23 inhibitors. However, among three HBsAg-positive patients on prophylaxis, two (one on guselkumab, one on risankizumab) developed reactivation. This suggests that IL-23 inhibitors cannot be considered inherently safe in HBsAg-positive patients, and warrant close monitoring even with prophylaxis.

A recent meta-analysis reported HBV reactivation rates of 25.3% in high-risk and 5% in moderate-risk patients not receiving prophylaxis (22). In our study, these rates were 33.3% and 2.3%, respectively. While the discrepancy may be due to sample size, the results underscore the importance of considering HBsAg and anti-HBs status when using biologics.

Factors such as advanced age, prolonged immunosuppression, and high-potency immunosuppressants may contribute to reactivation despite antiviral prophylaxis (23). In the present study, two of six HBsAg-positive patients receiving antiviral prophylaxis experienced reactivation (33.3%). The study's findings indicated that both subjects were anti-HBs negative and on IL-23 inhibitors, suggesting that the absence of anti-HBs may be an additional risk factor that warrants further consideration. The potential for antiviral resistance should be considered, although it should be noted that resistance testing was not performed in the present study.

Anti-HBs positivity has consistently been associated with a lower risk of reactivation in patients receiving biologics. Some studies suggest that only high titers (e.g., ≥100 IU/L) confer significant protection (24,25,26). Moreover, anti-HBs titers may decline over time in immunosuppressed individuals, increasing vulnerability to reactivation. High-dose vaccination strategies may also fail to elicit protective titers in this population (27). All reactivation cases in our study occurred in patients with anti-HBs levels <10 IU/L. The absence of reactivation among anti-HBs-positive patients supports the antibody's protective role. Therefore, both the presence and the quantitative level of anti-HBs should be considered when formulating prophylactic or monitoring strategies.

This study represents one of the few comprehensive investigations of HBV reactivation risk associated with various immunosuppressive therapies in psoriasis. Stratification by HBsAg, anti-HBc, and anti-HBs status, as well as separate analysis of patients receiving prophylaxis, enabled precise evaluation of serological risk profiles. Additionally, drug-specific reactivation rates offer clinically actionable insights for therapeutic decision-making.

Study Limitations

The retrospective design of the study limits the ability to establish causality. Small sample sizes in some subgroups may reduce the statistical power of the analyses. Moreover, the absence of antiviral resistance testing precluded clarification of the underlying mechanisms in patients who developed reactivation despite prophylaxis. Future prospective studies with larger cohorts and genotypic resistance assessments are warranted to validate our findings.

Conclusion

HBV reactivation was most frequently observed in HBsAg-positive and anti-HBs-negative patients, and less commonly in those with isolated anti-HBc positivity. No reactivation occurred in patients who were anti-HBs positive, underscoring the protective role of this antibody.

Reactivation despite antiviral prophylaxis suggests that additional risk factors—such as advanced age, prolonged immunosuppressive treatment, potent immunosuppression, and possible antiviral resistance—should be considered. Notably, MTX-induced reactivation in HBsAg-positive patients challenges its current classification as a universally low-risk agent.

Therefore, comprehensive pre-treatment HBV serological screening is essential before initiating immunosuppressive therapy in psoriasis. Prophylaxis should be implemented as indicated, and anti-HBs-negative patients require close monitoring during therapy. Importantly, even patients receiving antiviral prophylaxis must undergo regular HBV-DNA surveillance to ensure early detection of reactivation and prevention of serious complications. Furthermore, no reactivation events were observed among anti-HBs-positive patients treated with anti-TNF agents, supporting their continued classification as low-risk options. Nevertheless, even these agents should be used with caution in seronegative individuals until larger studies confirm their safety.

Ethics

Ethics Committee Approval: The study was approved by the Scientific Research Evaluation and Ethics Committee of the University of Health Sciences Türkiye, Ankara Etlik City Hospital (approval number: AEŞH-BADEK-2025-0290, date: 26.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: G.T.A., O.K.Y., H.K., B.Ç.C., S.P.K., Design: G.T.A., A.H.S., O.K.Y., H.K., B.Ç.C., Data Collection or Processing: G.T.A., O.K.Y., H.K., Analysis or Interpretation: G.T.A., A.H.S., Literature Search: G.T.A., A.H.S., B.Ç.C., S.P.K., Writing: G.T.A., A.H.S., B.Ç.C., S.P.K.

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Research Article

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Hepatitis A Seroprevalence by Age Groups in Mardin Province

Mardin İlinde Yaş Gruplarına Göre Hepatit A Seroprevalansı

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ABSTRACT

Objective: Türkiye is a medium endemic country for hepatitis A virus (HAV) and the seroprevalence of HAV varies regionally. The aim of this study was to determine the immunity status against HAV according to age groups in Mardin province, where no seroprevalence study has been conducted.

Materials and Methods: Anti-HAV immunoglobulin G (IgG) tests which were requested from outpatient clinics of Mardin Training and Research Hospital between May 2024 and September 2024 were evaluated. Anti-HAV IgG was analysed with Cobas® 6000 system (Roche Diagnostics, Rotkreuz, Switzerland) by enzyme-linked immunosorbent assay method.

Results: Anti-HAV IgG results of 2765 patients were included in the study. The mean age of the patients was 34.72±19.27 years, 1459 were female (52.8%) and 1306 were male (47.2%). Anti-HAV IgG positivity was detected in 94.6% of the patients. This rate was 95.3% in males and 94.0% in females. The lowest rate of anti-HAV IgG positivity was in the age group of 13-18 years (66.7%). At the age of 50 years and older, anti-HAV IgG positivity was 100%. The mean age of seropositive patients was higher than seronegative patients (35.6 vs. 19.8, p<0.001). The seropositivity rate was found to be higher in children born after 2012 (when routine HAV vaccination began in childhood) than in children aged 13-18 born before 2012 (95.3% vs. 66.7%, p<0.001).

Conclusion: HAV seroprevalence was found to be high in Mardin province. Furthermore, the HAV vaccination programme has yielded positive results. As the 13-18 age group did not benefit from the programme, they are the most susceptible to HAV. Therefore, special vaccination programmes should be implemented for this age group.

Keywords: HAV seroprevalence, hepatitis A, vaccination

ÖZ

Amaç: Türkiye hepatit A virüsü (HAV) için orta endemik bir ülkedir ve HAV seroprevalansı bölgesel olarak değişmektedir. Bu çalışmanın amacı, daha önce seroprevalans çalışması yapılmamış olan Mardin ilinde yaş gruplarına göre HAV'ye karşı bağışıklık durumunu belirlemektir.

Gereç ve Yöntemler: Mayıs 2024 ve Eylül 2024 tarihleri arasında Mardin Eğitim ve Araştırma Hastanesi polikliniklerinden istenen anti-HAV immünoglobulin G (IgG) test sonuçları değerlendirilmiştir. Anti-HAV IgG, Cobas® 6000 sistemi (Roche Diagnostics, Rotkreuz, Switzerland) ile enzime bağlı immünosorbent assay yöntemi ile analiz edilmiştir.

Bulgular: Çalışmaya 2765 hastanın anti-HAV IgG sonuçları dahil edilmiştir. Hastaların yaş ortalaması 34,72±19,27 yıl, 1459'u kadın (%52,8) ve 1306'sı erkek (%47,2) idi. Hastaların %94,6'sında anti-HAV IgG pozitif saptanmıştır. Bu oran erkeklerde %95,3 iken kadınlarda ise %94,0 idi. Anti-HAV IgG pozitiflik oranı en düşük 13-18 yaş grubunda görülmüştür (%66,7). Elli yaş ve üzerinde anti-HAV IgG pozitifliği %100 bulunmuştur. Seropozitif hastaların yaş ortalamasının seronegatif hastalardan daha yüksek olduğu görülmüştür (35,6 vs. 19,8, p<0,001). Seropozitiflik oranı 2012 yılından sonra doğan çocuklarda (çocukluk çağında rutin HAV aşılamasının başladığı yıl) 2012'den önce doğan 13-18 yaş arası çocuklara göre daha yüksek bulunmuştur (%95,3'e karşı %66,7, p<0,001).

Sonuç: Mardin ilinde HAV seroprevalansı yüksek bulunmuştur. Bununla birlikte HAV aşılama programının olumlu sonuçları gözlemlenmiştir. HAV aşılama programından faydalanamamış olan 13-18 yaş grubu HAV'a karşı en duyarlı gruptur. Bu nedenle, bu yaş grubuna yönelik özel aşılama programları yapılmalıdır.

Anahtar Kelimeler: HAV seroprevalansı, hepatit A, aşılama

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Introduction

Hepatitis A virus (HAV) is a worldwide common viral infection transmitted by the fecal-oral route. The disease is usually self-limited, supportive care is usually sufficient for treatment and chronic infection does not occur (1). Clinical manifestations depend on the age of the patient. Less than 30% of infected young children are symptomatic, while approximately 80% of infected adults show severe hepatitis with markedly elevated serum aminotransferases. Fulminant hepatitis is rare, with a reported incidence of 0.015% to 0.5% (2). The first exposure to HAV occurs later in life in developed countries than in low-income countries (3). The majority of HAV infections in developing countries are not clinically apparent. In contrast, infections in developed countries are often characterised by jaundice and acute hepatitis, particularly in adolescents and adults (4). HAV is more prevalent in developing countries and low-income areas (5). The incidence of the disease depends mainly on socioeconomic status and access to clean water. In developing countries with poor sanitation, there is almost 100% seropositivity for anti-HAV immunoglobulin G (IgG) (6). In hyperendemic countries, the age at midpoint of population immunity (AMPI) can be as low as one year of age. Türkiye is a medium endemic country for HAV (7). However, the incidence of HAV varies regionally (8). In this study, we aimed to determine the seroprevalence of HAV in Mardin province, which had not been evaluated before.

Materials and Methods

Data Collection

In this cross-sectional prevalence study, the anti-HAV IgG test results of patients who applied to the outpatient clinics of Mardin Training and Research Hospital between May 2024 and September 2024 and who were requested for any reason were evaluated. The test results of the patients for whom the anti-HAV IgG was requested were recorded retrospectively. Patients were divided into 8 groups according to age: 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70 years and older.

Anti-HAV IgG tests were performed by enzyme-linked immunosorbent assay method using Cobas® 6000 system (Roche Diagnostics, Rotkreuz, Switzerland) in the microbiology laboratory. Anti-HAV IgG results below 1 signal cut-off (S/CO) were considered positive and anti-HAV IgG with >1 S/CO values were considered negative.

Statistical Analysis

The statistical analyses were conducted using SPSS version 27.0 (Statistical Package for the Social Sciences; IBM Corp., Armonk, NY, USA). Descriptive statistical methods, including mean, standard deviation, frequency, and ratio, were employed to evaluate the study data. A chi-square test was employed for the comparison of qualitative data. A Student's t-test was employed for the purpose of comparing variables that were normally distributed between two groups. In instances where the variables in question did not demonstrate a normal distribution, a Mann-Whitney U test was employed to facilitate comparison between the two groups. The level of statistical significance was set at $p<0.05$.

Ethics

The research was conducted in accordance with the principles of the Declaration of Helsinki. This study was ethically approved by the decision of Mardin Artuklu University Non-Interventional Clinical Research Ethics Committee dated 07.04.2025 and numbered 2025/3-8.

Results

The anti-HAV IgG results from the outpatient clinics of our hospital between the study dates were listed. Of the total 2999 tests, 85 repeated results and 149 tests that were not accepted by the laboratory were excluded from the study. Anti-HAV IgG results of 2765 patients were included in the study. The mean age of the patients was 34.72±19.27 years, 1459 were female (52.8%) and 1306 were male (47.2%). Anti-HAV IgG positivity was detected in 94.6% of all patients. This rate was 95.3% in males and 94.0% in females. There was no statistical difference between both genders in terms of anti-HAV IgG positivity ($p>0.05$). The lowest rate of anti-HAV IgG positivity was observed in the 10-19 age group (73.1%). All patients aged 50 years and older were found to be anti-HAV IgG positive. When anti-HAV IgG positivity rates were compared according to age groups, a statistically significant difference was found ($p<0.001$). Furthermore, the mean age of patients with anti-HAV IgG positivity was higher than that of patients with seronegativity (35.6 vs. 19.8, $p<0.001$). Seropositivity status according to age groups and gender is shown in Table 1.

In order to evaluate the effectiveness of the HAV vaccine, the pediatric patients were divided into two groups and the seropositivity rates were compared. The first group consisted of children aged 0-12 years who were born after 2012, when HAV vaccination was added to the vaccination schedule. The second group consisted of children aged 13-18 years. The seropositivity rate was 95.3% in those born after 2012 and 66.7% in those born before 2012 (odds ratio:10.1, 95% confidence interval: 5.35-19.23, $p<0.001$).

Discussion

In our study, a high rate of the anti-HAV IgG positivity (94.6%) was found in Mardin province. In 2011 and later studies in which all age groups were evaluated, anti-HAV IgG positivity rates were reported between 38.1% and 97.3% in different provinces of Türkiye (9,10,11,12,13,14,15). Nevertheless, the prevalence of HAV increases from west to east in Türkiye (8). In a study conducted on patients aged between 5-24 years in Istanbul, which contains many cultural elements in Türkiye, HAV seropositivity was found to be higher in people with low socioeconomic status. In the same study, anti-HAV IgG positivity was found to be higher in patients with low maternal education level (16). In the study conducted by Halicioglu et al. (17) in the pediatric age group in İzmir, seropositivity was found to be higher in those with a mother and father education period of 5 years or less, low income level and living in crowded families. Similar to the Southeastern Anatolia region in general, our province has a low socioeconomic level and overcrowded families. Rural life, difficulties in accessing clean water and inadequate sanitation may also be among the reasons for frequent prevalence of HAV in our province.

Table 1. The rates of anti-HAV IgG positivity according to age groups and gender

Age range and gender	Patient count	Anti-HAV IgG positivity		p-value
		n	%	
0-9 years	260	247	95.0	<0.001
10-19 years	242	177	73.1	
20-29 years	746	692	92.8	
30-39 years	589	575	97.6	
40-49 years	331	329	99.4	
50-59 years	216	216	100.0	
60-69 years	208	208	100.0	
70 years and above	173	173	100.0	
Female	1459	1390	95.3	0.124
Male	1306	1227	94.0	
Total	2765	2617	94.6	
0-12 years	297	283	95.3	<0.001
13-18 years	144	96	66.7	
0-18 years	441	379	85.9	
Anti-HAV IgG	Patient count	Mean age ± SD		p-value
Positive	2617	35.57±19.37		0.000
Negative	148	19.80±8.14		

HAV: Hepatitis A virus, IgG: Immunoglobulin G, SD: Standard deviation

Table 2. Evaluation of the effectiveness of hepatitis A vaccination based on studies assessing hepatitis A seroprevalence by age group

Author and publication year	Province and data dates	Age range	Patient count	Anti-HAV IgG positivity rate (%)	Interpretation of the effects of the hepatitis A vaccine
Our study	Mardin 2024	All ages	2765	94.6	Seropositivity was 95.3% in the 0-12 age group and 66.7% in the 13-18 age group (OR:10.1, 95% CI: 5.35-19.23, p<0.001).
					Children aged 0-12 who were born after the hepatitis A vaccination programme had higher rates of seropositivity compared to children born before the programme.
Samancı and Akdeniz (21) 2022	Diyarbakır 2009-2018	0 to 18 years	21267	53.8	Seropositivity was higher in those born after the vaccination programme than in those born before it (81.9% vs. 41.2%, p<0.001).
					The effect of the hepatitis A vaccine was examined directly, and it was found that seropositivity was significantly higher in the vaccinated group.
Atik et al. (10) 2021	Balıkesir 2017-2019	All ages	3450	68.6	Seropositivity was 63.1% in the 0-10 age group and 38.8% in the 11-17 age group.
					Although the effect of the hepatitis A vaccine has not been investigated directly, seropositivity was found to be higher in the 0-10 age group that had received partial vaccination than in the 11-17 age group that had not been vaccinated at all.

Table 2. Continued

Author and publication year	Province and data dates	Age range	Patient count	Anti-HAV IgG positivity rate (%)	Interpretation of the effects of the hepatitis A vaccine
Düzenli et al. (11) 2021	Çorum 2017-2020	All ages	10458	84.4	Seropositivity was 84.6% in the 0-10 age group and 71.6% in the 11-20 age group.
					The efficacy of the hepatitis A vaccine was not directly examined in this study, but it was shown that seropositivity was higher in partially vaccinated individuals aged 0-10 years than in unvaccinated individuals aged 11-20 years.
Yilmaz (12) 2020	Erzurum 2015-2018	All ages	25007	87.3	Seropositivity was 86.4% in the 0-4 age group, 73.2% in the 5-9 age group, 58.7% in the 10-14 age group and 75.2% in the 15-19 age group.
					This study did not directly examine the efficacy of the hepatitis A vaccine. However, it was found that seropositivity was higher in the 0-4 age group, most of whom were born after 2012, than in other childhood age groups.
Çalık et al. (19) 2019	İzmir 2015-2016	All ages	1336	74	Seropositivity was 87.5% in the 0-4 age group, 28% in the 5-9 age group, 20.8% in the 10-14 age group and 28.9% in the 15-19 age group.
					Also, this study did not directly examine the effectiveness of the hepatitis A vaccine. However, seropositivity was higher in the 0-4 age group, most of whom were born during the routine vaccination period, compared to other age groups in childhood.

HAV: Hepatitis A virus, IgG: Immunoglobulin G, OR: Odds ratio, CI: Confidence interval

In our province, the most susceptible group to HAV was found to be 13-18 age group. In addition, although HAV seropositivity is higher in older age groups, seropositivity is lower in the 10-19 age group compared to the 0-9 age group (95.0% vs. 73.1%). Similarly, in a study conducted in Balıkesir between 2017-2019, seropositivity was found to be 63.1% in the 0-10 age group and 38.8% in the 11-17 age group (10). In the study conducted by Atik et al. (10) in Çorum between 2017 and 2020, 84.6% of children aged 0-10 years had immunity against HAV, while this rate decreased to 71.6% between 11-20 years (11). In the studies conducted recently in Erzurum, Yozgat and İzmir, the lowest seropositivity was found in 10-14, 6-9 and 10-14 age groups, respectively (12,18,19). The most likely reason for this situation is the introduction of HAV vaccination into the routine vaccination schedule since 2012 (20). Seropositivity was generally lower in children born before 2012. In a study directly examining the effect of HAV vaccination, Samancı and Akdeniz (21) divided the anti-HAV IgG results of pediatric patients in Diyarbakır into two groups as before and after September 2012. While the anti-HAV IgG positivity rate between 2009-2012 was 41.2%, this rate increased to 81.9% between 2012-2018 ($p<0.001$) (21). In our study, the 95.3% seropositivity rate in the 0-12 age group, which includes children born after the routine vaccination period, can be considered as a success of childhood vaccination. Table 2 presents data from recent studies that evaluated HAV seroprevalence by age group in order to assess the effectiveness of the HAV vaccine. On the other hand, given the observed immunity gap among 10-19 years old, screening programmes should be implemented in high-risk environments such as schools, military bases and refugee camps to prevent potential HAV outbreaks in this age group. Other vulnerable population groups, such as migrants, people with limited access to clean water, and individuals planning to travel to endemic areas, should also be targeted. Especially for people in high-risk groups, catch-up vaccination strategies should be created. In addition, all children born before 2012 who visit a healthcare organisation for any reason should be screened for anti-HAV IgG.

The mean age of seropositive patients was found to be statistically higher than seronegative patients in our study. Similarly, in the study of Çeviker et al. (22), the mean age of seropositive and seronegative patients was found to be 37.5 and 23.0 years, respectively, and a statistically significant difference was found. In our study and in the majority of other studies, it has been shown that immunity against HAV is markedly increased at the age of 20 years and older (9,11,12,14,18). In the study conducted by Koroglu et al. (7) in 2015, the AMPI for HAV was found to be 17 years of age in Türkiye. While seropositivity rates ranged between 28% and 66.3% in different provinces in studies examining the childhood period (17,21,23,24,25,26); this rate was reported between 75% and 97.4% in studies covering only the adult age group (27,28,29,30,31).

In our study, no difference was found between both genders in terms of anti-HAV IgG seropositivity. In the studies of Şimşek Bozok and Bozok (9), Yilmaz (12) and Acikgoz et al. (32), seropositivity was found to be significantly higher in males than females. In contrast, seropositivity was found to be higher in women in the study by Çeviker et al. (22). However, no significant difference was found between genders in terms of anti-HAV IgG positivity in most studies (10,14,24,29,33).

Study Limitations

This study has several limitations. Firstly, it was conducted retrospectively using anti-HAV IgG test results from a single tertiary hospital, so it may not accurately represent the general population of Mardin province, particularly those without access to healthcare facilities. Secondly, important sociodemographic factors such as education level, household income, living conditions and access to clean water were not considered. Thirdly, due to the cross-sectional design of the study, it was not possible to assess causality.

Conclusion

A high community immunity rate against HAV was found in Mardin. In addition, the seropositivity rate of 95.3% in the 0-12 age group who received the HAV vaccine demonstrates the programme's effectiveness. However, special vaccination programmes need to be implemented for the 10-19 age group, particularly the 13-18 age group.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Mardin Artuklu University Non-Interventional Clinical Research Ethics Committee (approval number: 2025/3-8, date: 07.04.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.S.T., D.İ., Design: M.S.T., Data Collection or Processing: M.S.T., D.İ., Analysis or Interpretation: M.S.T., Literature Search: M.S.T., D.İ., Writing: M.S.T., D.İ.

Conflict of Interest: No conflict of interest was declared by the authors.

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