E-ISSN: 2147-2939

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

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August 2026
2
Volume 32

galenos

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

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Yayıncı Sertifika No: 14521
Online Publication Date: September 2026
E-ISSN: 2147-2939
International scientific journal published quarterly.

VIRAL HEPATITIS SOCIETY

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The journal is published online.
Owner: Viral Hepatitis Society
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VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

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DOI: 10.4274/vhd.galenos.2026.2025-10-5
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Innovative Multisectoral Approaches to Overcome Hepatitis B Elimination Barriers in Indonesia: Systematic Literature Review

Endonezya'da Hepatit B Eliminasyonundaki Engelleri Aşmak için Yenilikçi Çok Sektörlü Yaklaşımlar: Sistematik Literatür İncelemesi

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ABSTRACT

This study aims to identify the main challenges and multisectoral strategies in hepatitis B elimination efforts in Indonesia, using a global, evidence-based systematic literature review approach. This study was motivated by the high prevalence of chronic hepatitis B and the slow progress in achieving the World Health Organization elimination target of 2030. The literature search was conducted in the Scopus database using the keywords "hepatitis B elimination", "Indonesia", and "multisectoral challenges", covering publications between 2019 and 2025. The analysis followed the PRISMA 2020 guidelines and comprised four main stages: identification, screening, eligibility assessment, and inclusion. Of the initial 135 articles, 20 studies met the criteria and were thematically analyzed to identify trends, challenges, and elimination strategies. The synthesis identified three main dimensions of barriers: (1) biomedical, including limited detection of latent infection (occult hepatitis B infection) and the presence of covalently closed circular DNA; (2) health-system, including weak surveillance, poor cross-program coordination, and manual reporting; and (3) social, including stigma and low vaccination awareness. On the other hand, innovative strategies such as the implementation of digital surveillance systems, the strengthening of cross-country networks, and the development of national vaccines with high effectiveness show the potential to accelerate elimination. This study emphasizes the need for an integrative, cross-sectoral, and evidence-based approach to achieve hepatitis B elimination in Indonesia. The results make conceptual and practical contributions to strengthening global public health policy, particularly in developing countries.

Keywords: Hepatitis B, elimination, multisectoral approach, policy challenges, systematic literature review, Indonesia

ÖZ

Bu çalışma, küresel, kanıta dayalı sistematik bir literatür taraması yaklaşımı kullanarak, Endonezya'daki hepatit B eliminasyon çabalarındaki temel zorlukları ve çok sektörlü stratejileri belirlemeyi amaçlamaktadır. Bu çalışma, kronik hepatit B'nin yüksek prevalansı ve Dünya Sağlık Örgütü'nün 2030 eliminasyon hedefine ulaşmada yavaş ilerleme nedeniyle motive edilmiştir. Literatür taraması, 2019 ile 2025 yılları arasındaki yayınları kapsayan "hepatit B eliminasyonu", "Endonezya" ve "çok sektörlü zorluklar" anahtar kelimeleri kullanılarak Scopus veri tabanında yapılmıştır. Analiz, PRISMA 2020 kılavuzlarını takip etmiş ve dört ana aşamadan oluşmuştur: tanımlama, tarama, uygunluk değerlendirmesi ve dahil etme. Başlangıçtaki 135 makaleden 20 çalışma kriterleri karşılamış ve eğilimleri, zorlukları ve eliminasyon stratejilerini belirlemek için tematik olarak analiz edilmiştir. Sentez, üç ana engel boyutunu belirlemiştir: (1) biyomedikal, latent enfeksiyonun (gizli hepatit B enfeksiyonu) ve kovalent olarak kapalı dairesel DNA varlığının sınırlı tespiti dahil; (2) zayıf gözetim, programlar arası yetersiz koordinasyon ve manuel raporlama dahil olmak üzere sağlık sistemi; ve (3) damgalanma ve düşük aşılama farkındalığı dahil olmak üzere sosyal faktörler. Öte yandan, dijital gözetim sistemlerinin uygulanması, ülkeler arası ağların güçlendirilmesi ve yüksek etkinliğe sahip ulusal aşıların geliştirilmesi gibi yenilikçi stratejiler, eliminasyonu hızlandırma potansiyeli göstermektedir. Bu çalışma, Endonezya'da hepatit B'nin eliminasyonuna ulaşmak için bütünleyici, sektörler arası ve kanıta dayalı bir yaklaşıma duyulan ihtiyacı vurgulamaktadır. Sonuçlar, özellikle gelişmekte olan ülkelerde küresel halk sağlığı politikasının güçlendirilmesine kavramsal ve pratik katkılar sağlamaktadır.

Anahtar Kelimeler: Hepatit B, eliminasyon, çok sektörlü yaklaşım, politika zorlukları, sistematik literatür incelemesi, Endonezya

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Received: 28.10.2025 **Accepted:** 02.07.2026 **Epub:** 21.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Tamrin N, Awaluddin A, Rizky VA, Kanthi AS, Joni MS. Innovative multisectoral approaches to overcome hepatitis B elimination barriers in Indonesia: systematic literature review. Viral Hepat J. 2026;32(2):31-40

Introduction

Elimination of hepatitis B virus has become a global public health priority of the World Health Organization (WHO), with a target of achieving it by 2030. This effort reflects an international commitment to reduce the number of new infections and mortality from cirrhosis and hepatocellular carcinoma caused by hepatitis B virus. Hepatitis B is a chronic infectious disease with a significant global burden: more than 250 million people worldwide live with chronic infection, and approximately 820,000 deaths are reported annually. In the Indonesian context, hepatitis B is still the leading cause of chronic liver disease and liver cancer, which have a major impact on national productivity and health financing. Elimination efforts at the national level have been integrated into policy through programs such as the elimination of mother-to-child transmission (EMTCT) program and universal basic immunization; however, achievement of WHO targets remains suboptimal. The obstacles do not only stem from biomedical factors, but also from the complexity of social, policy, and governance of health systems that have not been effectively integrated (1,2,3).

In the past two decades, global research has shown that approaches to hepatitis B elimination have evolved from a purely biomedical paradigm to multidimensional approaches that incorporate social, structural, and health- policy aspects. Armini et al. (4) in Indonesia found that the implementation of the EMTCT program in Bali is still faced with social barriers such as stigma, bureaucracy, and poor communication between patients and health workers. Meanwhile, Torimiro et al. (5) through MICHep B Network initiative in sub-Saharan Africa showed that cross-country and cross-sectoral cooperation can increase birth dose vaccination coverage to 87%, confirming that multisectoral collaboration is an effective strategy to accelerate the achievement of elimination (6). From a biomedical perspective, Bucio-Ortiz et al. (7) highlighted the presence of occult hepatitis B infection (OBI) as a latent threat that is difficult to detect, whereas Kaewdech et al. (8) emphasized the disparity in elimination achievements between Asian countries due to differences in political support, health infrastructure, and surveillance systems. Al Awaidy et al. (9) showcases best practices from Gulf Cooperation Council (GCC) countries, which have reduced HBsAg prevalence in children under five years old to below 0.5% thanks to strong surveillance systems and consistent political support. The synthesis of the research shows that the challenge of hepatitis B elimination is cross-dimensional-demanding integration between health policy, laboratory capacity, and social and behavioral approaches (10).

In the biomedical context, the main challenges to hepatitis B elimination are the persistence of latent infection and the limitations in early detection. Zhuang et al. (11) identified that although nucleos(t)ide analog therapy can suppress viral replication, covalently closed circular DNA (cccDNA) persists in hepatocytes, allowing reactivation of infection. This is exacerbated by the limitations of molecular laboratories in developing countries such as Indonesia, which makes diagnosis of OBI difficult (7). From a health system perspective, Armini et al. (12) showed that the integration of the EMTCT program into the health information system is still not optimal, causing inaccurate and unreliable case reporting for national elimination monitoring. Meanwhile, from a social perspective, Machmud et al. (13) found that only 15% of Indonesian adults had received the hepatitis B vaccine, indicating low public awareness and weak health promotion. These factors interact: weak case detection leads to inaccurate data; fragmented health systems impede follow-up; and low public awareness exacerbates horizontal transmission. This research seeks to integrate all these factors into a conceptual framework that explains how interactions across dimensions hinder the achievement of hepatitis B elimination in Indonesia. The importance of a multisectoral approach is also reinforced by lessons learned from other countries. Torimiro et al. (5) demonstrated the effectiveness of cross-sector and cross-country cooperation through the MICHep B Network, which expanded vaccination capacity and improved national policy advocacy. Al Awaidy et al. (9) showed that the success of GCC countries in reducing childhood HBsAg prevalence was not only due to immunization programs, but also due to strong epidemiological surveillance systems and national data integration. On the other hand, a study Taye et al. (14) proved that increasing the coverage of antiviral therapy based on at-risk populations can significantly reduce hepatitis B mortality and complications, but the success of these interventions still depends on community involvement and inclusive public policy support. These three studies demonstrate that innovative approaches based on cross-sector collaboration and socio-cultural adaptation are key to achieving sustainable elimination at both global and national levels.

Thus, this study has three main objectives. First, we systematically analyzed the trends and development of multidimensional approaches to hepatitis B elimination over the past two decades, covering biomedical, health system, and social dimensions [research question (RQ) 1]. Second, the study aimed to identify and synthesize the main challenges faced in the implementation of the hepatitis B elimination policy, especially those related to surveillance, latent infection detection, and cross-sector coordination, and to explain the interrelationships between these factors as described in the conceptual model of previous research (RQ2). Third, to evaluate strategies and innovations proposed in the scientific literature to accelerate the achievement of elimination targets and to assess their effectiveness and limitations based on empirical evidence (RQ3). By answering these three questions, the authors expect that this study will make a theoretical contribution by expanding the conceptual understanding of hepatitis B elimination as a multidimensional issue and will offer practical implications for policymakers and program implementers in Indonesia.

Conceptually, this study attempts to bridge the gap between biomedical and public policy approaches by presenting an integrative, evidence-based model. The originality of this research lies in its attempt to combine social, structural, and biomedical dimensions in the Indonesian context, which has not been done in previous studies. By framing hepatitis B elimination as a cross-sectoral issue that requiring synergy among the government, health workers, the

scientific community, and the community, this research is expected to inspire health policies that are more adaptive, collaborative, and sustainable. Through a global systematic literature review (SLR), this study also seeks to enrich the academic literature on health policy innovation in developing countries and to strengthen Indonesia's position in international scientific discourse on hepatitis elimination.

Materials and Methods

This study employed a SLR with a descriptive-analytic approach to identify, evaluate, and synthesize research findings related to challenges to and strategies for hepatitis B elimination in Indonesia. This approach was chosen because it is able to present a comprehensive overview of research developments across dimensions-biomedical, health systems, and social-in the last two decades as described in previous studies by Armini et al. (4) (Figure 1).

The research was conducted following the PRISMA 2020 guidelines, as shown in the study identification flow diagram. The SLR process consists of four main stages: identification, screening, eligibility, and inclusion. This systematic approach is designed to ensure transparency, replicability, and traceability of the study results, enabling them to serve as a solid conceptual basis for future research (Figure 2).

The identification stage was carried out by searching the Scopus database for scientific articles, because it is a credible index of internationally reputable journals. The search strategy used keywords combined through Boolean operators, namely: "hepatitis B virus in Indonesia", "elimination of hepatitis B virus", and "Indonesia challenges hepatitis B". The keyword search yielded 135 articles, as shown in the PRISMA diagram. The initial data were then filtered by removing duplicates (n=2) and publications that did not meet the analysis year criteria (2020-2025; n=73), leaving 60 relevant articles for the initial selection stage. Of these, 23 articles were excluded because they were not in tier Q1 or Q2 journals, and 6 lacked abstracts for analysis. The restriction to Q1-Q2 journals was applied to ensure methodological rigor, stronger peer-review standards, and higher scientific reliability of the included studies. After the initial screening, 31 articles were included in the subsequent screening stage. An additional identification process was conducted using other sources (n=1) to ensure that no important literature was missed, particularly national policy reports or health institution reports relevant to the Indonesian context.

At the screening stage, an evaluation was conducted to assess the suitability of the study topic and context with respect to the focus of this research, namely, the challenges and strategies for hepatitis B elimination in Indonesia. A total of 31 articles were screened, and none were excluded at this stage, as they all met the topical criteria. However, 12 articles were not fully accessible and were therefore excluded from the final analysis. The final eligibility stage yielded 19 primary articles that met the inclusion criteria and 1 additional article obtained from an external source, for a total of 20 articles analyzed in this review. Inclusion criteria were: (1) articles published in reputable journals Q1-Q2, (2) articles focusing on hepatitis B in the context of Indonesia or countries with similar health system characteristics, (3) articles available in English or Indonesian, and (4) articles including empirical data or conceptual analysis relevant to hepatitis B elimination. The exclusion criteria included articles that did not report original research results (e.g., editorials or commentaries), studies with a focus on non-B hepatitis, and publications that were not available in full text.

The main research instrument used in this SLR was a thematic data-extraction sheet designed to organize information extracted from each selected article. Variables recorded included: author name, year of publication, country or regional context, research design, target population, key outcomes, identified challenges, and proposed strategies and policy recommendations. Data from all articles were categorized into three broad themes corresponding to the RQ1-RQ3: (1) trends and developments in the multidimensional approach to hepatitis B elimination, (2) key challenges and interrelationships among inhibiting factors in policy implementation, and (3) strategies and innovations to accelerate elimination. Each category was

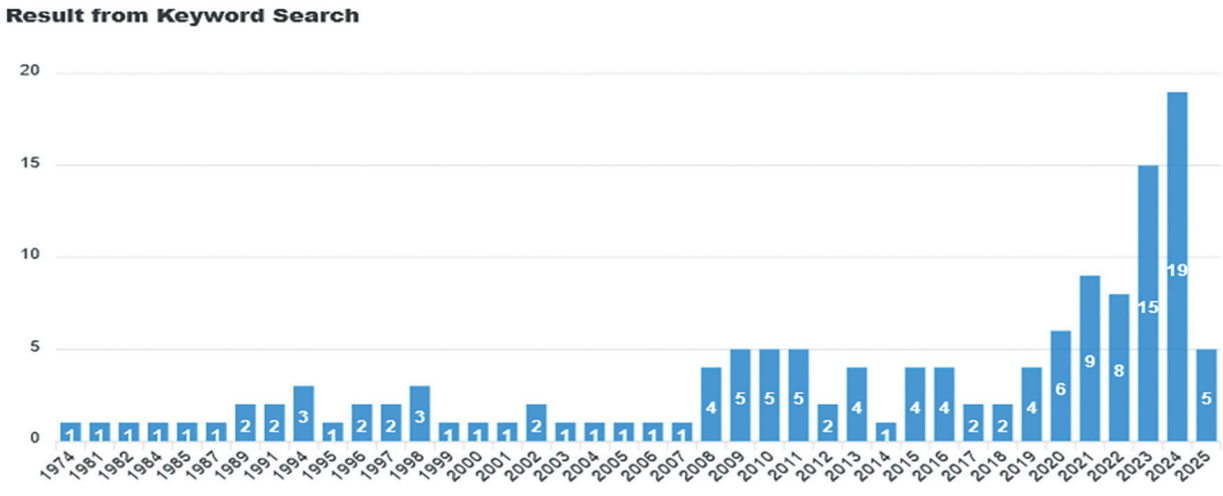

Figure 1. Growth trend of keyword-based publications on hepatitis B research

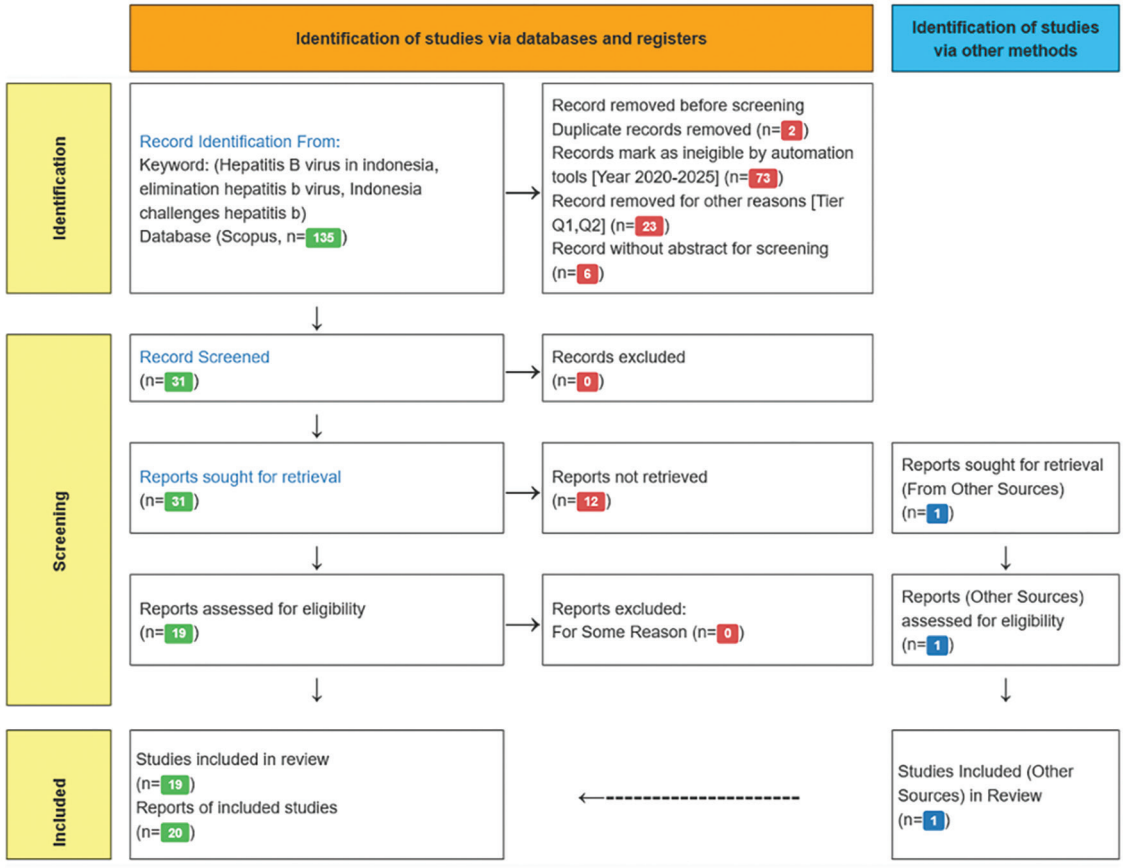

Figure 2. Flowchart depicting article selection for PRISMA

analyzed using narrative synthesis, in which findings from different studies were compared, synthesized, and interpreted to identify patterns and relationships among variables. This analytical approach follows the principle of thematic synthesis, which combines deductive (based on an initial theoretical framework) and inductive (based on new empirical findings) methods, as is done in systematic studies.

Data were collected electronically through online searches, downloading article metadata, and reference tracking to ensure completeness of the literature. Each selected article was evaluated for quality using adaptive criteria that considered journal reputation, methodological transparency, and consistency of results with research objectives. The results of the analysis are then presented as summary tables and graphs to illustrate annual publication trends, as shown in the search-results graph, which indicates a significant increase in the number of publications from 2018 to a peak in 2024. This visualization shows that hepatitis B elimination has become an increasingly important scientific concern at both the global and national levels over the past five years. To maintain the internal validity and reliability, all stages of extraction and analysis were conducted independently by two researchers and cross-verified to minimize interpretation bias. With this design, procedures, and instruments described systematically, this research can be replicated by other researchers in similar contexts or with similar keywords in further studies on hepatitis B elimination policies in Indonesia and other developing countries.

Results

1. General Characteristics of Included Studies

This systematic review included 20 scientific articles that met the inclusion criteria and represented both global and national studies related to hepatitis B elimination. Based on the data extraction results in Table 1 SLR hepatitis B elimination. The publication time span covers 2019-2025, with a significant increase in publications

Table 1. Study characteristics

Study aspect	Total articles	Percentage (%)
Focus biomedis (OBI, cccDNA, therapy)	6	30
Health system focus (surveillance, policy, EMTCT)	7	35
Socio-behavioral focus (stigma, vaccine acceptance)	4	20
Multisectoral integrative approach	3	15
Total	**20**	**100**

OBI: Occult hepatitis B infection, cccDNA: Covalently closed circular DNA, EMTCT: Elimination of mother-to-child transmission

from 2021 to 2024, indicating growing scientific attention to multidimensional hepatitis B elimination. In terms of research regions, 35% of the studies came from Asia, 25% from Africa, 20% from Europe, 10% from the Middle East, and 10% from Australia/Oceania. 40% of the studies were conducted in middle-income countries such as Indonesia, the Philippines, and Ghana, while 60% were conducted in high-income countries such as Japan, South Korea, Italy, and Australia. In terms of methodology, 45% of the studies used descriptive or qualitative approaches, 30% used epidemiological or dynamic modeling, 15% were systematic reviews and meta-analyses, and the rest were experimental clinical trials. The majority of studies (70%) focused on vaccination and surveillance strategies, whereas 30% addressed biomedical and molecular aspects of the detection of latent infection.

The thematic distribution shows that the biomedical, systemic, and social dimensions have begun to connect through integrative studies, although they remain predominantly within the framework of health policy and primary prevention. The rapid increase in publications after 2020 coincides with the WHO's intensified global push to accelerate the elimination of viral hepatitis by 2030, a push that is influencing the direction of academic research and national policies in many countries.

2. Trends in Multidimensional Approach to Hepatitis B Elimination (RQ1)

Longitudinal analysis indicates that research on hepatitis B elimination is shifting from a clinical-biomedical approach towards a multidimensional approach that includes social aspects, health systems, and public governance. Early studies such as Zhuang et al. (11) and de Almeida and de Paula (15) focused on biomedical challenges such as the detection of cccDNA and OBI which are the main barriers to complete elimination. Data show that the prevalence of OBI ranges from 5-15% in the general population and can reach 25% in high-risk groups, such as blood transfusion recipients and immunosuppressed patients. This confirms that biomedical elimination cannot be fully achieved without improved molecular diagnostic capacity.

Subsequently, the research trend shifted to health system and public policy aspects, as seen in studies by Kaewdech et al. (8) highlighted the elimination gap between developed and developing countries, with birth dose vaccination coverage above 95% in Japan and South Korea compared to only 78% in Indonesia. Al Awaidy et al. (9) showed that GCC countries managed to reduce the prevalence of HBsAg in children under five years old to <0.5%, thanks to integrated national surveillance and strong political policies. Torimiro et al. (5) documented an increase in birth-dose vaccination coverage in Sub-Saharan Africa to 87% following the implementation of the cross-country MICHep B Network.

National studies in Indonesia such as Armini et al. (4) show that the implementation of the EMTCT program is still faced with bureaucratic barriers, lack of communication, and social stigma. Based on field data from Bali, only 68% of pregnant women underwent HBsAg testing, and 55% of babies born to HBsAg-positive mothers received timely birth-dose immunization. These results show that research on hepatitis B elimination has evolved towards a multidimensional and multisectoral approach, highlighting not only medical interventions but also social and institutional dimensions (16).

3. Key Challenges and Interrelationships Between Constraining Factors (RQ2)

The literature synthesis revealed three broad categories of challenges in hepatitis B elimination efforts: biomedical challenges, health system challenges, and socio-policy challenges. Biomedical challenges mainly relate to the presence of cccDNA and latent OBI infection, make complete cure difficult to achieve. Bucio-Ortiz et al. (7) showed that the limited detection of hepatitis B virus DNA results in many cases not being identified, especially in developing countries that do not have molecular facilities. de Almeida and de Paula (15) confirmed that OBI can cause transmission through transfusion and organ transplantation despite negative serology results. Epidemiologically, this biases national disease burden estimates because latent cases are not recorded in surveillance systems.

In terms of the health system, research Armini et al. (12) show that manual and unsynchronized reporting between agencies makes national hepatitis B data difficult to verify (17). Only a small number of provinces have implemented integrated digital reporting. Kaewdech et al. (8) reinforced these findings by identifying infrastructure and human resource gaps as barriers to achieving elimination in middle Asian countries. On the social side, Machmud et al. (13) found that only 15% of Indonesian adults had received hepatitis B vaccine, with the main barriers being cost and low risk perception. Armini et al. (12) added that stigma towards hepatitis B patients inhibits participation in screening and follow-up.

Examination of the interconnectedness of various factors revealed synergistic relationships among these dimensions. For example, poor detection of OBI (biomedical) contributes to inaccurate surveillance data (health system), while poor communication between health workers and patients reduces vaccine acceptance (social). The following Table 2 summarizes the interconnectedness of challenges across dimensions, based on a synthesis of 20 studies:

These complex linkages show that the elimination of hepatitis B cannot be achieved through a single approach but rather requires strong cross-sectoral integration.

4. Identified Strategies and Innovations (RQ3)

The literature review revealed various strategies and innovations proposed to accelerate hepatitis B elimination across the biomedical, health-system, and cross-sector collaboration dimensions.

In the biomedical dimension, research Zhuang et al. (11) identified the development of therapies based on RNA interference, *CRISPR-Cas9* gene editing, and the small molecule CCC_R08 to target cccDNA. Although still in the experimental stage, these innovations suggest a new direction in chronic hepatitis B therapy. In terms of prevention, research de Villiers et al. (18) estimates that increasing

Table 2. Multidimensional challenges in hepatitis B elimination

Dimension	Example challenges	Impact on elimination
Biomedical	Limited detection of OBI and cccDNA	Prevalence data is inaccurate
Health system	Manual reporting, weak coordination	Non-evidence-based policy
Social-policy	Stigma, low vaccine awareness	Low vaccination coverage
Cross-sector integration	Fragmentation between EMTCT programs	Failure of national coordination

OBI: Occult hepatitis B infection, cccDNA: Covalently closed circular DNA, EMTCT: Elimination of mother-to-child transmission

Table 3. Key strategic innovations and outcome indicators for hepatitis B elimination

Strategy area	Key innovations	Outcome/effectiveness indicator
Primary prevention	Birth dose vaccination, national vaccine	↑ Coverage 90%, ↓ Vertical transmission
Early detection	NAT and HBV-DNA detection	↑ Validity of prevalence data
Therapy	*CRISPR-Cas9*, RNAi	Functional healing potential
Surveillance system	National database, integration EMTCT	↑ Reporting accuracy, ↓ Duplication
Multisectoral collaboration	MICHep B network, regional cooperation	↑ Policy advocacy, ↑ Vaccine coverage

EMTCT: Elimination of mother-to-child transmission, NAT: Nucleic acid testing, HBV: Hepatitis B virus

birth dose vaccine coverage to 90% could prevent more than 500,000 deaths from hepatitis B complications by 2030. Meanwhile, research Lestari et al. (19) showed that infants who received the birth dose vaccine within the first 24 hours had a 40% higher antibody protection rate than infants who received the dose after 24 hours. Nency et al. (20) reported that Bio Farma's national hepatitis B vaccine has 98.7% immunogenicity and safety equivalent to international vaccines, signaling national independence in vaccine supply.

In terms of health systems and policies, Torimiro et al. (5) through the MICHep B Network demonstrated that cross-country and cross-sector collaboration can significantly improve vaccination coverage and national policy advocacy capacity. Al Awaidy et al. (9) documented the success of the GCC surveillance system with an integrated national database that allows verification of case data of HBsAg positive pregnant women in real time. Kaewdech et al. (8) recommended the public health continuum of care model to link prevention, diagnosis and treatment as a continuous system.

The synthesis also showed that there are innovative community-based strategies, such as involving local communities in vaccination campaigns and family-based education to prevent stigma (4,5). Taye et al. (14) added that population-based antiviral therapy interventions can reduce hepatitis B mortality by 35% if therapy coverage reaches 80% of the target population. The following Table 3 summarizes the key strategies identified:

5. Overview of Quantitative Synthesis

Based on the aggregate analysis of the 20 identified studies, the following key numerical patterns can be inferred:

- Average global birth dose vaccination coverage: 84%.

- Average HBsAg prevalence of children <5 years in developed countries: 0.5%.

- Average HBsAg prevalence of children <5 years old in developing countries: 1.9%.

- Indonesia's average vaccination rate (2019-2024): 68%.

- Average HBsAg detection in pregnant women (Indonesian data) was 72%.

- Global antiviral therapy coverage is average, with 4[5]% of the population chronically diagnosed.

- Estimated potential prevention of deaths due to increased vaccination: >500,000 lives (18).

The PRISMA flow diagram shows that, of the initial 135 articles, only 20 met the final inclusion criteria, demonstrating the high selectivity and relevance of this study. Yearly publication trends showed the sharpest increase from 2021 to 2024, consistent with growing scientific urgency toward global viral hepatitis elimination.

Overall, the results show that global and national hepatitis B elimination efforts continue to make progress, but face complex structural, social, and biomedical challenges. A multidimensional approach that integrates vaccine innovation, latent-infection detection, surveillance-system strengthening, and cross-sector collaboration is a dominant theme in the reviewed literature. This synthesis illustrates that hepatitis B elimination in Indonesia is inseparable from global dynamics and requires a national collaboration model that is data-driven, intersectoral, and sustainable.

Discussion

Trends and Developments in Multidimensional Approaches to Hepatitis B Elimination Efforts

Based on the synthesis of 20 articles included in this systematic review, it can be concluded that hepatitis B elimination efforts at the global and national levels have undergone a paradigm shift from a narrow biomedical approach to a multidimensional approach that

emphasizes the interconnection between biomedical, health system, and socio-cultural aspects. This shift is in line with the findings shown by Kaewdech al. (8) and Torimiro et al. (5) who emphasized that the success of hepatitis B elimination is not only determined by the effectiveness of vaccines or antiviral therapy, but also by health system capacity, policy sustainability, and community social participation. In the last two decades, this trend has intensified along with the WHO push towards viral hepatitis elimination targets by 2030, which requires each country to integrate elimination strategies into the national health system In the Indonesian context, research results Armini et al. (4) show that the multidimensional approach is still at an early stage of implementation. The study shows that the implementation of the hepatitis B EMTCT program still faces social and administrative barriers, such as stigma toward pregnant women who are HBsAg positive and limited communication between health workers and patients. These elements illustrate the social aspects that are often overlooked in the biomedical policy framework. On the other hand, a study Armini et al. (12) reinforced these findings by showing a gap in coordination between programs at the regional level. Non-integrated surveillance data and manual reporting are important barriers to national elimination monitoring. These results suggest that although vaccination programs and elimination policies are in place, implementation remains fragmented across sectors; therefore, a multidimensional approach has not been fully realized in Indonesia.

Comparisons with other countries show that successful elimination is strongly influenced by cross-sectoral integration and political commitment. A study Torimiro et al. (5) in sub-Saharan Africa showed that inter-country and inter-agency collaboration within the MICHep B Network increased birth dose vaccination coverage to 87%, while in GCC countries, strong surveillance systems and political support resulted in a decrease in the prevalence of HBsAg in children under five years old to below 0.5% (9). This suggests that structural and governance elements have the same significance as medical advances in influencing the efficacy of elimination efforts.

The findings of this study confirm that a multidimensional approach to hepatitis B elimination is necessary for Indonesia to adopt. Expanding vaccination is not sufficient; strengthening digital surveillance systems, improving public health communication, and fostering cooperation across ministries and agencies are also required. This approach not only expands the scope of intervention but also connects the micro (biological) and macro (policy) dimensions. The scientific significance of this finding is its contribution to expanding the conceptual framework of hepatitis B elimination from the biomedical domain to a multidimensional model that includes social, structural, and health-political interactions (8).

Key Challenges in Hepatitis B Elimination Policy Implementation and Interrelationships Between Factors

The synthesis shows that the challenges to hepatitis B elimination in Indonesia and other developing countries are complex and interrelated. Based on the study results Bucio-Ortiz et al. (7), the main biomedical challenge comes from the presence of OBI and cccDNA which makes latent infection difficult to detect and cure. Epidemiologically, the prevalence of OBI reaches 5-15% in the general population and up to 25% in high-risk groups. The presence of latent infection not only poses clinical problems but also impacts the accuracy of national surveillance data, as many cases are not recorded in the conventional HBsAg serology-based reporting system.

This limitation in latent infection detection is closely related to health-system challenges. Research by Armini et al. (12) found that EMTCT data reporting is still done manually, which causes delays and inaccuracies in information. This hinders the government's ability to validate national-level elimination achievements. Similar challenges were also identified by Kaewdech al. (8) which showed that in the Southeast Asian region, many countries including Indonesia still lack reference laboratories capable of conducting molecular tests for hepatitis B virus DNA. These limitations prevent effective monitoring of chronic and latent cases. Thus, biomedical weaknesses (latent detection) interact directly with structural weaknesses (surveillance and reporting), forming a cycle of barriers that is difficult to break.

Social and policy factors exacerbate the challenge. Research Machmud et al. (13) showed that only 15% of the Indonesian adult population had received the hepatitis B vaccine, with the main reasons being low-risk perception and the high cost of vaccination. On the other hand, Armini et al. (4) added that stigma against hepatitis B patients is still strong, especially among pregnant women, which has an impact on low participation in screening. In the socio-ecological framework, as used by Armini et al. (4), individual factors such as perceptions and family support interact with structural factors such as health policies and service infrastructure, resulting in a cumulative effect on the effectiveness of elimination programs.

This multidimensional challenge has major implications for national elimination strategies. First, without effective early detection, vaccination and therapeutic efforts cannot be properly targeted. Second, in the absence of a cohesive surveillance framework, it is impossible to formulate national policies based on reliable data. Third, without community engagement and stigma mitigation, medical interventions are likely to be ineffective due to resistance to behavior change. Consequently, these observations illustrate the complex interconnections between biomedical, health system, and social factors that present significant challenges to Indonesia's hepatitis B eradication efforts.

This study's contribution is mapping the causal relationships among the three dimensions within the context of elimination policy. Previous research by Bucio-Ortiz et al. (7) only highlighted the biomedical aspect, while Kaewdech et al. (8) focused on regional disparities, and Machmud et al. (13) focused on community behavior. This research brings them together into an integrative and contextualized analytical framework for Indonesia. Its significance lies in providing an empirical basis for designing a holistic elimination policy that integrates technical, institutional and social strategies.

Strategies and Innovations to Accelerate Achievement of Hepatitis B Elimination Targets

Strategies and innovations to accelerate hepatitis B elimination can be classified into three main dimensions: biomedical innovations, health system reforms, and socio-multisectoral approaches. In the biomedical dimension, research Zhuang et al. (11) highlights scientific advances in the form of *CRISPR-Cas9-based* gene editing therapy, RNA interference, and the small molecule CCC_R08 targeting cccDNA. Although it has not yet reached the clinical stage in humans, this research suggests a new direction toward a functional cure for chronic hepatitis B. Meanwhile, Nency et al. (20) showed that Indonesia has the capacity to produce its own hepatitis B vaccine with effectiveness and safety equivalent to international vaccines. This is a strategic innovation to strengthen national independence in vaccine supply and ensure the sustainability of the immunization program.

In terms of prevention, studies Lestari et al. (19) showed that timely vaccination of the birth dose has the greatest preventive impact. According to (19), infants who received the vaccine within the first 24 hours had a 40% lower risk of infection than infants who received the vaccine after 24 hours. It was estimated that increasing birth-dose vaccine coverage to ^{9}0% could prevent more than 500,000 deaths from hepatitis B by 2030 (18). In Indonesia, birth-dose vaccination coverage has reached only 68%, indicating considerable room for improvement.

In the health system dimension, research Al Awaidy et al. (9) showed that integrated national surveillance systems and databases of pregnant women are key factors for successful elimination in GCC countries. Torimiro et al. (5) reinforced these findings with evidence that cross-sector and cross-country networks such as the MICHep B Network are able to increase vaccination coverage and strengthen policy advocacy. Both studies demonstrate the importance of collaborative and data-driven health governance in accelerating hepatitis B elimination.

In terms of social and policy, emphasized the importance of community-based interventions to reduce stigma and increase vaccination awareness (4,13). Armini et al. (12) showed that family involvement and support from social institutions played an important role in the success of the EMTCT program in Bali. These findings suggest that innovative community-based strategies are as important as medical interventions.

The significance of these results lies in understanding that no single strategy is sufficient to achieve hepatitis B elimination. Successful elimination requires a multi-layered approach: strengthened primary vaccination, improved detection of latent infection, expanded antiviral therapy, and an integrated national surveillance system. This study makes a conceptual contribution by developing an integrative model that explains the synergistic relationship between these strategies in the Indonesian context. It expands scientific understanding of how medical, systemic, and social innovations can interact to accelerate hepatitis B elimination in developing countries.

Scientific Significance and Contribution to Scientific Fields

Conceptually, this study contributes to expanding the hepatitis B elimination paradigm from a biomedical approach to a multidimensional and multisectoral one. The findings of this study reinforce the view that successful elimination cannot be measured only through medical indicators such as vaccination coverage or the number of patients treated, but also through social indicators such as the level of public awareness, data system integration, and cross-agency participation. By integrating the findings of Bucio-Ortiz et al. (7), Kaewdech et al. (8) and Torimiro et al. (5) this study forms a scientific framework that explains that hepatitis B elimination is the result of synergies between technological innovation, institutional reform, and social adaptation (4).

The empirical contribution of this study lies in the synthesis of cross-study findings relevant to the Indonesian context, providing a scientific basis for the formulation of a more comprehensive national elimination policy. In addition, the practical contribution is to provide evidence-based recommendations to strengthen surveillance systems, improve diagnostic capacity, and expand community-based interventions. This study enriches the scientific literature in global public health, chronic infection epidemiology, and health policy in developing countries.

Policy and Practical Implications

The findings of this study have several important policy implications. First, strengthening the integrated surveillance system is a key prerequisite for hepatitis B elimination. The Indonesian Ministry of Health needs to integrate EMTCT reporting into a national digital information system to avoid data redundancy. Second, the involvement of non-health sectors, such as education and media, needs to be expanded in hepatitis B awareness campaigns to reduce social stigma as identified by Armini et al. (4). Third, strengthening molecular diagnostic capacity is needed to detect OBI and ensure accurate prevalence data, as recommended by Bucio-Ortiz et al. (7). Fourth, domestic vaccine production needs to be expanded and subsidized to ensure the sustainability of the birth dose immunization program, as supported by the findings of Nency et al. (20).

Another scientific implication is the need for an interdisciplinary research approach that involves biomedical, public health, and social sciences to understand the complexities of hepatitis B elimination in Indonesia.

Study Limitations

This study has several limitations that need to be recognized. This analysis includes only Scopus-indexed articles from 2019-2025 that meet the Q1-Q2 journal criteria; consequently, some relevant literature may be excluded. Secondly, most of the data were derived from secondary reports and systematic reviews that do not always exhibit methodological uniformity. Third, this study did not conduct a quantitative meta-analysis because of heterogeneity in research results and variation in indicators across studies. Fourth, limited access to primary data in Indonesia implies that some conclusions

remain are conceptual and cannot be statistically verified. However, these limitations do not diminish the validity of the findings, as this analysis remains grounded in scientific evidence from credible and relevant literature (Figure 3).

The results of this study confirm that hepatitis B elimination in Indonesia is a multidimensional challenge requiring an integrative, multisectoral approach. This study makes a significant contribution to identifying the linkages among biomedical, health system, and social dimensions and offers a conceptual framework to understand the complex interactions among these factors. By emphasizing vaccination innovation, detection of latent infection, integrated surveillance systems, and strengthened social collaboration, this study contributes to the development of a contextualized and sustainable hepatitis B elimination policy model for Indonesia.

Conclusion

This review demonstrates that hepatitis B elimination in Indonesia remains constrained by interconnected biomedical, health system, and socio-behavioral barriers. Strengthening surveillance systems, expanding birth-dose vaccination, improving molecular diagnostic capacity, and enhancing multisectoral collaboration are essential to accelerate elimination efforts. These findings provide an evidence-based framework to guide the development of future hepatitis B elimination policies in Indonesia.

Suggestions for Future Research

Further empirical studies using primary data are recommended to test the conceptual model generated in this study. An important focus is the direct measurement of the effectiveness of multisectoral strategies, including inter-ministerial collaboration, the role of local communities, and the impact of surveillance digitization policies. Longitudinal studies assessing the relationship between increased molecular laboratory capacity and reduced prevalence of chronic hepatitis B in Indonesia are also needed. In addition, future studies should integrate a mixed-methods approach to better capture social dynamics and community behavior. Researchers also need to evaluate the economic efficiency of national vaccine innovations and community-based EMTCT programs. Thus, future research will not only strengthen the scientific basis for hepatitis B elimination policies but will also directly contribute to achieving the global target of viral hepatitis elimination by 2030 in the Indonesian context.

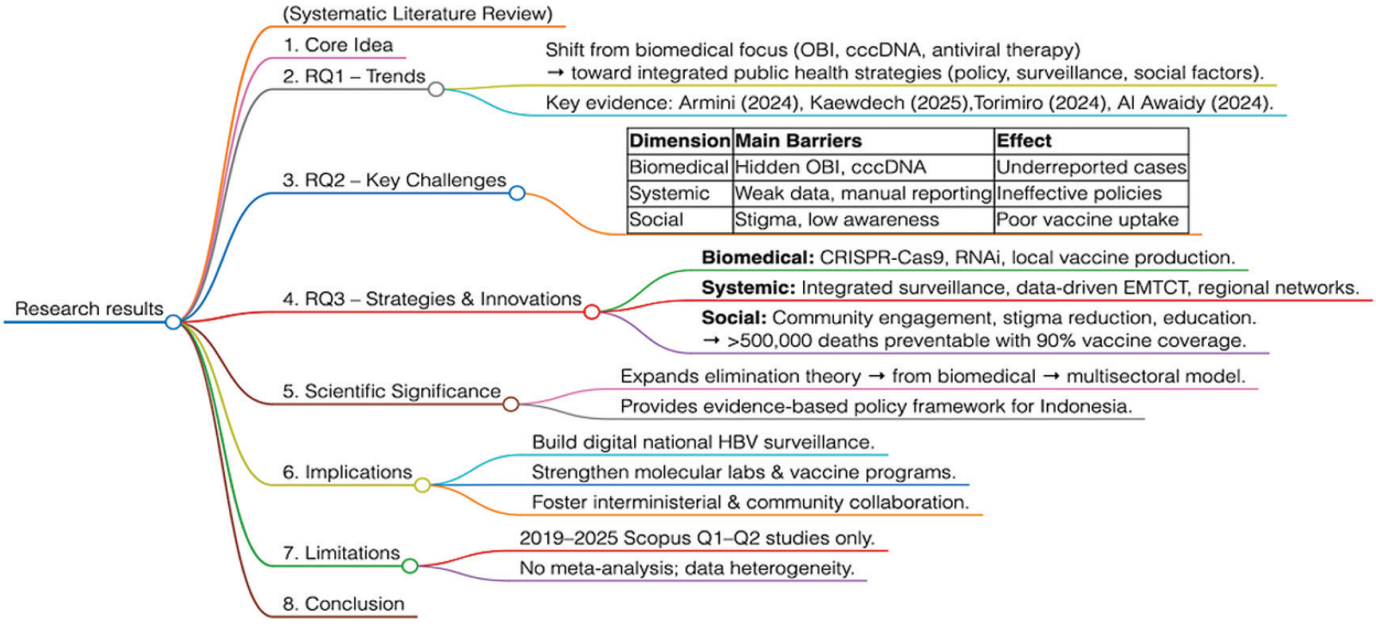

Figure 3. Mind map of research outcomes: trends, barriers, and policy implications for HBV elimination

OBI: Occult hepatitis B infection, cccDNA: Covalently closed circular DNA, HBV: Hepatitis B virus, EMTCT: Elimination of mother-to-child transmission

Footnotes

Authorship Contributions

Concept: N.T., A.A., Design: N.T., A.S.K., Data Collection or Processing: N.T., V.A.R., Analysis or Interpretation: N.T., M.S.J., Literature Search: N.T., A.A., M.S.J., Writing: N.T., V.A.R.

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

Financial Disclosure: The authors declare no financial support.

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DOI: 10.4274/vhd.galenos.2026.2026-1-3
Viral Hepat J 2026;32(2):41-45

Seroprevalence of Hepatitis A Virus, Hepatitis B Virus, and Hepatitis C Virus Among Human Immunodeficiency Virus-Infected Patients: A Single-Center Retrospective Cross-Sectional Study

İnsan İmmün Yetmezlik Virüsü (HIV) ile Enfekte Hastalarda Hepatit A Virüsü, Hepatit B Virüsü ve Hepatit C Virüsünün Seroprevalansı: Tek Merkezli Retrospektif Kesitsel Çalışma

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ABSTRACT

Objectives: Human immunodeficiency virus (HIV) may adversely affect the course of viral hepatitis infections that share similar routes of transmission. This study aimed to evaluate the seroprevalence of hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) among individuals infected with HIV.

Materials and Methods: This retrospective study included HIV-infected patients aged ≥18 years who were followed at the outpatient clinic between October 1, 2020, and September 1, 2024. Demographic characteristics and viral hepatitis serological markers [anti-HAV immunoglobulin G (IgG), hepatitis B surface antigen (HBsAg), anti-HBs, total anti-HBc, anti-HCV] were recorded for these patients.

Results: A total of 210 HIV-infected patients were included in the study; 86.7% were male, and the median age was 35 (18-73) years. HBV and HCV serological data were available for 196 patients. Positivity rates for anti-HBs, total anti-HBc, HBsAg, and anti-HCV were 51%, 18.4%, 2.6%, and 0.5%, respectively. Concomitant positivity for anti-HBs and total anti-HBc was observed in 15.3% of patients, whereas isolated total anti-HBc positivity was detected in only one patient (0.5%). Among 152 patients with available anti-HAV IgG data, 68.4% were seropositive. Anti-HAV IgG negativity was significantly associated with younger age, higher educational level, and men who have sex with men status ($p<0.05$).

Conclusion: This study indicates that HBV and HCV coinfections occur at a low frequency among individuals living with HIV, whereas susceptibility to HAV and HBV remains an important clinical concern. It also emphasizes the necessity of routine serological screening and vaccination against viral hepatitis during HIV follow-up.

Keywords: Hepatitis A virus, hepatitis B virus, hepatitis C virus, human immunodeficiency virus, seroprevalence

ÖZ

Amaç: İnsan immün yetmezlik virüsü (HIV), benzer bulaş yollarını paylaşan viral hepatit enfeksiyonlarının seyrini olumsuz yönde etkileyebilmektedir. Bu çalışmanın amacı, HIV ile enfekte bireylerde hepatit A virüsü (HAV), hepatit B virüsü (HBV) ve hepatit C virüsü (HCV) seroprevalansını değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya, 1 Ekim 2020 ile 1 Eylül 2024 tarihleri arasında poliklinikte takipli, ≥18 yaşındaki HIV ile enfekte hastalar dahil edildi. Hastalara ait demografik özellikler ve viral hepatit serolojik belirteçleri [anti-HAV immünoglobulin G (IgG), hepatit B yüzey antijeni (HBsAg), anti-HBs, total anti-HBc, anti-HCV] kaydedildi.

Bulgular: Çalışmaya toplam 210 HIV ile enfekte hasta dahil edildi; hastaların %86,7'si erkekti ve medyan yaş 35 (18-73) yıl olarak saptandı. HBV ve HCV serolojik verileri 196 hasta için mevcuttu. Anti-HBs, total anti-HBc, HBsAg ve anti-HCV pozitiflik oranları sırasıyla %51, %18,4, %2,6 ve %0,5 olarak bulundu. Hastaların %15,3'ünde eş zamanlı anti-HBs ve total anti-HBc pozitifliği saptanırken, izole total anti-HBc pozitifliği yalnızca bir hastada (%0,5) tespit edildi. Anti-HAV IgG verisi bulunan 152 hastanın %68,4'ü seropozitifti. Anti-HAV IgG negatifliği; genç yaş, yüksek eğitim düzeyi ve erkeklerle seks yapan erkek olma durumu ile anlamlı şekilde ilişkili bulundu ($p<0,05$).

Sonuç: Bu çalışma HIV ile yaşayan bireylerde HBV ve HCV koenfeksiyonlarının düşük sıklıkta olduğunu, buna karşın HAV ve HBV'ye duyarlılığın önemli bir klinik sorun olmaya devam ettiğini göstermektedir. Ayrıca HIV izleminde viral hepatitler açısından rutin serolojik tarama ve aşılama uygulamalarının gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Hepatit A virüsü, hepatit B virüsü, hepatit C virüsü, insan immün yetmezlik virüsü, seroprevalans

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Received: 12.01.2026 **Accepted:** 20.05.2026 **Epub:** 09.06.2026 **Publication Date:** 01.09.2026

Cite this article as: Tayşi MR, Gezer Y. Seroprevalence of hepatitis A virus, hepatitis B virus, and hepatitis C virus among human immunodeficiency virus-infected patients: a single-center retrospective cross-sectional study. Viral Hepat J. 2026;32(2):41-45

Introduction

The life expectancy and quality of life of individuals living with human immunodeficiency virus (HIV) have significantly improved with highly active antiretroviral therapy (ART) (1,2). However, due to similar routes of transmission, these individuals remain at risk for viral hepatitis infections (3,4). HIV's immunosuppressive effects, particularly in the presence of hepatitis B virus (HBV) or hepatitis C virus (HCV), may alter the disease course by increasing viral replication, leading to chronicity and reduced response to treatment. For these reasons, patients with such coinfections have higher rates of liver-related complications and mortality compared with those with HIV mono-infection (5,6). In coinfection with hepatitis A virus (HAV) and HIV, overall mortality is low. However, HIV infection may result in a longer duration of HAV viremia and more severe clinical manifestations (7). Considering these risks, screening HIV-positive individuals for hepatitis markers is of vital importance for appropriate clinical management, early intervention, and the determination of vaccination strategies. This study aims to evaluate the seroprevalence of HAV, HBV, and HCV among individuals infected with HIV.

Materials and Methods

This retrospective cross-sectional study included HIV-infected patients aged 18 years and older who were followed in the Infectious Diseases and Clinical Microbiology outpatient clinic at Konya City Hospital between 01.10.2020 and 01.09.2024. Demographic data (age, sex, and education level) and viral hepatitis serological markers [immunoglobulin G to HAV (anti-HAV IgG); hepatitis B surface antigen (HBsAg); antibody to hepatitis B surface antigen (anti-HBs); total antibody to hepatitis B core antigen (total anti-HBc); antibody to HCV (anti-HCV)] were recorded. HCV-RNA and HBV-DNA levels were recorded for patients positive for HBsAg, anti-HCV, or both.

The serological markers were analyzed by enzyme immunoassay. HBV-DNA and HCV-RNA levels were determined using the AltoStar reverse transcription-polymerase chain reaction kit (detection ranges: 20 IU/mL-10^7 IU/mL for HBV and 25 IU/mL-10^7 IU/mL for HCV). HIV infection was defined as the presence of reactive antigens and/or antibodies to HIV 1/2, confirmed by a rapid confirmatory test performed at a central public health laboratory (Geenius HIV-1/2 Supplemental Assay, Bio-Rad Laboratories, Redmond, WA, USA).

This study received approval from the Konya City Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2025/242, dated: 08.12.2025) and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median [minimum-maximum and interquartile range (25^{th}-75^{th} percentile)]. Non-parametric methods were used because the continuous variables did not follow a normal distribution according to the Shapiro-Wilk test. Categorical variables were reported as frequencies and percentages. For comparisons between groups, the Mann-Whitney U test was used for non-normally distributed continuous variables, and the chi-square test was applied for categorical variables. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Chicago, IL, USA). A p-value <0.05 was considered statistically significant.

Results

During the specified years, 210 HIV-infected patients were followed up at our outpatient clinic. Of these, 182 (86.7%) were male, and the median age was 35 years (range, 18-73). Serological data for HBsAg, anti-HBs, total anti-HBc, and anti-HCV were available for 196 patients. Among these patients, anti-HBs, total anti-HBc, HBsAg, and anti-HCV were positive in 100 (51%), 36 (18.4%), 5 (2.6%), and 1 (0.5%) patients, respectively (Table 1). Both anti-HBs and total anti-HBc were positive in 30 patients (15.3%), whereas anti-HBs was positive and total anti-HBc was negative in 70 patients (35.7%). Isolated total anti-HBc positivity was present in one patient (0.5%). HBV-DNA levels were requested in all HBsAg-positive patients while on ART. HBV-DNA levels were below the detection limit in four of these patients, while one patient had a level of 164 IU/mL. The baseline HCV-RNA level of the patient with a positive anti-HCV test was 6,394,236 IU/mL.

Anti-HAV IgG serological data were available for 152 patients, and 104 of them (68.4%) were seropositive (Table 1). None of these patients had a history of vaccination against HAV. Anti-HAV negativity was significantly more common among younger patients

Table 1. Demographic characteristics of patients infected with human immunodeficiency virus and serological findings for hepatitis A, hepatitis B, and hepatitis C viruses

Variables	
Age (year)	
Mean ± SD	36.9±11.7
Median (min-max)	35 (18-73)
Male n (%)	182 (86.7)
Educational status n (%)	
Primary school	23 (28.7)
Secondary (middle) school	16 (20)
High school	21 (26.3)
University	20 (25)
MSM n (%)	32 (22.5)
Serological tests n (%)	
HBsAg (+)	5 (2.6)
Anti-HBs (+)	100 (51)
Total anti-HBc (+)	36 (18.4)
Anti-HCV (+)	1 (0.5)
Anti-HAV IgG (+)	104 (68.4)

Educational status information was available for 80 patients, MSM information for 142 patients, anti-HBs, total anti-HBc, HBsAg and anti-HCV test data for 196 patients, and anti-HAV IgG test data for 152 patients. Anti-HAV: Anti-hepatitis A virus, IgG: Immunoglobulin G, Anti-HBs: Antibody to hepatitis B surface antigen, Total anti-HBc: Total antibody to hepatitis B core antigen, Anti-HCV: Antibody to hepatitis C virus, HBsAg: Hepatitis B surface antigen, MSM: Men who have sex with men, SD: Standard deviation

(p<0.001), men who have sex with men (MSM) (p<0.001), and those with higher levels of education (p=0.002) (Table 2).

Discussion

This single-center study evaluated the seroprevalence of HAV, HBV, and HCV among HIV-infected patients followed in Türkiye. HBsAg and anti-HCV seroprevalence rates were 2.6% and 0.5%, respectively; these rates are known to vary considerably by geographic region, population characteristics, and predominant risk factors. Globally, approximately 8% of individuals living with HIV are reported to be coinfected with HBV (8,9,10). Studies from Türkiye have shown that the seroprevalence of HBsAg ranges between 3% and 7% (11,12,13). Regarding HCV, a global meta-analysis and systematic review reported an HCV coinfection prevalence of 6.2% among individuals living with HIV (14). In a multicenter study based in Istanbul, anti-HCV positivity was found to be 0.9% among HIV-infected individuals (15). Another nationwide multicenter study from Türkiye reported this rate as 0.5% (16). The HBV, HCV seroprevalence rates observed in our study are consistent with the prevalence of chronic viral hepatitis reported among HIV-infected individuals in Türkiye. The particularly low rates of HBV and HCV coinfections, compared with global data, are consistent with the fact that HIV transmission in Türkiye occurs predominantly through sexual contact and that intravenous drug use is relatively less common. In contrast, in countries where a higher seroprevalence of chronic viral hepatitis among HIV-infected individuals has been reported, this situation is generally attributed to the higher prevalence of injection drug use (10,11,12,13,14).

In our study, anti-HAV IgG positivity was 68.4% and anti-HBs positivity was 51%, indicating that approximately one-third of HIV-infected individuals were susceptible to HAV infection and approximately one-half were susceptible to HBV infection. These findings demonstrate that immunity against vaccine-preventable viral hepatitis is not sufficient among individuals living with HIV. It has been reported that HIV infection prolongs the duration of viremia associated with HAV and increases viremia levels, leading to more severe HAV-related liver abnormalities. In addition, HIV infection is associated with higher viremia levels for HBV, HBV reactivation, an increased likelihood of progression to chronic infection after acute infection, and an increased risk of cirrhosis and liver-related mortality (17,18,19). In line with these potential clinical outcomes, the Advisory Committee on Immunization Practices recommends evaluation of HAV and HBV serologies in all individuals living with HIV and routine vaccination of those found to be seronegative (20). These vaccination recommendations are also included in the guidelines of the Turkish Ministry of Health (21).

Table 2. Demographic characteristics of HIV-infected patients according to anti-HAV IgG serostatus

Variables	Anti-HAV IgG (-) (n=48)	Anti-HAV IgG (+) (n=104)	p
Male n (%)	46 (95.8)	90 (86.5)	0.083
Age (year) (mean ± SD)	27.4±5.3	40.3±11.5	**<0.001**
MSM n (%)	24/48 (50)	8/96 (8.5)	**<0.001**
Educational status n (%)			**0.002**
Primary school	2 (9.5)	16 (32)	
Secondary (middle) school	1 (4.8)	15 (30)	
High school	7 (33.3)	11 (22)	
University	11 (52.4)	8 (16)	

Anti-HAV: Anti-hepatitis A virus, IgG: Immunoglobulin G, HIV: Human immunodeficiency virus, MSM: Men who have sex with men, SD: Standard deviation

It is known that higher educational level reduces natural exposure to HAV during childhood due to improved hygiene conditions (22,23). In addition, studies have shown that childhood HAV exposure is lower in MSM populations; however, HAV transmission through sexual contact becomes more prominent in adulthood, and this group carries a higher risk for outbreaks (24,25). In our study, consistent with these findings, HAV susceptibility was significantly higher among younger individuals, individuals with higher education levels, and MSM. These data highlight the importance of evaluating anti-HAV IgG in these risk groups among HIV-infected individuals.

In our study, concomitant positivity for anti-HBs and total anti-HBc in 15.3% of patients indicated a past, resolved HBV infection. This serological distribution suggests that exposure to HBV among individuals living with HIV is not negligible. It has been reported that spontaneous reverse seroconversion, characterized by loss of anti-HBs and reappearance of HBsAg, may occur, particularly in HIV patients with CD4+ T lymphocyte counts below 200 cells/mm^3. Therefore, reassessment of HBV serological markers is recommended when unexplained elevations in liver enzymes or signs of liver disease develop in an HIV-infected patient who was previously anti-HBs positive (26,27). In studies reported from Türkiye, isolated total anti-HBc positivity was found to be 4.6% in a nationwide study conducted by Tozun et al. (13) and 8.2% in a single-center cohort of 1,394 HIV-infected individuals reported by Zerdali et al. (12). In our study, this rate was only 0.5%. Isolated total anti-HBc positivity is known to be an indicator of loss of anti-HBs levels after past HBV infection, false positivity, or occult HBV infection (28). In a study conducted in Taiwan with an average follow-up period of approximately 5 years, 41% of 179 patients with isolated total anti-HBc positivity—most of whom were receiving ART—became anti-HBs positive, while 4% developed HBsAg positivity (27). These findings support that isolated total anti-HBc IgG positivity in individuals living with HIV carries a risk of HBV reactivation and that careful follow-up is required in this patient group (29).

One of the main strengths of the present study is that it increases awareness of viral hepatitis among individuals living with HIV and demonstrates that comprehensive screening and effective vaccination strategies should be integral components of follow-up. The study contributes meaningfully to the literature by providing up-to-date, Türkiye-specific seroepidemiological data.

Study Limitations

The main limitations of this study are the limited availability of data and the risk of misclassification due to its retrospective design. The inability to access serological data for all patients limited sample integrity and narrowed the scope of subgroup analyses. Moreover, the single-center design limits the generalizability of the findings to other geographic and sociodemographic populations. Therefore, current multicenter studies including individuals from different regions of Türkiye and having diverse demographic characteristics are needed.

Conclusion

This study provides comprehensive and up-to-date data on the seroepidemiology of viral hepatitis among individuals living with HIV in Türkiye and demonstrates that, despite the relatively low prevalence of chronic HBV and HCV coinfections, susceptibility to vaccine-preventable hepatitis remains an important clinical and public health problem.

Ethics

Ethics Committee Approval: This study received approval from the Konya City Hospital Non-Interventional Clinical Research Ethics Committee (approval number: 2025/242, dated: 08.12.2025) and was conducted in accordance with the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: M.R.T., Y.G., Design: M.R.T., Y.G., Data Collection or Processing: M.R.T., Y.G., Analysis or Interpretation: M.R.T., Y.G., Literature Search: M.R.T., Y.G., Writing: M.R.T., Y.G.

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

Financial Disclosure: The authors declare no financial support.

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DOI: 10.4274/vhd.galenos.2026.2025-11-2
Viral Hepat J 2026;32(2):46-50

Increase in Adult Acute Hepatitis A Cases Following the Earthquake: An Epidemiological and Clinical Evaluation

Deprem Sonrası Erişkin Akut Hepatit A Olgularında Artış: Epidemiyolojik ve Klinik Değerlendirme

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ABSTRACT

Objectives: Acute hepatitis A continues to be an important public health problem in developing countries. This study aimed to evaluate the epidemiological, clinical, and laboratory characteristics of adult cases of acute hepatitis A observed in Adana and surrounding areas over the last five years, and to highlight the increase in cases after the 2023 earthquakes. Examine the potential association between the post-disaster period and the observed trend in case numbers.

Materials and Methods: This retrospective cross-sectional study included adult patients diagnosed with acute hepatitis A between January 2020 and May 2025. The patients' demographic data, clinical findings, laboratory results, and the development of complications were examined.

Results: The median age of the 31 adults with acute hepatitis A included in the study was 23 years (range 18-51), and 64.5% cases were male. The most common presenting complaints were nausea-vomiting (83.9%), abdominal pain (64.5%), and dark urine (58.1%). The mean alanine transaminase level was 2205±1223 U/L, while the median aspartate aminotransferase level was 1102 U/L. Although the highest frequency of cases occurred during the winter (54.8%), a notable clustering in case numbers was observed in 2023 and 2024, temporally coinciding with the period following the February 6 earthquakes. Risk factors included living in crowded environments (25.8%) and being military personnel (12.9%), alongside documented instances of intra-familial transmission.

Conclusion: The vast majority of acute hepatitis A cases occurred in young adults, and a marked increase in case numbers was observed, particularly in the post-earthquake period. These findings suggest that hepatitis A remains an important public health problem and that environmental factors may affect the epidemiology of hepatitis A. The increase in cases may be associated with post-earthquake living conditions, inadequate

ÖZ

Amaç: Akut hepatit A, gelişmekte olan ülkelerde hala önemli bir halk sağlığı sorunu olmaya devam etmektedir. Bu çalışmanın amacı, Adana ve çevresinde son beş yılda izlenen erişkin akut hepatit A olgularının epidemiyolojik, klinik ve laboratuvar özelliklerini değerlendirmek ve 2023 yılında meydana gelen depremler sonrasında gözlenen olgu artışına dikkat çekmektir. Afet sonrası dönem ile olgu sayılarındaki gözlemlenen eğilim arasındaki olası ilişkiyi incelemektir.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışma, Ocak 2020-Mayıs 2025 tarihleri arasında görülen akut hepatit A tanısı almış erişkin hastaların verileri kullanılarak gerçekleştirilmiştir. Hastaların demografik verileri, klinik bulguları, laboratuvar sonuçları ve komplikasyon gelişimi incelenmiştir.

Bulgular: Çalışmaya dahil edilen 31 erişkin akut hepatit A olgusunun medyan yaşı 23 (18-51) yıl idi ve olguların %64,5'i erkekti. En sık başvuru yakınmaları bulantı-kusma (%83,9), karın ağrısı (%64,5) ve idrar renginde koyulaşmaydı (%58,1). Ortalama alanin transaminaz düzeyi 2205±1223 U/L, ortanca aspartat aminotransferaz 1102 U/L olarak saptanmıştır. Olgu sıklığının kış aylarında en yüksek oranda (%54,8) saptanmasına karşın; 2023 ve 2024 yıllarında, zamansal olarak 6 Şubat depremlerinin sonrasındaki dönemle örtüşen, olgu sayılarında belirgin bir kümelenme gözlenmiştir. Risk faktörleri incelendiğinde; olguların %25,8'inde kalabalık yaşam koşulları ve %12,9'unda askeri personel olma durumu dikkat çekerken, aile içi bulaş olguları da tespit edilmiştir.

Sonuç: Çalışma, akut hepatit A olgularının büyük çoğunluğunun genç erişkinlerde görüldüğünü ve özellikle deprem sonrası dönemde olgu sayılarında belirgin bir artış yaşandığını saptamıştır. Bu bulgular, hepatit A'nın hala önemli bir halk sağlığı sorunu olmaya devam ettiğini ve çevresel faktörlerin hastalığın epidemiyolojisi üzerinde etkiye sahip olabileceğini düşündürmektedir. Olgu artışının deprem sonrası yaşam koşulları, hijyen yetersizliği ve nüfus hareketleriyle ilişkili olabileceği düşünülmektedir. Bu

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Received: 23.11.2025 **Accepted:** 02.07.2026 **Epub:** 21.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Tüfek Ö, Turunç T, Arslan Gülen T. Increase in adult acute hepatitis A cases following the earthquake: an epidemiological and clinical evaluation. Viral Hepat J. 2026;32(2):46-50

hygiene, and population movements. Therefore, strengthening sanitation and effectively maintaining vaccination in high-risk groups post-disaster are of great importance.
Keywords: Hepatitis A, earthquake, viral hepatitis

nedenle, afet sonrası dönemlerde sanitasyonun güçlendirilmesi ve riskli gruplarda aşılamanın etkin biçimde sürdürülmesi önem arz etmektedir.
Anahtar Kelimeler: Hepatit A, deprem, viral hepatit

Introduction

Hepatitis A virus (HAV) is a 27-32 nm, non-enveloped RNA virus with icosahedral symmetry belonging to the genus *Hepatovirus* of the *Picornaviridae* family (1). Transmission of the disease occurs through contaminated water or food, inadequate sanitation, poor personal hygiene, and oral-anal sex (2). In its latest report, the Centers for Disease Control and Prevention stated that the number of HAV cases in 2023 increased 1.2-fold compared to 2015 (3). In our country, the incidence of HAV infection was determined as 0.6 (per one hundred thousand) in 2024, while the incidence in the Southeastern Anatolia and Eastern Anatolia regions was found to be higher compared to other regions (4).

The clinical spectrum of HAV infection ranges from asymptomatic infection to fulminant hepatitis. Clinical manifestations vary depending on the host's age. While fewer than 30% of young children are symptomatic, approximately 80% of adults exhibit severe hepatitis symptoms (5).

Over the last five years, two major developments have significantly influenced the dynamics of infectious diseases in our region. The coronavirus disease-2019 (COVID-19) pandemic, which emerged in early 2020, initially led to a temporary decline in the incidence of infections transmitted via the fecal-oral route due to intensified hygiene practices, social distancing, and lockdown measures.

Subsequently, the devastating earthquakes on February 6, 2023, severely disrupted public health stability in southern Türkiye. Extensive damage to sewage and clean water networks, combined with communal living in temporary shelters such as container cities and tents, posed a significant risk of transmission of water- and foodborne pathogens such as HAV.

Our aim in this study is to retrospectively evaluate adult cases of acute HAV diagnosed in our clinic between 2020 and the first five months of 2025 and to comprehensively assess the epidemiological distribution, clinical course, laboratory findings, development of complications, and risk factors of the disease.

It is anticipated that our study will provide insight into infectious disease dynamics in the post-disaster period and contribute to both regional public health policies and epidemiological surveillance strategies.

Materials and Methods

This retrospective cross-sectional study was conducted using data from adult patients diagnosed with acute HAV in a tertiary healthcare institution in Adana, Türkiye between January 2020 and May 2025. The study included adult patients (aged ≥18 years) diagnosed with acute HAV based on anti-HAV immunoglobulin M (IgM) positivity and consistent clinical findings. Individuals under 18 years of age, patients with incomplete clinical records, and cases of viral hepatitis other than acute HAV were excluded.

All patients' sociodemographic data at admission, laboratory parameters, complications developing during follow-up, and liver ultrasonography findings were recorded. The distribution of cases by year was examined. Data were obtained from the hospital information management system and personal data were anonymized for analysis.

While the diagnosis was primarily based on anti-HAV IgM positivity accompanied by clinical findings, anti-HAV IgG levels and antibody titer changes were not recorded during the follow-up period.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.). Descriptive statistics were expressed as numbers and percentages for categorical variables. For continuous variables, data were presented as medians and ranges (minimum-maximum) or means ± standard deviations, depending on the normality of the distribution.

Ethics

Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Adana City Training and Research Hospital Clinical Scientific Ethics Committee (decision no: 588, date: 10 July 2025). The study was conducted in accordance with the ethical principles of the 1964 Declaration of Helsinki and its later amendments.

Results

The median age of the 31 adult cases of acute HAV included in the study was 23 years (18-51). Among the patients, 64.5% (n=20) were male and 35.5% (n=11) were female.

When the distribution of cases by year was examined, no cases were detected in 2020; four (12.9%) cases were detected in 2021; two (6.45%) cases were detected in 2022; 11 (35.4%) cases were detected in 2023; 13 (41.9%) cases were detected in 2024; and one (3.2%) case of HAV infection was detected in the first five months of 2025 (Figure 1). Regarding the seasonal distribution, the highest number of cases was observed in winter (n=17, 54.8%). Six (19.35%) cases were detected in autumn, four (12.90%) cases in spring, and four (12.90%) cases in summer. January (n=8, 25.8%), December (n=7, 22.5%), and October (n=3, 9.6%) were the months with the highest number of cases.

In our study, the distribution of cases by place of residence showed that 18 cases were reported from districts of Adana province,

five from Hatay, two from Mersin, and two from Osmaniye. In addition, four cases were detected among individuals on military duty in Syria. Figure 2 shows the distribution of cases by residence: intra-provincial (within the province) and extra-provincial (outside the province).

The median time from symptom onset to admission was 5 days (range, 2-12), and the median length of hospital stay was 5 days (range, 1-12). When exposure histories were evaluated, eight cases (25.8%) had crowded living conditions, three (9.7%) had a history of travel, one (3.2%) had rural living conditions, and one (3.2%) had a history of close household contact. Two patients (6.4%) had a history of using tap water.

When presenting complaints were examined, the most frequently reported symptoms were nausea and vomiting (n=26, 83.9%), abdominal pain (n=20, 64.5%), and darkening of urine color (n=18, 58.1%). These were followed by fatigue (n=17, 54.8%), fever (n=8, 25.8%), myalgia (n=6, 19.4%), pale stools (n=4, 12.9%), and pruritus (n=1, 3.2%). Among the patients evaluated by abdominal ultrasonography, gallbladder wall thickening and pericholecystic edema were each observed in 8 (25.8%) cases.

When the patients' laboratory data were evaluated, the median aspartate aminotransferase was 1102 U/L, the mean alanine transaminase (ALT) was 2205±1223 U/L, the median total bilirubin was 6.3 mg/dL, the median direct bilirubin was 4.04 mg/dL, the mean prothrombin time was 16.5±3.4 seconds, and the median international normalized ratio was 1.39. Other laboratory findings are shown in Table 1. Additionally, bilirubinuria was detected in seven (22.6%) patients, and urobilinogenuria was detected in one (3.2%) patient. Chronic HBV coinfection was detected in one case, while anti-hepatitis C virus and anti-human immunodeficiency virus tests were negative in all patients.

Hematological complications were detected in four cases (12.9%), including leukopenia in one case (3.2%) and thrombocytopenia in three cases (9.6%). None of the patients developed a relapse or fulminant hepatitis. Only one patient (3.2%) was followed as an outpatient, while 30 patients (96.8%) were hospitalized and monitored in our clinic. None of our cases were fatal.

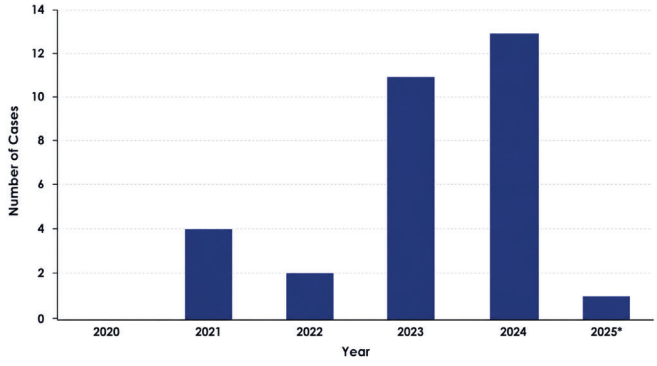

Figure 1. Number of acute hepatitis A cases by year (* the first five months)

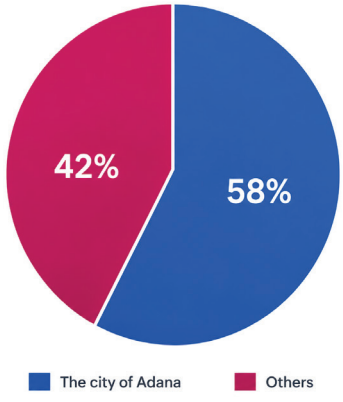

Figure 2. Distribution of cases

Discussion

HAV is one of the leading causes of acute hepatitis worldwide. When the global distribution is examined, the incidence and seroprevalence vary greatly between countries (6). Highly endemic regions such as South Asia and sub-Saharan Africa are characterized by poor hygiene conditions, while low-endemic regions are countries with high socioeconomic levels (7). In their multicenter study, Tosun et al. (8) reported that HAV seropositivity increased significantly with age; HAV seronegativity was detected in one-fourth of individuals younger than 26 years and in one-fifth of the 27-33 age group, whereas in individuals aged 40 years and older, seronegativity decreased significantly to 5% and below.

Table 1. Baseline laboratory findings in adult patients with acute hepatitis A

Parameter	Mean ± SD/median (min-max)
WBC (cells/mm^3)*	6327.8±1597.4
Hemoglobin (g/dL)**	14.1 (6.1-18)
Hematocrit (%)*	41.7±6.3
Platelet (/mm^3)**	205000 (113000-434000)
AST (U/L)**	1102 (74-3743)
ALT (U/L)*	2205±1223
ALP (U/L)**	151 (89-309)
GGT (U/L)**	140.5 (73-565)
Total Bilirubin (mg/dL)**	6.3 (0.58-32)
Direct Bilirubin (mg/dL)**	4.04 (0.17-22.08)
PT (sec)*	16.5±3.4
INR**	1.39 (0.9-2.36)
Albumin (g/L)*	38.7±4.8
Creatinine (mg/dL)**	0.67 (0.37-1.41)

Variables indicated with * are mean ± SD; variables indicated with ** are median (min-max). SD: Standard deviation,WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transpeptidase, PT: Prothrombin time, INR: International normalized ratio

When the seasonal distribution reported in the literature is examined, a study conducted in Brazil showed that HAV infections were higher in spring and autumn, concluding that they increased during hot seasons with heavy rainfall (9). In a study from Türkiye, spring (38.1%) and winter (28.6%) were the seasons in which the highest number of cases were detected (10). In our study, contrary to the literature, the highest number of cases was observed in winter (54.8%).

This rate can be explained by the increased stability of HAV in cold, damp environments and by the inevitable close contact in overcrowded temporary shelters with inadequate ventilation following the earthquake. Furthermore, logistical challenges maintaining water chlorination and personal hygiene during cold weather may have weakened the fundamental barriers to fecal-oral transmission.

In our study, the highest numbers of cases were reported in 2023 (11 cases, 35.5%) and in 2024 (13 cases, 41.9%). The complete absence of cases in 2020 suggests that the stringent hygiene measures and lockdowns implemented during the COVID-19 pandemic effectively suppressed the fecal-oral transmission of HAV. However, this period of minimal circulation likely created an "immunity gap" by interrupting natural community exposure.

There was a significant increase in acute HAV cases in 2023 and 2024. This increase is thought to be closely related to changes in regional and personal living conditions. Data from the communicable diseases unit of the general directorate of public health indicate that 72 cases were observed in Adana province during the same period as our study. While 31 cases aged 18 years and older were seen only at our hospital, 28 such cases were reported to the system. This discrepancy indicates deficiencies in case reporting. When the distribution by year is examined, a total of 25 cases were observed in 2023 and 24 in 2024 among both children and adults. In the province of Adana, an increase in the number of cases was also observed, consistent with data from our center.

Following the major earthquakes that occurred on February 6, 2023, significant damage occurred in the infrastructure systems due to the displacement of fault lines (11). This made access to clean water difficult and created a food safety problem. Sewage systems and personal hygiene practices deteriorated. As a temporary post-disaster housing solution, container settlements were established, and the population was compelled to live in communal living areas with limited resources (12). Although temporary field hospitals were set up because of inadequate regional health infrastructure, our hospital received a high volume of patient transfers from neighboring provinces until fully equipped hospitals opened.

In a review conducted by Saatchi et al. (13), HAV infections were also reported among the most frequently observed infectious diseases following earthquakes. HAV and E showed higher prevalence rates immediately after the earthquakes that occurred in the city of Düzce in 1999 (14).

The incubation period of HAV ranges from 15 to 50 days and is reported to be an average of 28 days (3). This long incubation period increases the potential for infected individuals to transmit the virus before becoming symptomatic, making infection control particularly challenging in communal living environments. As also indicated in our study, we had four military personnel who were serving in a military unit and were diagnosed as cases. Shared accommodation environments make the spread of HAV—transmitted via the fecal-oral route—inevitable. By 2025, the detection of only one adult case during the first five months of our study is thought to be related to improvements in environmental and personal conditions and a reduced need for referrals to our centrally located hospital.

The primary transmission route of the HAV is fecal-oral, and factors such as the consumption of contaminated water and food, close household contact, and crowded living environments play a significant role in transmission. The presentation of four acute HAV cases from the same family in Rize with complaints of jaundice and/or fatigue indicates that close household contact is an effective mode of transmission (15). In our study, two cases from the same family were diagnosed with acute HAV one month apart and subsequently monitored.

HAV outbreaks in Europe and the United States have been linked to sun-dried tomatoes imported from Türkiye (16) and pomegranate arils (17), respectively (18). In an outbreak reported in Milan with 353 cases, 172 cases were identified as "men who have sex with men" (19). Because HAV transmission is influenced by various environmental and behavioral factors, outbreaks emerge through multiple routes. In our study, the presence of four cases reported from a military unit is noteworthy, as it highlights the risk posed by crowded living conditions. Examples of outbreaks reported in different regions demonstrate the decisive role of these factors in the spread of HAV and emphasize the importance of implementing comprehensive public health measures to control the disease.

Chen et al. (20) reported that the most common presenting symptoms of acute HAV were dark urine (67.1%), nausea/vomiting (58.5%), fever (56%), and fatigue (55.6%). In our series, the most common presenting symptoms were nausea and vomiting, abdominal pain, and dark urine.

Study Limitations

Our study has several limitations, primarily its retrospective, single-center design and its relatively small sample size. Furthermore, the diagnosis was established solely on the basis of anti-HAV IgM positivity, in accordance with the inclusion criteria. The absence of anti-HAV IgG follow-up limits our ability to definitively exclude rare instances of false-positive IgM results. Nevertheless, the significantly elevated transaminase levels (mean ALT: 2205 U/L) and typical clinical presentation observed in 96.8% of our patients strongly support the accuracy of the acute HAV diagnosis. Therefore, the increase in reported cases in 2023 and 2024 should not be considered merely a random fluctuation but rather an indication of the impact of socioeconomic and environmental factors on infectious diseases. This underscores, once again, the importance, in post-disaster public health planning, of active surveillance, hygiene education, improvements in living conditions, and vaccination strategies aimed

at preventing infectious diseases such as HAV. Due to the absence of a control group and the lack of analysis of confounding factors such as migration and vaccination rates, these results should be interpreted as indicative of an association rather than a direct causal link.

Conclusion

Although the epidemiological pattern of HAV infection varies regionally, disrupted environmental conditions and inadequate hygiene in communal living areas following mass and regional disasters can significantly affect the epidemiological dynamics of infectious diseases. Our findings also highlight the necessity of integrating viral hepatitis surveillance into disaster preparedness and recovery plans.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Adana City Training and Scientific Hospital Clinical Research Ethics Committee (decision no: 588, date: 10 July 2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.T., T.T., T.A.G., Concept: Ö.T., T.T., T.A.G., Design: Ö.T., T.T., T.A.G., Data Collection or Processing: Ö.T., T.T., T.A.G., Analysis or Interpretation: Ö.T., T.T., T.A.G., Literature Search: Ö.T., T.T., T.A.G., Writing: Ö.T., T.T., T.A.G.

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

Financial Disclosure: The authors declare no financial support.

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DOI: 10.4274/vhd.galenos.2026.2025-10-3
Viral Hepat J 2026;32(2):51-59

Longitudinal Renal Function Changes and Pilot Mitochondrial Epigenetic Analysis in Chronic Hepatitis B Patients Treated with Nucleos(t)ide Analogues

Nükleoz(t)id Analogları ile Tedavi Edilen Kronik Hepatit B Hastalarında Böbrek Fonksiyonlarındaki Uzun Dönemli Değişimler ve Pilot Mitokondriyal Epigenetik Analiz

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ABSTRACT

Objectives: Long-term use of nucleos(t)ide analogues (NAs) has been associated with mitochondrial dysfunction and potential adverse effects. This study aimed to evaluate nephrotoxicity in treated and treatment-naïve chronic hepatitis B (CHB) patients and to explore DNA methyltransferase 1 (DNMT1) expression as a potential epigenetic mechanism.

Materials and Methods: Adult CHB patients receiving tenofovir disoproxil fumarate (TDF) or entecavir (ETV) for ≥12 months comprised the "under treatment" group, while untreated patients formed the "treatment-naïve" group. Renal parameters at baseline and months 3, 6, and 12 were analyzed retrospectively. Longitudinal changes in glomerular filtration rate (GFR) were assessed using linear mixed-effects modeling. DNMT1 expression in peripheral blood mononuclear cells was evaluated as a pilot analysis.

Results: A total of 158 patients were analyzed; 91 were treated and 67 were treatment-naïve. Median GFR values declined significantly from 102.3 at the baseline to 102.1 at the 12th month in the treated group (p=0.012). In longitudinal analysis, each additional time point was associated with a mean GFR decline of 1.65 mL/min/1.73 m^2 (95% confidence interval: -3.13 to -0.16; p=0.030). Age was independently associated with a reduction in GFR (β=-0.75 per year; p<0.001). No significant differences in renal outcomes were observed between TDF and ETV. In the pilot epigenetic analysis (n=25), DNMT1 expression was comparable between treated and treatment-naïve patients (median 1.1789 vs. 0.7565; p=0.466).

ÖZ

Amaç: Nükleos(t)id analoglarının (NA) uzun süreli kullanımı, mitokondriyal işlev bozukluğu ve olası yan etkilerle ilişkilendirilmiştir. Bu çalışmada, tedavi altındaki ve tedavi-naiv kronik hepatit B (KHB) hastalarında nefrotoksisitenin değerlendirilmesi ve potansiyel bir epigenetik mekanizma olarak DNA metiltransferaz 1 (DNMT1) ekspresyonunun araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Tenofovir disoproksil fumarat (TDF) veya entekavir (ETV) tedavisini ≥12 ay boyunca alan yetişkin KHB hastaları "tedavi altındaki" grubu oluştururken, tedavi görmemiş hastalar ise "tedavi-naiv" grubu oluşturdu. Başlangıçta ve 3., 6. ve 12. aylarda ölçülen böbrek parametreleri retrospektif olarak analiz edildi. Glomerüler filtrasyon hızındaki (GFR) uzunlamasına değişiklikler, doğrusal karışık etki modellemesi kullanılarak değerlendirildi. Pilot çalışma olarak, periferik kan mononükleer hücrelerinde DNMT1 ekspresyonu değerlendirildi.

Bulgular: Toplam 158 hasta analiz edildi; 91'i tedavi altında, 67'si tedavi-naiv hastaydı. Tedavi altındaki grupta medyan GFR değerleri, başlangıçtaki 102,3'ten 12. ayda 102,1'e istatistiksel olarak anlamlı bir düşüş gösterdi (p=0,012). Boylamsal analizde, her bir ek zaman noktası ortalama 1,65 mL/dk/1,73 m^2'lik bir GFR düşüşü ile ilişkilendirildi (%95 güven aralığı: -3,13 ila -0,16; p=0,030). Yaş, GFR azalmasıyla bağımsız olarak ilişkilendirildi (yılda -0,75 β; p<0,001). TDF ve ETV arasında böbrek fonksiyon sonuçlarında anlamlı bir fark gözlenmedi. Pilot epigenetik analizde (n=25), DNMT1 ekspresyonu tedavi görmüş ve tedavi görmemiş hastalar arasında benzerdi (medyan 1,1789'a karşı 0,7565; p=0,466).

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Received: 13.10.2025 **Accepted:** 02.07.2026 **Epub:** 21.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Uyar Güleç G, Kırdar S, Ak C, Kılıç Eren M, Örün H. Longitudinal renal function changes and pilot mitochondrial epigenetic analysis in chronic hepatitis B patients treated with nucleos(t)ide analogues. Viral Hepat J. 2026;32(2):51-59

Conclusion: Long-term NA therapy is associated with a modest decline in renal function. Although DNMT1 expression was not significantly altered, potential mitochondrial effects warrant further investigation in larger prospective studies.
Keywords: DNA methyltransferase 1, epigenetics, hepatitis B virus, nephrotoxicity, nucleos(t)ide analogues

Sonuç: Uzun süreli NA tedavisi, böbrek fonksiyonunda hafif bir düşüşle ilişkili bulunmuştur. DNMT1 ekspresyonunda istatistiksel olarak anlamlı bir değişiklik gözlenmemiş olsa da, olası mitokondriyal etkiler nedeniyle daha geniş kapsamlı prospektif çalışmalarla bu konunun daha ayrıntılı olarak araştırılması gerekmektedir.
Anahtar Kelimeler: DNA metiltransferaz 1, epigenetik, hepatit B virüsü, nefrotoksisite, nükleos(t)id analogları

Introduction

Although its prevalence varies by country, chronic hepatitis B (CHB) remains a global problem. According to World Health Organization data for 2022, the number of people with CHB is 254 million; the number of new cases is 1.2 million per year; and the number of deaths from cirrhosis and hepatocellular carcinoma (HCC) attributable to hepatitis B virus (HBV) infection is 1.1 million (1).

The main objective in treating CHB is to enhance patients' life expectancy, to improve their quality of life, and to prevent complications, such as HCC or liver failure, caused by CHB. Prevention of HBV reactivations and transmission from mother to infant are secondary targets of treatment (2).

Nucleos(t)ide analogues (NA) and pegylated interferon alpha (PegIFNa) are two main treatment options for CHB. NAs approved for HBV treatment include lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF). While ETV, TDF, and TAF are associated with a high barrier against HBV resistance, LAM, ADV, and LdT are associated with a low barrier to HBV resistance (3).

Due to the risk of virological relapse and hepatic decompensation after discontinuation of treatment, patients must continue NA treatment for life, exposing them to several side effects of long-term treatment (4).

Both HBV infection and long-term NA use may adversely affect renal function. All NAs are excreted by the kidneys in unchanged form and some of them cause nephrotoxicity through dose-dependent proximal tubular damage. Nephrotoxicity is manifested by elevated serum creatinine, proteinuria, nephrogenic diabetes insipidus, hypophosphatemia or the more severe form of Fanconi syndrome (5).

The prevalence and course of extrahepatic side effects which are most frequently reported during NA treatment are not known exactly and may be associated with mitochondrial dysfunction (6). Since NA, which exerts its effects by inhibiting the viral DNA polymerase, can also inhibit the DNA polymerase involved in mitochondrial DNA (mtDNA) replication, mitochondrial side effects may occur. Furthermore, it has been shown that mtDNA, like nuclear DNA, contains 5-methylcytosine (5mC) at CpG dinucleotides and thus epigenetic modification may play a potential role in the regulation of transcription of mtDNA (7,8). So far, very few experimental data are available regarding the epigenetic regulation of mtDNA in physiological and various pathological conditions.

Different types of epigenetic processes have been described. However, methylation of CpG islands is an important mechanism in higher-order eukaryotes. Vertebrate nuclear DNA contains three DNA methyltransferases (DNMTs): DNMT1, DNMT3A, and DNMT3B. Under the action of these enzymes, a methyl group is added to the 5′ position of the base cytosine to form 5mC, and they can methylate DNA *de novo*. Mitochondria have been reported to contain a specific DNMT isoform (mtDNMT1), suggesting a potential role for DNA methylation in mitochondrial gene regulation. DNMT3A has been reported to associate with mitochondria under certain conditions. Emerging evidence indicates that alterations in mtDNA methylation may be linked to DNMT1 expression in patients receiving NA therapy, supporting the exploratory evaluation of DNMT1 as an epigenetic marker in the present study (9,10). To the best of our knowledge, no research in our country has examined the epigenetic effects of NA treatment in patients with CHB.

This study investigated the effect of NA treatment on the development of nephrotoxicity in patients with CHB and the potential modulation of DNMT1 as an epigenetic mechanism.

Materials and Methods

Patient Selection and Nephrotoxicity Analyses

This study included adult patients with CHB who were followed and treated at the Infectious Diseases and Clinical Microbiology Outpatient Clinic of Aydın Adnan Menderes University Hospital from January 2010 to December 2024. Ethical approval was obtained from the Aydın Adnan Menderes University Clinical Research Ethics Committee (approval no: 2019/07, date: 11/06/2020).

According to the health practice communiqué in our country, patients who meet the treatment criteria may initiate therapy with TDF or ETV. The decision is left to the clinician. Patients who were older than 18 years and had complete data were included in the study. Patients co-infected with other hepatitis viruses and human immunodeficiency virus (HIV), pregnant women, patients with known kidney disease, and patients using nephrotoxic drugs were excluded from the study. Patients with CHB who initiated NA treatment (TDF or ETV) for the first time and continued it for at least 12 months were included in the "under treatment" group. Those with CHB who were followed without treatment were classified as "treatment-naïve".

Nephrotoxicity was assessed by retrospective review of patient data from the hospital information system. Age, gender, comorbidities (diabetes mellitus and hypertension), medication

and its duration, baseline HBV-DNA level, HBeAg and anti-HBe, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, creatinine, glomerular filtration rate (GFR) (mL/min/1.73 m^2), and phosphorus levels were recorded. GFR was calculated using the short modification of diet in renal disease formula, which includes sex, age, race, and serum creatinine values. To assess the development of nephrotoxicity, urea, creatinine, GFR, and phosphorus values at 3 months (T1), 6 months (T2), and 12 months (T3) after the start of treatment were recorded. Renal endpoints were defined as creatinine clearance <50 mL/min, serum creatinine ≥0.5 mg/dL increase from baseline and serum phosphate <2 mg/dL as defined in Buti et al. (11).

mRNA Isolation and qRT-PCR Analysis

Epigenetic analyses were designed as pilot analyses to generate preliminary data on DNMT1 expression. Blood samples were collected into ethylenediaminetetraacetic acid tubes from patients diagnosed with CHB who attended the outpatient clinic for their routine check-ups and provided informed consent between June 2022 and January 2023. The mRNA was isolated from peripheral blood mononuclear cells (PBMCs) of the patients included in the study using a total RNA isolation kit (Thermo Fisher Scientific, Massachusetts, USA). After RNA isolation, DNA contamination was removed by treatment with DNase I (Thermo Fisher Scientific, Massachusetts, USA). Synthesis of cDNA from the obtained RNA was performed using one µg of RNA, random hexamer primers, and reverse transcriptase (Thermo Fisher Scientific, Massachusetts, USA). Gene expression analysis was performed with SYBR Green PCR Master Mix (ABM, Richmond, Canada) on a StepOne Real-Time PCR System (Applied Biosystems, Foster City, CA, USA), using mtDNMT1 gene-specific forward (5′-TCCCTGGGCATGGCCGGCTC-3′) and reverse (5′-CTCTTTCCAAATCTTTGAGCCGCC-3′) primers, and forward (5′-TCCGAGATGCCGGCGCGTACC-3′) and reverse (5′-CTCTTTTCCAAATCTTTGAGCCGCC-3′) primers for total DNMT1. The *GAPDH* gene was used as an internal control, and forward (5′-GAAGGTGAAGGTCGGAGT-3′) and reverse (5′-CATGGGTGGAATCATATATTGGA-3′) primers were used to amplify it. Real-time PCR was performed after denaturation at 95 °C for 3 minutes, followed by 40 cycles of 15 seconds at 95 °C, 30 seconds at 58 °C, and 30 seconds at 72 °C. For quantification of mRNA levels, each sample was run in duplicate, and the average of the duplicate measurements was used to calculate the gene's mRNA expression. Relative mRNA levels were calculated according to the 2 -(ΔCt) approach.

Statistical Analysis

Descriptive statistics are provided as frequencies and percentages for categorical variables, and as mean ± standard deviation or median (min-max) for continuous variables. The normality of distributions was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For normally distributed continuous variables, comparisons between two groups were made using the Student's t-test, while the Mann-Whitney U test was used for non-normally distributed variables. Dependent groups were analyzed using the Friedman test because the data were not normally distributed.

GFR measurements in treated patients at baseline (T0), 3 months (T1), 6 months (T2), and 12 months (T3) were analyzed longitudinally using a linear mixed-effects model with a random intercept for each patient. Time was entered as a categorical fixed effect with T0 as the reference level. The final model included time, antiviral agent (TDF vs. ETV), age, sex, prior diabetes mellitus, and prior hypertension as fixed effects. To explore potential drug-specific renal trajectories, a time-by-drug interaction was initially tested; however, because this term did not improve model fit, the simpler model without the interaction was retained based on fit indices, including Akaike's information criterion. Regression coefficients, standard errors, p-values, and 95% confidence intervals (CIs) were reported.

The distribution of DNMT1 values was tested for normality using the Shapiro-Wilk test because the sample size was small. Since the data did not conform to a normal distribution, the difference between the two groups was analyzed using the Mann-Whitney U test.

All analyses were performed in R version 4.5.0. Data import and management were conducted using the readxl, dplyr, and tidyr packages; standard statistical tests were performed using base R/stats; linear mixed-effects models were fitted using lme4 and lmerTest; adjusted marginal means and contrasts were obtained using emmeans; and figures were generated using ggplot2 and patchwork. A two-sided p-value of <0.05 was considered statistically significant.

Results

Data from 158 patients were analyzed for nephrotoxicity. The mean age of the patients was 49.25±12.9 years. Of these, 71 (45%) were female. The "under treatment" group included 91 (57.6%) patients, while the "treatment-naïve" group included 67 (42.4%) patients. Patient characteristics by treatment status are presented in Table 1. The duration of treatment varied between 12 and 164 months. Age, HBV-DNA, basal ALT, and AST levels were significantly higher in the treatment group. Basal phosphorus level was lower in the treatment group than in the treatment-naïve group (p=0.004). No significant differences were observed between the two groups in basal urea, creatinine, and GFR. HBeAg was positive in 16.5% of the treatment group and 1.5% of the treatment-naïve group.

In the treatment group, renal parameters were analyzed longitudinally by comparing baseline (T0) values with follow-up measurements (T1, T2, and T3). Phosphorus, urea, and creatinine levels remained stable over time, whereas GFR demonstrated a statistically significant decline (p=0.012) (Figure 1). Longitudinal changes in renal function parameters across follow-up visits are summarized in Table 2.

When the treatment group was analyzed according to the therapeutic agent, 74 (81.3%) were receiving TDF and 17 (18.7%) were receiving ETV. No significant difference was found when baseline and control values of renal parameters were compared by treatment type. However, basal urea values were higher in the ETV group than in the TDF group (p=0.039 and p=0.014); this difference disappeared over time (Table 3).

Table 1. Characteristics of the study group by the under treatment or not

Variables	Treatment-naïve (n=67)	Under the treatment (n=91)	p-value	X^2	z	t
Age (years)	46.0 (19-68)	53.0 (24-76)	**0.003**		-2.958	
Sex			**0.011**	6.524		
Female	38 (56.7)	33 (36.3)				
Male	29 (43.3)	58 (63.7)				
Pre-existing* diabetes	9 (42.9)	12 (57.1)	0.964	0.002		
Pre-existing* primary hypertension	20 (66.7)	10 (33.3)	**0.003**	8.925		
Duration of the treatment (months)	NA	76.1±40.6 (12-164)	NA			
HBV-DNA	958 (10-170000000)	590000 (0-224766065)	**<0.001**		-6.850	
HbeAg			**0.005**	7.953		
Negative	66 (98.5)	76 (83.5)				
Positive	1 (1.5)	15 (16.5)				
Anti-HBe			**0.005**	7.953		
Negative	1 (1.5)	15 (16.5)				
Positive	66 (98.5)	76 (83.5)				
ALT	20.0 (12-166)	31.0 (10-646)	**<0.001**		-4.674	
AST	21.0 (9-105)	29.0 (13-656)	**<0.001**		-4.405	
P at the baseline	3.4±0.6	3.1±0.6	**0.004**			2.909
Urea at the baseline	25 (12-64)	27 (11-53)	0.092		-1.683	
Creatinine at the baseline	0.75 (0.52-1.73)	0.77 (0.53-1.07)	0.058		-1.899	
GFR at the baseline	104.7 (30.7-130.9)	102.3 (71.0-136.7)	0.329		-0.976	

*: Prior to treatment initiation for NA treated patients or prior to hepatitis B diagnosis for treatment-naïve group. HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, P: Phosphorus, GFR: Glomerular filtration rate, NA: Nucleos(t)ide analogues

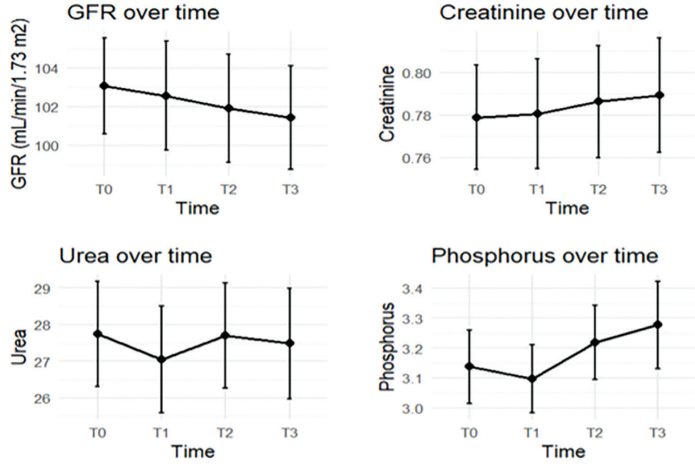

Figure 1. Descriptive trends in renal function parameters over time in nucleos(t)ide analogues-treated patients. Mean values with 95% confidence intervals are shown for glomerular filtration rate (GFR), creatinine, urea, and phosphorus at T0, T1, T2, and T3

Table 2. Longitudinal changes in renal function parameters across follow-up visits in treated patients (n=91)

Parameters	Baseline	T1	T2	T3	p-value	X^2
Phosphorus	3.1 (1.9-4.7)	3.1 (1.9-4.4)	3.2 (1.6-4.8)	3.2 (1.3-5.6)	0.076	6.877
Urea	27 (11-53)	26 (5-51)	27 (11-50)	27 (14-49)	0.909	0.544
Creatinine	0.77 (0.53-1.07)	0.79 (0.46)	0.79 (0.53-1.16)	0.79 (0.56-1.19)	0.551	2.103
GFR	102.3 (71.0-136.7)	102.0 (65.0-139.6)	102.8 (64.4-134.0)	102.1 (62.0-127.6)	**0.012***	10.907

*: The difference due to the third time point (12th month, T3), for all post-hoc analysis with Wilcoxon signed-rank p>0.05 except for between the baseline (T0) and T3 with p=0.012. GFR: Glomerular filtration rate

Table 3. Laboratory parameters by therapeutic agents

Parameters	TDF (n=74)	ETV (n=17)	p-value	t	z
P at baseline	3.16±0.63	3.06±0.40	0.430	0.798	
P at T1	3.1 (1.9-4.4)	3.1 (2.2-4.1)	0.580		-0.553
P at T2	3.2 (1.6-4.8)	3.1 (2.3-3.7)	0.520		-0.643
P at T3	3.27±0.74	3.31±0.47	0.648	-0.456	
Urea at baseline	27 (11-53)	34 (18-42)	**0.039**		-2.065
Urea at T1	26 (5-44)	29 (23-51)	**0.014**		-2.452
Urea at T2	27 (11-50)	30 (17-43)	0.130		-1.515
Urea at T3	27.0±7.5	29.4±6.0	0.239	-1.185	
Creatinine at baseline	0.77±0.11	0.82±0.14	0.116	-1.587	
Creatinine at T1	0.77±0.13	0.81±0.13	0.286	-1.074	
Creatinine at T2	0.79±0.13	0.78±0.15	0.858	0.180	
Creatinine at T3	0.78 (0.56-1.19)	0.80 (0.56-1.03)	0.558		-0.586
GFR at baseline	103.8±12.2	100.2±11.9	0.273	1.103	
GFR at T1	103.1±13.8	100.4±13.6	0.478	0.712	
GFR at T2	101.8±13.7	102.2±14.4	0.931	-0.087	
GFR at T3	101.6±12.8	100.8±14.9	0.830	0.216	

P: Phosphorus, GFR: Glomerular filtration rate, TDF: Tenofovir disoproxil fumarate, ETV: Entecavir

In the adjusted linear mixed-effects model that included time, antiviral agent, age, sex, prior diabetes mellitus, and prior hypertension, GFR at 12 months was significantly lower than at baseline (β=-1.65 mL/min/1.73 m^2, 95% CI: -3.13 to -0.16; p=0.030). The differences at 3 months (β=-0.52, p=0.495) and 6 months (β=-1.18, p=0.121) were not statistically significant. Increasing age was independently associated with lower GFR (β=-0.75 per year, 95% CI: -0.87 to -0.62; p<0.001). No statistically significant associations were observed for antiviral agent, sex, prior diabetes, or prior hypertension (Table 4).

Renal end points defined by Buti et al. (11) were found in three patients. When these patients were analyzed in detail, the first case was a 70-year-old woman who had been receiving TDF for 102 months and had been diagnosed with hypertension and osteoporosis. Increased creatinine and decreased GFR were detected. Case 2 was a 59-year-old male patient who developed increased creatinine and proteinuria in the 107th month of TDF treatment. Hypophosphatemia was detected in the test results of the 3rd patient, a 62-year-old male with diabetes, hypertension, and coronary artery disease. He was followed up by the nephrology service and was diagnosed with chronic kidney disease. He had been receiving TDF for 42 months. Treatment was changed to TAF in these three patients.

DNMT1 gene expression in RNA samples extracted from the PBMCs of the eight CHB patients treated with NA, compared with the 17 treatment-naïve patients, was analyzed by real-time PCR assay (Figure 2). Ten (40%) of the patients were female, 15 (60%) were male, and the mean age was 51+14.37 years. In epigenetic analysis, median DNMT1 levels in the under treatment group were 1.1789 [interquartile range (IQR) 0.3202-1.5584)] and in the treatment-naïve group were 0.7565 (IQR 0.2740-1.3293). DNMT1 levels were similar between the two groups (p=0.466; z=-0.728) (Figure 3).

Table 4. Adjusted linear mixed-effects model for GFR during the first 12 months of NA therapy

Variable	β estimate	95% CI	p-value
Time: T1 (3 months) vs. T0	-0.52	-2.00 to 0.96	0.495
Time: T2 (6 months) vs. T0	-1.18	-2.66 to 0.31	0.121
Time: T3 (9 months) vs. T0	-1.65	-3.13 to -0.16	0.030
Drug: ETV vs. TDF	-0.42	-4.18 to 3.34	0.828
Age (per year)	-0.75	-0.87 to -0.62	<0.001
Sex: female vs. male	0.06	-3.01 to 3.12	0.972
Prior diabetes: yes vs. no	-1.49	-6.18 to 3.19	0.534
Prior hypertension: yes vs. no	-1.88	-7.30 to 3.53	0.497

Linear mixed-effects model with random intercept for patient ID. Reference categories: T0, TDF, male sex, no prior diabetes, and no prior hypertension. GFR: Glomerular filtration rate, TDF: Tenofovir disoproxil fumarate, ETV: Entecavir, CI: Confidence interval, NA: Nucleos(t)ide analogues

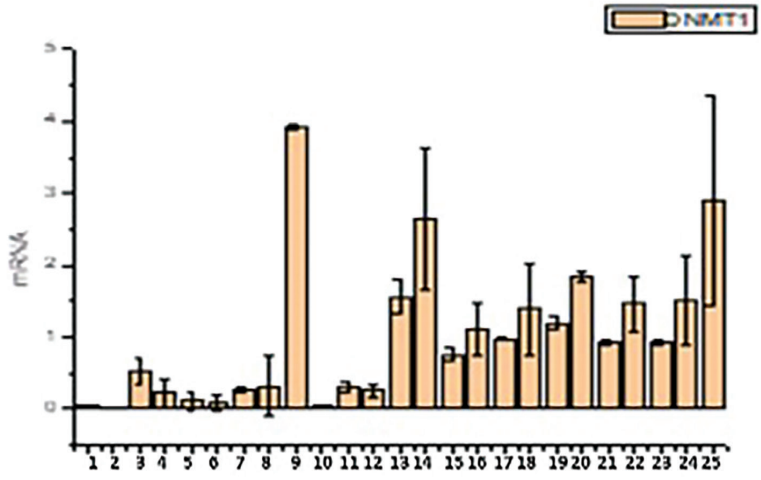

Figure 2. Schematic representation of DNMT1 values in samples subjected to epigenetic analysis
DNMT1: DNA methyltransferase 1

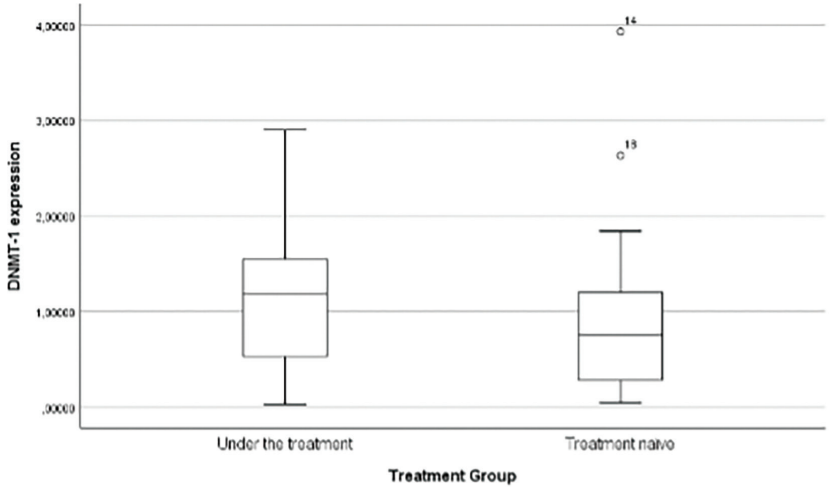

Figure 3. Comparison of DNMT1 values according to treatment status
DNMT1: DNA methyltransferase 1

Discussion

Of the two currently approved treatment classes for CHB—peg-IFN alpha and NAs—the NAs represent the cornerstone of therapy. They effectively suppress viral replication, improve liver inflammation, and reduce the risk of progression to cirrhosis and HCC. However, functional cure (sustained loss of HBsAg with undetectable HBV-DNA) is achieved in ≤1% of patients, necessitating long-term treatment. This is largely due to the persistence of covalently closed circular DNA and integrated HBV-DNA, which are not targeted by NAs. Although NAs have an excellent safety profile, long-term use may be associated with increased healthcare costs, drug non-adherence, and risk of renal and bone toxicity. Consequently, there exists a clear demand for innovative, brief therapeutic interventions that can result in a significant rate of functional enhancement (12,13). While oral administration offers advantages, NAs have limited immunomodulatory effects and do not adequately induce cell-mediated immunity (14).

In this study, we investigated whether nephrotoxicity, one of the possible side effects, developed in patients treated with NA. One hundred and fifty-eight patients with CHB whose follow-up values were recorded at 3-6 month intervals were analyzed. Data from 91 patients who received treatment with NA and from 67 treatment-naïve patients were compared. Our findings suggest a modest decline in renal function during the first 12 months of NA therapy. Although the follow-up period was relatively short, the magnitude of decline was small. Age emerged as the strongest independent predictor of lower GFR. Although no significant difference was detected between TDF and ETV, the comparison should be interpreted cautiously given the marked imbalance in sample sizes between treatment groups (TDF: 74 vs. ETV: 17).

Although deterioration in renal function after NA use was reported in similar studies, its potential effect on renal failure remains uncertain.

In a study involving 110 patients receiving TDF for 48-171 weeks, creatinine levels increased significantly at weeks 12, 24, 48, 72, and 96, and eGFR levels decreased significantly at these five time points. They found that being over 60 years of age and basal bilirubin values were independent risk factors for renal failure (15). Age-related decline in renal function is a well-recognized physiological process that may, in part, explain the observed longitudinal reduction in GFR. In our mixed-effects model, age was independently associated with GFR decline, suggesting that treatment-related effects should be interpreted in the context of baseline renal aging.

In a prospective study involving 105 patients, including 33 with cirrhosis and 72 without, GFR significantly decreased in the non-cirrhotic group during the first year of treatment with TDF ($p<0.001$). Fortunately, GFR partially recovered by week 96 without the need for interruption of treatment (16).

Among patients treated with NA, baseline and follow-up renal values did not differ significantly between the TDF and ETV groups. In a retrospective cohort study of 1917 patients receiving ETV and 1509 patients receiving TDF, TDF treatment was associated with a higher risk of renal dysfunction (17).

A retrospective study of 10,642 patients with CHB found that NA treatment—particularly TDF—was associated with a higher risk of chronic kidney disease progression compared with untreated patients. In contrast, ETV and TAF showed similar risks to untreated patients, with no difference between the two (18).

In a meta-analysis of randomized controlled trials of HBV patients treated with ETV, TDF and TAF, increases in creatinine and decreases in GFR were compared with respect to renal side effects. ETV and TAF had less effect on GFR than TDF, while ETV had less effect on an increase in creatinine than TAF and TDF. As a result, it was concluded that TDF negatively affected renal tissue compared to ETV and TAF (19).

In a retrospective study of 1061 untreated CHB patients and 366 patients receiving TAF, 190 besifovir dipivoxil maleate (BSV) and 2029 ETV, renal function decline for ≥3 consecutive months was assessed as the primary outcome. Compared with each matched untreated group, changes in estimated GFR over time were higher in the ETV group ($p=0.010$), although similar in the TAF ($p=0.073$) and BSV groups ($p=0.926$) (20). Consistent with these findings, TDF therapy was switched to TAF in three patients in our cohort who developed renal involvement during follow-up.

Real-world cohort and meta-analysis data have shown that there is no clinically significant difference in renal dysfunction between commonly used agents such as tenofovir and ETV, and that they have similar renal safety profiles. Differences in study design, patient populations, baseline renal risk, and follow-up duration must be taken into account when evaluating nephrotoxicity associated with NA.

Drugs can impair mitochondrial function through multiple mechanisms. Several antibiotics and antiviral agents have been shown to inhibit mitochondrial protein synthesis or interfere with mtDNA replication. Consequently, many drugs currently in clinical use may cause organ toxicity, at least in part, through mitochondrial disruption (21). In particular, nucleoside reverse transcriptase inhibitors used in HIV treatment have been associated with mitochondrial toxicity due to inhibition of mtDNA polymerase-γ, leading to impaired mtDNA replication and mitochondrial dysfunction (22). Although tenofovir and ETV appear to have relatively low mitochondrial toxicity compared with earlier agents, experimental and clinical studies suggest that mitochondrial alterations may still occur, particularly in renal proximal tubular cells (9,23-25).

DNMT1 has been implicated in HBV-related hepatocarcinogenesis, and increased DNMT1 expression has been associated with HCC in previous studies (26,27). However, epigenetic alterations potentially related to NA therapy in patients with CHB have not been extensively investigated.

The median DNMT1 level was 1.1789 (IQR: 0.3202-1.5584) in the treatment group and 0.7565 (IQR: 0.2740-1.3293) in the treatment-naïve group; there was no statistically significant difference between

the groups. In contrast, Madeddu et al. (9) reported significantly higher DNMT1 expression in NA-treated patients compared with untreated patients [HBV-naïve: 0.61 (IQR 0.34-0.82); NA-treated: 4.09 (IQR 3.52-5.15); p<0.00001], and DNMT1 expression was also associated with treatment duration.

The absence of a significant difference in DNMT1 expression between treated and treatment-naïve patients in our study may have several biological explanations. MtDNA methylation is a dynamic and context-dependent process that may be influenced by mitochondrial stress responses rather than direct drug exposure alone. Compensatory mechanisms may therefore maintain mitochondrial epigenetic homeostasis despite prolonged NA therapy. Furthermore, DNMT1 expression measured in PBMCs may not fully reflect mitochondrial epigenetic alterations occurring in target tissues such as renal tubular cells or hepatocytes.

Another possible explanation is treatment heterogeneity. TDF and ETV differ in their effects on mtDNA polymerase-γ and mitochondrial function. Due to the limited number of ETV-treated patients in our cohort, drug-specific effects could not be evaluated separately, and pooling the treatments may have attenuated detectable epigenetic differences. In addition, the epigenetic component of this study was designed as a pilot exploratory analysis with a small sample size, which limited statistical power and increased the risk of type II error.

Taken together, these findings should be interpreted cautiously and primarily as hypothesis-generating. Larger prospective studies incorporating tissue-specific analyses and drug-stratified designs are needed to clarify the potential relationship between long-term antiviral therapy and mitochondrial epigenetic regulation. Nevertheless, these preliminary findings contribute to the limited body of clinical data exploring mitochondrial epigenetic modulation in patients with CHB receiving long-term NA therapy.

Study Limitations

This study has several limitations. The relatively small sample size may have reduced statistical power and limited the generalizability of the findings. Furthermore, the retrospective design restricted the availability of detailed clinical and laboratory data.

The epigenetic analysis was conducted in a limited subgroup of patients and restricted to DNMT1 expression due to practical limitations. The inability to assess additional mitochondrial epigenetic regulators limits mechanistic interpretation. Nevertheless, this study provides preliminary insights into the potential epigenetic effects of NA therapy and may serve as a foundation for future studies.

Conclusion

Long-term NA therapy in patients with CHB was associated with modest longitudinal changes in renal function. While these findings are consistent with previous reports suggesting potential nephrotoxic effects of antiviral therapy, the observed decline in renal function may also partially reflect age-related physiological changes. Therefore, careful assessment of baseline renal function and regular monitoring during therapy remain important in clinical practice. The exploratory evaluation of DNMT1 expression did not reveal significant differences between treated and untreated patients, and therefore does provide direct evidence for mitochondrial epigenetic alterations associated with therapy. Nevertheless, these findings contribute to the limited clinical data exploring mitochondrial epigenetic regulation in the context of long-term antiviral treatment. Larger prospective studies are needed to clarify the potential relationship between antiviral therapy, mitochondrial function, and renal outcomes.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Aydın Adnan Menderes University Clinical Research Ethics Committee (approval no: 2019/07, date: 11/06/2020).

Informed Consent: Informed consent was obtained from the patients included in the pilot epigenetic part of the study.

Footnotes

Authorship Contributions

Concept: G.U.G., S.K., M.K.E., Design: G.U.G., S.K., M.K.E., H.Ö., Data Collection or Processing: G.U.G., C.A., M.K.E., Analysis or Interpretation: G.U.G., S.K., H.Ö., Literature Search: G.U.G., S.K., C.A., Writing: G.U.G., S.K., H.Ö.

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

Financial Disclosure: This research was supported by Aydın Adnan Menderes University Research Fund (project number: TPF-19038).

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Research Article 60

DOI: 10.4274/vhd.galenos.2026.2025-12-2
Viral Hepat J 2026;32(2):60-65

Has the COVID-19 Pandemic Affected HBsAg Seroclearance Rates in Chronic Hepatitis B Patients?

COVID-19 Pandemisi Kronik Hepatit B Hastalarında HBsAg Seroklirens Oranlarını Etkiledi mi?

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ABSTRACT

Objectives: The aim of this study is to document the increase in hepatitis B surface antigen (HBsAg) seroclearance that we observed during the coronavirus disease-2019 (COVID-19) pandemic.

Materials and Methods: Patients with chronic hepatitis B aged 18 years and older who were followed between 2010 and 2023 at three hospitals in Türkiye were included in this study. Rates of HBsAg seroclearance, seroconversion, and serological response among the patients were determined. Data from patients other than those who developed HBsAg seroclearance before the COVID-19 pandemic (before 2020) were analyzed.

Results: A total of 188 patients were included in the study. In total, 26 (13.8%) patients developed HBsAg seroclearance, 28 (15%) developed HBsAg seroconversion, and 21 (11.2%) developed a serological response. Of the patients who developed HBsAg seroclearance, 22 (84.6%) occurred in 2020 or later, and 4 (15.4%) occurred before 2020. The annual incidence rates of HBsAg seroclearance were 0.78% in 2014, 0.6% in 2017, 1.15% in 2019, 1.71% in 2020, 2.23% in 2021, 7.4% in 2022, and 1.2% in 2023. 95% of the patients were vaccinated with Pfizer-BioNTech and/or Sinovac-CoronaVac vaccines, and 36.4% had a COVID-19 infection.

Conclusion: In this study, the annual incidence rate of HBsAg seroclearance in the pre-pandemic period was consistent with the

ÖZ

Amaç: Bu çalışmanın amacı, koronavirüs hastalığı-2019 (COVID-19) pandemisi sırasında gözlemlediğimiz hepatit B yüzey antijeni (HBsAg) seroklirensindeki artışı belgelemektir.

Gereç ve Yöntemler: Bu çalışmaya, Türkiye'deki üç hastanede 2010-2023 yılları arasında takip edilen 18 yaş ve üzeri kronik hepatit B hastaları dahil edildi. Hastaların HBsAg seroklirens, HBsAg serokonversiyonu ve serolojik yanıt oranları belirlendi. COVID-19 pandemisinden önce (2020 öncesi) HBsAg seroklirensi gelişen hastalar dışındaki hastaların verileri analiz edildi.

Bulgular: Çalışmaya toplam 188 hasta dahil edildi. Toplamda 26 (%13,8) hastada HBsAg seroklirensi, 28 hastada (%15) HBsAg serokonversiyonu ve 21 (%11,2) hastada serolojik yanıt gelişti. HBsAg seroklirensi gelişen hastaların 22'si (%84,6) 2020 ve sonrasında, 4'ü (%15,4) ise 2020 öncesi dönemdeydi. HBsAg seroklirensinin yıllık görülme oranları sırasıyla 2014'te %0,78, 2017'de %0,6, 2019'da %1,15, 2020'de %1,71, 2021'de %2,23, 2022'de %7,4 ve 2023'te %1,2 idi. Hastaların %95'i Pfizer-BioNTech ve/veya Sinovac-CoronaVac aşılarıyla aşılanmış ve %36,4'ünde COVID-19 enfeksiyonu tespit edilmiştir.

Sonuç: Bu çalışmada, pandemi öncesi dönemde HBsAg serokleransının yıllık görülme sıklığı literatürle tutarlıydı (%0-1,15), ancak bu oran

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Received: 15.12.2025 **Accepted:** 17.07.2026 **Epub:** 22.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Mumcu N, Taştan S, Balcı Sandıkçı B, Cevahir F, Gözel MG, Altındiş M. Has the COVID-19 pandemic affected HBsAg seroclearance rates in chronic hepatitis B patients? Viral Hepat J. 2026;32(2):60-65

literature (0-1.15%), but this rate tended to increase during the pandemic (7.4%). We suggest that this increase may be related to COVID-19 infection and vaccination.
Keywords: Hepatitis B, COVID-19, HBsAg seroclearance

pandemiyle birlikte artma eğilimindeydi (%7,4). Bu artışın nedenlerinin COVID-19 enfeksiyonu ve aşı ile ilgili olabileceğini düşünmekteyiz.
Anahtar Kelimeler: Hepatit B, COVID-19, HBsAg seroklirensi

Introduction

Hepatitis B virus (HBV) infection remains a significant global public health problem, causing substantial morbidity and mortality. All patients with chronic hepatitis B (CHB) have a high-risk of progression to cirrhosis and hepatocellular carcinoma (HCC). The main aim of treatment is to prevent the progression of the disease by suppressing HBV replication and to achieve the loss of hepatitis B surface antigen (HBsAg), which is the desired optimal end point (1,2). HBsAg can also be cleared from the patient's blood during the natural course of CHB. Loss of HBsAg can prevent disease progression to cirrhosis or HCC and increase the survival rate of affected patients (1,3). Factors such as age, gender, medication use, HBeAg (HBV e antigen, secreted dimeric protein) negativity, low HBV-DNA level and low HBsAg level are effective in HBsAg seroclearance and seroconversion (4,5). Spontaneous HBsAg seroclearance in patients with CHB infection varies by 0.5-1% per year (1,5,6).

Coronavirus disease-2019 (COVID-19) is a respiratory disease that can cause clinical manifestations of varying severity, ranging from upper respiratory tract infection to pneumonia, acute respiratory distress syndrome, and death. Although the main target of the new severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is the respiratory system, it can also affect other organs and systems such as the gastrointestinal system, hepatobiliary, cardiovascular, renal and central nervous systems (7). It also causes impairment of both acquired and innate immunity (8). It has also been reported in the literature that COVID-19 infection and vaccines cause reactivation of latent infections and opportunistic infections (9,10,11,12). Some studies (13,14) stated that the severity of disease and mortality rates were lower or that there was no difference in patients with CHB co-infection with COVID-19, while other studies (15,16,17) stated that co-infection caused a more severe clinical picture. Although many studies have investigated the relationship between COVID-19 and CHB co-infection, the association between these two infections has not been fully elucidated.

We observed an increase in HBsAg seroclearance among CHB patients who presented to our outpatient clinic after the coronavirus outbreak in 2019. We found no studies investigating whether COVID-19 infection affects HBsAg seroclearance. This study was conducted to document this observed increase.

Materials and Methods

Patients and Study Plan

This multicenter observational study was conducted in the infectious diseases and clinical microbiology units of two state hospitals and one university hospital located in different provinces of Türkiye.

Demographic data, comorbid diseases, HBV diagnosis date, treatments received and treatment durations, HBsAg seroclearance and seroconversion status and dates, and HBeAg and anti-HBe (serum antibodies against HBeAg) serological status for all patients were recorded on the prepared form. In addition, whether they had received the COVID-19 vaccine, which type and how many doses they had received, and whether they had a COVID-19 infection [confirmed by SARS-CoV-2 polymerase chain reaction (PCR)] were also examined. Patients who showed a serological response and did not have cirrhosis were followed for one year.

HBsAg seroclearance, seroconversion, and serological response rates among CHB patients followed in designated centers between 2010 and 2023 were determined. Data from patients other than patients who developed HBsAg seroclearance before the COVID-19 pandemic (before 2020) were analyzed. Patients who developed HBsAg seroclearance were not included in the evaluation the following year.

Inclusion Criteria

Patients with CHB aged 18 years or older who regularly attended follow-up appointments at these centers between 2010 and 2023 were included in the study.

Methods Used for Virological Markers

Serological tests were performed using a third-generation enzyme immunoassay for HBsAg, HBeAg, anti-HBe, and anti-HBs (Cobas; Roche, USA). HBsAg values were considered negative if between 0 and 1, and positive if >1. Anti-HBs values were considered negative if 0-10 and positive if >10. HBV-DNA level was measured by the real-time PCR (RT-PCR) method (Abbott real-time HBV; Abbott Laboratories, Germany). HBV-DNA levels below 10 IU/mL were considered negative.

Definitions

HBsAg seroclearance was defined as negative results in two consecutive serum samples, taken at least 6 months apart. HBsAg seroconversion was defined as the presence of anti-HBs antibodies (>10 IU/L) persisting for more than 6 months. The serological response to HBsAg is defined as HBsAg loss, i.e., HBsAg seroconversion (development of anti-HBs). Reduction of HBV-DNA to a level undetectable by PCR was defined as negativity (1,18,19).

Statistical Analysis

Descriptive statistics for all patients and for those who developed seroclearance after 2020 were evaluated using the SPSS 25.0 statistical package. Median (minimum-maximum) values were reported; the Shapiro-Wilk normality test was applied to continuous variables.

Ethics Committee Approval

The study protocol was approved by the Kafkas University Ethics Committee (decision no: 2022/03, date: 31.03.2022). Due to

the retrospective nature of the study, the requirement for informed consent was waived by the Ethics Committee.

Results

A total of 188 patients were included in the study. Most patients (91%) were HBeAg seronegative, and the average follow-up period was 10 years. In total, HBsAg seroclearance was detected in 26 patients (13.8%), HBsAg seroconversion in 28 patients (15%), and a serological response in 21 patients (11.1%). Of the patients who developed HBsAg seroclearance, 22 (84.6%) were in 2020 and later, and four (15.4%) were in the period before 2020. The annual incidence rates of HBsAg seroclearance are 0.78% (1/128) in 2014, 0.6% (1/168) in 2017, 1.15% (2/174) in 2019, 1.71% (3/175) in 2020, 2.23% (4/179) in 2021, 7.4% (13/175) in 2022, and 1.2% (2/162) in 2023, respectively (Table 1). Figure 1 shows the distribution of HBsAg seroclearance rates by year.

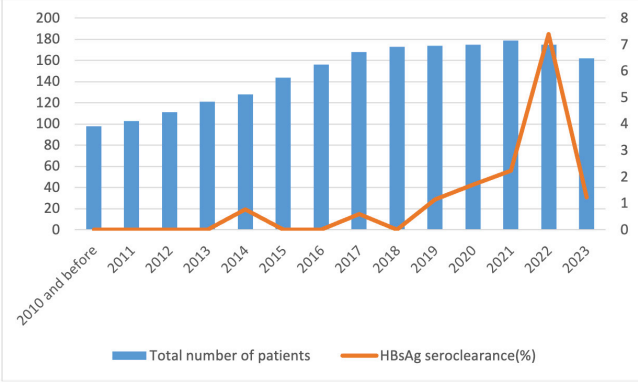

Figure 1. Distribution of HBsAg seroclearance rates by years
HBsAg: Hepatitis B surface antigen

Data from four patients whose HBsAg seroclearance occurred in the pre-pandemic period (before 2020) were not analyzed. Demographic data; comorbidities and treatment status; COVID-19 vaccination status and vaccine types; COVID-19 infection status; and other serological conditions for the remaining 184 patients and the 22 patients who developed HBsAg seroclearance in 2020 and later are presented in Table 2. The ages of the patients ranged from 25 to 88 years, with a median age of 53 years; most patients were male (59.8%). 46.7% of the patients had at least one comorbidity, and the three most common diseases were hypertension, diabetes mellitus, and cirrhosis (33.2%, 20.1%, and 6.5%, respectively). Most patients were HBeAg seronegative (90.7%) and anti-HBe positive (90.2%). Anti-HBs antibody was positive in 24 (13%) patients; a serological response to HBsAg was observed in 17 patients (9.2%); and anti-HBs antibody was detected in 7 (13.8%) patients despite HBsAg positivity (Table 2).

60.3% (n=111) of the patients had been receiving nucleos(t)ide treatment for an average of 60 months [of whom 64.8% (n=72) received tenofovir disoproxil, 28% (n=31) received entecavir, and 7.2% (n=8) received tenofovir alafenamide fumarate]. The final HBV-DNA level was negative in 69% of all patients. The treatment initiation date for 23.5% of patients was in 2020 or later (Table 2). Of the 111 patients treated, HBsAg seroclearance, HBsAg seroconversion, and serological response were detected in three (2.7%), three (2.7%), and two (1.8%) patients, respectively. HBsAg seroclearance was detected in 19 of 73 untreated patients (26%).

95% of patients had received at least one vaccine (Pfizer-BioNTech and/or Sinovac-CoronaVac). 53.3% received only Pfizer-BioNTech vaccines, 15.8% received only Sinovac-CoronaVac vaccines, and 26.1% received both Pfizer-BioNTech and Sinovac-CoronaVac vaccines. The average number of COVID-19 vaccine doses among the cases was 3. 36.4% of the cases had a COVID-19 infection, and 96.7% (n=178) had either received the COVID-19 vaccine or been infected (Table 2).

Table 1. Distribution of patients and HBsAg seroclearance rates by years

Years	Number of people followed (n)	HBsAg seroclearance (n)	Annual HBsAg seroclearance rate (per 100 persons/year)
2010	98	0	0
2011	103	0	0
2012	111	0	0
2013	121	0	0
2014	128	1	0.78
2015	144	0	0
2016	156	0	0
2017	168	1	0.6
2018	173	0	0
2019	174	2	1.15
2020	175	3	1.71
2021	179	4	2.23
2022	175	13	7.42
2023	164	2	1.21

HBsAg: Hepatitis B surface antigen

Table 2. Basic characteristics, COVID-19 vaccination and infection status, and other serological conditions of 184 patients and 22 patients who developed HBsAg seroclearance in 2020 and later

Variables	Total n=184 (%)	HBsAg seroclearance (2020 and later) n=22 (%)
Age median (min-max)	53 (25-88)	54 (32-72)
Male gender	110 (59.8)	18 (81.8)
Comorbidity Hypertension Diabetes mellitus Cirrhosis	86 (46.7) 61 (33.2) 37 (20.1) 12 (6.5)	14 (63.6) 13 (59.1) 6 (27.3) 1 (4.5)
Anti-HBs-positive status	24 (13)	17 (77.3)
HBsAg/anti-HBs double positive	7 (3.8)	-
Serological response for HBsAg	17 (9.2)	17 (77.3)
HBeAg-negative status	167 (90.7)	22 (100.0)
Anti HBe-positive status	166 (90.2)	22 (100.0)
Nucleosis(t)id treatment Tenofovir disoproxil Entecavir Tenofovir alafenamide fumarate	111 (60.3) 72 (64.8) 31 (28) 8 (7.2)	3 (13.6) 3 (100) 0 (0) 0 (0)
Tenofovir treatment duration (month)	60 (1-156)	108 (36-120)
Entecavir treatment duration (month)	48 (3-180)	0
Tenofovir alafenamide fumarate (month)	24 (10-48)	0
HBV-DNA negative	127 (69%)*	21 (95.4)#
COVID-19 vaccine Pfizer-BioNTech Sinovac-CoronaVac Pfizer-BioNTech and *Sinovac*-CoronaVac	175 (95%) 98 (53.3) 29 (15.8) 48 (26.1)	20 (91%) 12 (54.5) 1 (4.5) 7 (31.8)
Having COVID-19 infection	67 (36.4)	8 (36.4)
Vaccinated or infected with COVID-19	178 (96.7)	22 (100.0)
Total COVID-19 vaccination dose (mean)	3 (1-5)	3 (1-5)
Pfizer-BioNTech vaccine dose (mean)	2 (1-4)	2 (1-3)
Sinovac-CoronaVac vaccine dose (mean)	2 (1-5)	2 (2-5)

*: The last value measured at the time inclusion in the study
#: The value measured at the time HBsAg seroclearance developed. HBsAg: Hepatitis B surface antigen, COVID-19: Coronavirus disease-2019, HBV: Hepatitis B virus

Among 178 patients who contracted COVID-19 infection and/or were vaccinated during the pandemic, HBsAg seroclearance was detected in 22 (12.3%), HBsAg seroconversion in 22 (12.3%), and serological response in 17 (9.5%). Of the six patients who had not had a COVID-19 infection or had not been vaccinated during the pandemic, none showed HBsAg serological responses. HBsAg seroconversion was detected in two (33.3%) patients.

Discussion

In CHB, HBsAg seroclearance and seroconversion are important events in controlling the disease and preventing complications and constitute the main goal of treatment (5). In this study, annual HBsAg seroclearance rates increased during the pandemic period and peaked in 2022 (7.4%); the 10-year cumulative incidence rate of HBsAg seroclearance was 13.8% (Figure 1).

The main goal of treatment for CHB is to achieve HBsAg loss, which is the optimal endpoint. Spontaneous HBsAg loss may also occur over the long term in patients who do not receive treatment. Spontaneous HBsAg seroclearance is rare, with an incidence of only 1.5. Kobayashi et al. (4) found annual HBsAg seroclearance rates as 1.65% in the patient group not receiving treatment and 2.05% in the patient group receiving treatment. It is reported that the annual seroclearance rates of HBsAg are 2.4% in China (20),1.15% in Taiwan (21), and 0.5% in Alaska (22). Additionally, an analysis reported that annual HBsAg seroclearance rates were between 0.5% and 1% (5). Türkiye is a moderately endemic region (4%) in terms of CHB and the dominant genotype is D (23). In this study, the annual incidence rate of HBsAg seroclearance was 0-1. 15% in the pre-pandemic period, consistent with the literature; however, during the pandemic this rate showed an increasing trend and was found to be 7.4% in 2022 (Figure 1, Table 1). In a systematic review where the cumulative

incidence rates of HBsAg seroclearance were evaluated, the 10-year cumulative incidence rate was reported to be 8.16% (95% confidence interval, 5.24-11.72) in 12 studies analyzed (24). In this study, the 10-year cumulative incidence rate of HBsAg seroclearance (13.8%) was significantly higher than previously reported values. Differences in seroclearance rates of HBsAg by country may be related to variation in HBV genotypes and treatment conditions. Additionally, previous studies have found that factors such as age (≥50 years), gender (male), medication use, HBeAg negativity, low HBV-DNA level and low HBsAg level are effective in HBsAg seroclearance (4,5,24). In this study, most (81.8%) of the patients who developed HBsAg seroclearance were male; their median age was 54 years; all (100%) were HBeAg negative; and only three (13.6%) patients were receiving nucleos(t)ide therapy. HBV-DNA levels were negative in all but one patient at the time of seroclearance (Table 2).

In the study by Masrour-Roudsari et al. (19), the HBsAg seroconversion rate was found to be 5.5% and the serological response rate was 5% at an average follow-up of 15 years. In our study, at an average follow-up of 10 years, the HBsAg seroconversion and serological response rates were higher than those reported in the literature, at 13% and 9.2%, respectively.

Previous studies have reported that even in HBeAg-negative patients treated with nucleos(t)ide analogs for many years, HBsAg seroclearance and seroconversion rates are low and these rates are not related to treatment history (4,6,19,24). In the study conducted by Masrour-Roudsari et al. (19), HBsAg seroclearance was observed in 2.6% of the treated patients and HBsAg seroconversion in 2.6% of the treated patients during a 15-year follow-up. In our study, HBsAg seroclearance and HBsAg seroconversion were each observed in 2.7% of the treated patients during a 10-year follow-up.

In this study, although the factors affecting HBsAg seroclearance were similar to those previously reported, the annual and cumulative HBsAg seroclearance rates after the COVID-19 pandemic were significantly higher than those in the pre-pandemic period. However, we could not determine the reasons for this increase. In our study, all patients who developed post-pandemic seroclearance were either vaccinated against COVID-19 or had a COVID-19 infection, and 86.3% of the patients had received an average of two doses of the mRNA (Pfizer-BioNTech) vaccine (Table 2). While there are many studies investigating the relationship between COVID-19 infection and vaccines and CHB (25,26,27) in the literature, the interaction between these two infections and how the COVID-19 pandemic affected the course of hepatitis B infection remains unclear.

Study Limitations

Our study had some limitations. Statistical analysis could not be performed because the number of patients was small and most patients had either received the COVID-19 vaccine or had been infected with COVID-19. In addition, due to excessive strain on the healthcare system during the COVID-19 pandemic, routine check-ups of CHB patients were disrupted, and the course of the patients' biochemical parameters during this period could not be followed.

Conclusion

Although the reasons were not identified in this study, we found a significant increase in HBsAg seroclearance during the COVID-19 pandemic. We believe that this significant increase in HBsAg seroclearance during the pandemic should be investigated in more comprehensive studies.

Ethics

Ethics Committee Approval: The study protocol was approved by the Kafkas University Ethics Committee (decision no: 2022/03, date: 31.03.2022).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived by the Ethics Committee.

Footnotes

Authorship Contributions

Concept: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Design: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Data Collection or Processing: N.M., S.T., B.B.S., Analysis or Interpretation: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Literature Search: N.M., S.T., B.B.S., F.C., M.G.G., M.A., Writing: N.M., F.C.

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

Financial Disclosure: The authors declare no financial support.

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Research Article

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DOI: 10.4274/vhd.galenos.2026.2026-6-4
Viral Hepat J 2026;32(2):66-75

Cost-Effectiveness of Improving Hepatitis C Diagnosis and Treatment among People Who Inject Drugs in Türkiye

Türkiye'de Damar İçi Madde Kullanımı Olan Kişilerde Hepatit C Tanı ve Tedavisinin İyileştirilmesinin Maliyet-Etkililiği

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ABSTRACT

Objectives: This study aimed to develop a mathematical model of hepatitis C virus (HCV) transmission and disease progression among people who inject drugs (PWID) in Türkiye and to evaluate the cost-effectiveness of improving diagnosis and treatment over a 10-year time horizon.

Materials and Methods: A dynamic compartmental model was developed to estimate annual HCV prevalence and HCV-related mortality under four diagnosis-and-treatment coverage scenarios ranging from no diagnosis-and-treatment to high diagnosis-and-treatment coverage. A Bernoulli transmission model was used to estimate the force of infection and incorporated into the compartmental framework. Economic outcomes, including testing and treatment costs, and health outcomes, including infections prevented and quality-adjusted life years (QALYs), were projected for each scenario between 2020 and 2029. Incremental cost-effectiveness ratios (ICERs) were estimated for increasing diagnosis-and-treatment rates.

Results: Increasing diagnosis-and-treatment rates to 25%, 50%, and 75% compared with the no diagnosis-and-treatment scenario reduced cumulative HCV cases by 61%, 91%, and 98% over 10 years, respectively. HCV-related mortality decreased by 58%, 78%, and 86%, respectively. Increasing diagnosis-and-treatment coverage from 0% to 25% resulted in ICERs of $5,092 per infection prevented and $25,653 per QALY gained. Pairwise comparison of the 25% and 50% scenarios yielded ICERs of $880 per infection prevented and $4,715 per QALY gained. However, frontier analysis identified the medium strategy as dominated, as the high diagnosis-and-treatment strategy achieved greater health gains at a lower total cost and was therefore cost-saving.

Conclusion: PWID represent a key population in HCV transmission dynamics. Improving diagnosis and treatment among PWID in

ÖZ

Amaç: Bu çalışmanın amacı, Türkiye'de damar içi madde kullanan (DİMK) kişilerde hepatit C virüsü (HCV) bulaşı ve hastalık ilerlemesini modelleyen matematiksel bir model geliştirmek ve tanı ile tedavinin iyileştirilmesinin 10 yıllık bir zaman ufkunda maliyet-etkililiğini değerlendirmektir.

Gereç ve Yöntemler: Yıllık HCV prevalansı ve HCV'ye bağlı mortaliteyi, tanı ve tedavi yapılmayan senaryodan yüksek tanı ve tedavi kapsamına kadar uzanan dört farklı tanı ve tedavi kapsamı senaryosu altında tahmin etmek amacıyla dinamik bir kompartıman modeli geliştirilmiştir. Enfeksiyon kuvveti Bernoulli bulaş modeli kullanılarak tahmin edilmiş ve kompartıman modeline entegre edilmiştir. Test ve tedavi maliyetlerini içeren ekonomik sonuçlar ile önlenen enfeksiyon sayısı ve kaliteye uyarlanmış yaşam yıllarını (QALY) içeren sağlık sonuçları, 2020-2029 dönemi için her bir senaryo kapsamında projekte edilmiştir. Artan tanı ve tedavi oranları için artımlı maliyet-etkililik oranları (ICER) hesaplanmıştır.

Bulgular: Tanı ve tedavi oranının tanı ve tedavi yapılmayan senaryoya kıyasla %25, %50 ve %75'e yükseltilmesi, 10 yıllık dönemde kümülatif HCV olgu sayısını sırasıyla %61, %91 ve %98 azaltmıştır. HCV'ye bağlı mortalite ise sırasıyla %58, %78 ve %86 oranında azalmıştır. Tanı ve tedavi kapsamının %0'dan %25'e çıkarılması, önlenen enfeksiyon başına 5.092 ABD doları ve kazanılan QALY başına 25.653 ABD doları ICER ile sonuçlanmıştır. Tanı ve tedavi kapsamının %25'ten %50'ye çıkarılması, önlenen enfeksiyon başına 880 ABD doları ve kazanılan QALY başına 4.715 ABD doları ICER sağlamıştır. Bununla birlikte, maliyet-etkililik sınırı analizinde orta senaryonun, daha düşük maliyetle daha fazla sağlık kazanımı sağlayan yüksek senaryo tarafından domine edildiği gösterilmiş; yüksek tanı ve tedavi kapsamı maliyet tasarrufu sağlayan strateji olarak belirlenmiştir.

Sonuç: DİMK, HCV bulaş dinamiklerinde kilit bir risk grubunu oluşturmaktadır. Bu grupta tanı stratejilerinin geliştirilmesi ve tedaviye erişimin artırılması, Türkiye açısından maliyet-etkili, hatta maliyet tasarrufu

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Received: 25.06.2026 **Accepted:** 28.07.2026 **Publication Date:** 01.09.2026

Cite this article as: Yaylalı E, Üçler Ş, Üser Ü, Tabak F. Cost-effectiveness of improving hepatitis C diagnosis and treatment among people who inject drugs in Türkiye. Viral Hepat J. 2026;32(2):66-75

Türkiye could be cost-effective, and potentially cost-saving, while also contributing substantially toward achieving World Health Organization HCV elimination targets.
Keywords: Mathematical modelling, hepatitis C, cost-effectiveness analysis, testing and diagnosis

sağlayan bir yaklaşım olabilir ve aynı zamanda Dünya Sağlık Örgütü'nün HCV eliminasyon hedeflerine ulaşılmasına önemli katkı sağlayabilir.
Anahtar Kelimeler: Matematiksel modelleme, hepatit C, maliyet-etkililik analizi, test ve teşhis

Introduction

There are around 11 million people who inject drugs (PWID) globally and 39.4% have hepatitis C infection (1). The global rise in drug use, particularly injection drug use (IDU), has been pronounced in recent years, with notable increases reported across Europe and the Middle East (2,3). PWID are at heightened risk for blood-borne infections due to high-risk behaviors such as needle and equipment sharing. Hepatitis C virus (HCV) is especially prevalent in this population, with global estimates indicating a seroprevalence of approximately 67% among PWID (4). It is estimated that nearly 10 million PWID have been infected with HCV, with annual incidence rates ranging from 5% to 45% (5). A key challenge in controlling HCV transmission among PWID is the asymptomatic nature of the disease, which contributes to a substantial proportion of undiagnosed cases and the continuation of risky behaviors.

Türkiye's geopolitical position as a transit corridor between Europe and Asia further elevates its vulnerability to drug trafficking and associated public health risks. Despite this, there is currently no comprehensive national screening or surveillance program for HCV, impeding efforts to quantify and control the epidemic. Estimates place the national HCV prevalence around 1% (6,7); however, reliable data specific to the PWID population remain scarce. One of the few studies available reported an HCV seroprevalence of 47.1% among 4,694 inpatients at substance use treatment centers across Türkiye between 2012 and 2013 (8). Given the increasing trends in IDU and the absence of systematic monitoring, there is a pressing need to estimate the burden of HCV among PWID in Türkiye and to evaluate cost-effective prevention and treatment strategies tailored to this high-risk group.

Türkiye-specific HCV modelling and economic evaluation studies demonstrate that improving treatment rates are cost-effective in national scale and targeted screening and treatment for high-risk populations such as PWID, prisoners and refugees may yield substantial mortality reductions (9). Models by Örmeci et al. (10) and Idilman et al. (11) utilized Markov-based frameworks to evaluate the impact of improving treatment and reaching World Health Organization (WHO) targets, reporting up to 80% decrease in the number of infections and liver-related deaths. Although Idilman et al. (11) emphasize priority subpopulations, including PWID, these groups are not explicitly represented within the model structure.

Similarly, Çekin et al. (9) incorporated high-risk populations such as PWID, men who have sex with men, prisoners and refugees into their analysis; however, the underlying transmission dynamics within these populations were not explicitly defined. Despite these important contributions, a gap remains in integrating transmission dynamics, behavioral determinants of infection risk, and economic evaluation within a unified framework tailored specifically to PWID in Türkiye. This study addresses this gap by explicitly modeling PWID transmission dynamics—linking needle-sharing behavior to force of infection through a Bernoulli-based model and dynamic compartmental model—and embedding this within a cost-effectiveness framework to evaluate both epidemiologic and economic outcomes of diagnosis and treatment scale-up.

Materials and Methods

We developed a mathematical model of HCV transmission and progression for the 15-65 years old PWID population to understand HCV dynamics and to evaluate the cost-effectiveness of improved diagnosis and treatment in Türkiye for a 10-years interval. We utilized two models: Bernoulli process model and a dynamic compartmental model. Both models are populated with epidemiological, clinical, demographic and economic data from various sources and literature. Details of the model and data are explained in this section. This study was performed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (12) and the CHEERS checklist of the study is in the Supplemental Appendix. Since this study is based on mathematical modeling and simulation, no statistical analyses were performed.

Population and Data

The target population includes PWID aged 15-64 years in Türkiye. The population size of PWID is estimated from the United Nations global PWID study (13) with an HCV prevalence of 47% (8).

We used a cohort of 2,719 HCV patients collected across 32 centers in Türkiye. The cohort retrospectively collected in 2019 and includes a wide range of information such as demographic data, laboratory results, and treatment regimens. In our study, we utilized the fibrosis score distribution of the patients and the percentage of the patients with decompensated cirrhosis from this dataset to inform the initial conditions of our model. We only included the treatment-naïve Hepatitis C population.

The data extracted from the patient cohort were anonymized. The principal investigator of the cohort, who is also co-author of the submitted study permitted the use of cohort data for the study. Data extracted from cohort database were anonymized before access and analysis. Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa (approval no: 59491012-604.01.02, date: March 07, 2017). Verbal consent was obtained from all participants. The study was recorded on clinical trials.gov (https://clinicaltrials.gov/study/NCT03145844). The trial registry name was "Direct Acting Agents in Hepatitis C Patients (HEPCTURKEY)" and the registration number was NCT03145844.

Model Structure

Our model structure incorporates two modeling approaches: the Bernoulli process model and a dynamic compartmental model. The Bernoulli model was used to estimate the force of infection—defined as the per capita rate at which susceptible individuals contract the infection (14)—by incorporating transmission probabilities and contact rates. The dynamic compartmental model was employed to simulate HCV transmission and disease progression among the PWID population.

Bernoulli Process Model

The Bernoulli model was used to estimate HCV transmission risk associated with IDU. Each act of IDU is considered an independent Bernoulli trial, resulting in one of two outcomes: transmission occurs or does not occur. The infectivity of HCV per injection, denoted as a_p represents the probability of transmission during a single injection event. The number of contacts per year, represented by *m*, is calculated by multiplying the needle-sharing rate *x* by the annual number of injections *y*. All parameter values used in the Bernoulli model are presented in Table 1.

Table 1. Parameters of Bernoulli model

Parameters (symbol)	Value	Source
Transmission probability of a single injection (a_p)	0.001	(15)
Needle sharing rate (*x*)	0.73	(8)
Annual number of injections (*y*)	368	(15)
Number of contacts per year (*m*)	269	Calculated
Cumulative probability of HCV transmission (*q*)	0.24	Calculated with Eq. 1

HCV: Hepatitis C virus

The cumulative probability of HCV transmission through IDU q is given in Equation 1.

$$q = 1 - (1 - a_p)^m \quad \text{(Equation 1)}$$

The cumulative annual transmission probability (*q*) was incorporated into the dynamic compartmental model as the annual transmission coefficient. Assuming homogeneous mixing among PWID, the force of infection was defined in the Equation 2.

$$\lambda(t) = q\frac{I(t)}{N(t)} \quad \text{(Equation 2)}$$

where *I(t)* denotes the number of infectious PWID and *N(t)* the total PWID population. Thus, *I(t)/N(t)* represents the proportion of infectious injecting partners, and *λ(t)* defines the annual rate at which susceptible individuals acquire HCV infection and transition to the acute infection compartment. The complete formulation of the force of infection and the system of differential equations are provided in the Supplemental Appendix.

Dynamic Compartmental Model

The transmission and progression of HCV are captured through a dynamic compartmental model over a 10-year time horizon (2019-2029). The population is stratified by infection status (HCV-negative, HCV-positive), fibrosis stage [acute, F0-F1, F2-F3, F4, decompensated cirrhosis, hepatocellular carcinoma (HCC)], treatment status (on and not on treatment at each stage), recovery, and death—resulting in a total of 14 compartments, as illustrated in Figure 1.

The model is specified as a system of ordinary differential equations and solved numerically in R. The model formulation is shown in the Supplemental Appendix. Parameter values are provided in Table 2. The transition from the HCV-negative compartment to acute infection is governed by the force of infection, which is

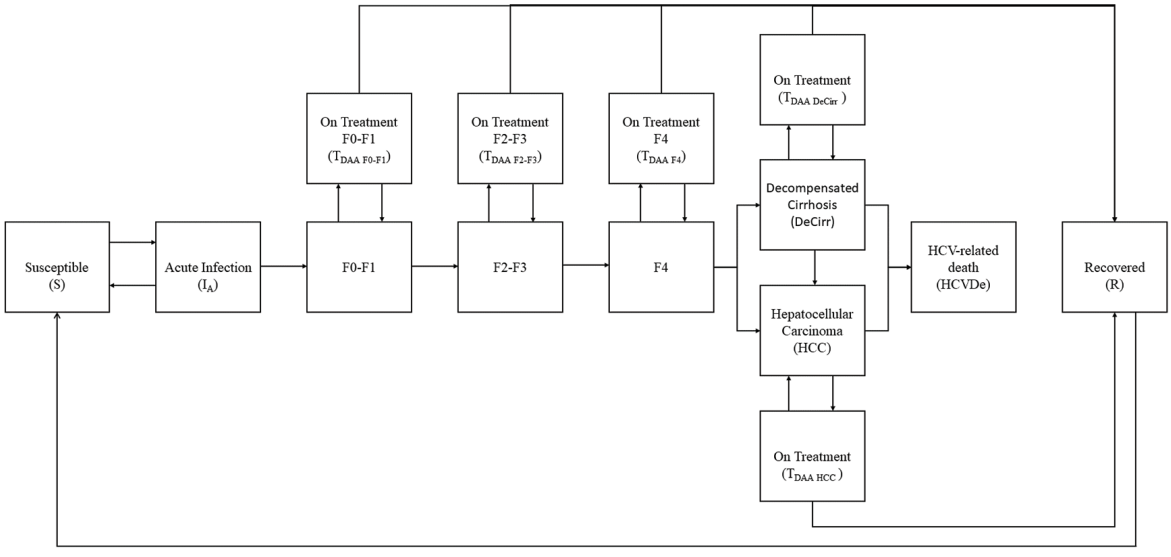

Figure 1. HCV model flow chart
HCV: Hepatitis C virus

informed by the cumulative transmission probability estimated from the Bernoulli model (see Equation 1). This integration allows the compartmental model to reflect injection-related transmission dynamics specific to the PWID population.

We modeled acute HCV infection with a fixed average duration of 6 months. At the end of the acute phase, 25% of incident infections are assumed to spontaneously clear and return to the susceptible state, while the remainder progress to chronic infection. Individuals who clear infection naturally or achieve sustained virologic response (SVR) after direct-acting antiviral (DAA) therapy are assumed to become susceptible again, allowing reinfections. Reinfection following successful DAA treatment has been documented, with elevated risk among PWID due to ongoing exposure through injecting networks (16,17,18).

Because of the lack of surveillance data, the true diagnosis rate of HCV in Türkiye is unknown. In our model, we implemented a scenario-based approach with four levels of diagnosis-and-treatment coverage: no coverage (0%), low (25%), medium (50%), and high (75%) of infected individuals. We assumed a 90% SVR following DAA therapy, reflecting a conservative estimate. Real-life studies from Türkiye, including recent long-term outcome analyses, have reported SVR12/24 rates between 85% and 100% across various regimens in chronic HCV (19,20,21,22,23,24,25), and systematic reviews and meta-analyses indicate that SVR rates may be lower in patients with decompensated cirrhosis or HCC (26,27,28,29).

Table 2. Key model parameters

Parameters (symbol)	**Values (ranges)**	**Source**
Percentage of HCV-positive initial population by disease stage, %		Dataset
F0-F1	42.7	
F2-F3	37.5	
F4	17.5	
Decompensated cirrhosis	2.3	
HCC	0	
HCV progression (rates across disease stages)		
Spontaneous clearance proportion (θ)	0.25 (0.21-0.29)	(20)
Duration of acute phase (ρ)	6 (1.6-2.5) months	(30)
Transition rate from F0/F1to F2/F3 (α_1)	0.195 (0.191-0.197)	(31)
Transition rate from F2/F3 to F4 (α_2)	0.2718 (0.2613-0.2824)	(31)
Transition rate from F4 to decompensated cirrhosis (v)	0.04 (0.032-0.052)	(32)
Transition rate from F4 to HCC (o)	0.021 (0.017-0.028)	(32)
Transition rate from decompensated cirrhosis to HCC (π)	0.021 (0.017-0.028)	(33)
HCV-related mortality rate		
Transition rate from HCC to HCV-related death (μ)	0.43 (0.32-0.5)	(33)
Transition rate from decompensated cirrhosis to HCV-related death (σ)	0.31 (0.13-0.40)	(32)
Treatment related parameters		
Treatment duration (χ)	12 (9.6-14.4) weeks	(20)
Proportion of achieving SVR among on DAA (γ)	0.9 (0.75-0.95)	(34)
Transition rate from recovered to susceptible (ψ)	1 (0.8-1.2) year	Expert opinion
Population parameters		
Initial population size (PWID)	396,772	(13)
Entry rate (c), %	0.7 (0.5-0.8)	(35)
The non-HCV related mortality rate (ω), %	0.5 (0.4-0.6)	(35)

HCV: Hepatitis C virus, HCC: Hepatocellular carcinoma, PWID: People who inject drugs, SVR: Sustained virologic response, DAA: Direct acting agents

Costs and QALYs

We incorporated HCV testing and treatment costs into the model based on published sources (Table 3). Testing costs included the anti-HCV antibody test for diagnosis, HCV-RNA testing for viral load confirmation, and FibroScan® assessment for fibrosis staging. DAA acquisition costs were included separately, based on average regimen prices reported in the literature. In Türkiye, DAAs have been reimbursed by the Social Security Institution (SGK) since 2016, making them accessible to all patients covered under the national health insurance scheme. In addition, treatment-related costs were stratified by disease stage, reflecting substantially higher expenditures for patients with advanced fibrosis, cirrhosis, HCC, or decompensated cirrhosis. All costs were estimated from the payer perspective and standardized to 2020 values using the health component of the Turkish consumer price index.

Health outcomes in the model is measured with quality-adjusted life years (QALYs). QALY values of each disaese stage and treatment status have been collected from the literature and presented in Table 4. In line with standard economic evaluation guidelines, both costs and health outcomes were discounted at an annual rate of 3% (36).

Scenario Analysis and Model Outcomes

Due to the absence of a national surveillance system for HCV, data on diagnosis rates are substantially limited in Türkiye. To assess the potential impact of diagnosis-and-treatment coverage on disease dynamics, we simulated four alternative scenarios within the compartmental model framework: (i) no diagnosis-and-treatment (0%), (ii) low diagnosis-and-treatment (25%), (iii) medium diagnosis-and-treatment (50%), and (iv) high diagnosis-and-treatment (75%). These values represent annual diagnosis-and-treatment coverage levels applied throughout the simulation period.

The intervention scenarios represent different levels of diagnosis and subsequent treatment coverage rather than diagnosis alone. In the model, individuals who are diagnosed are assumed to be promptly linked to care and initiate DAA treatment. This assumption reflects the Turkish healthcare system, in which universal health insurance through the SGK provides reimbursement for DAA therapy for all eligible patients with chronic HCV infection, minimizing financial barriers to treatment. Consequently, the intermediate steps of the care cascade (linkage to care, treatment initiation, and treatment completion) were not modeled explicitly. Following treatment, individuals achieve SVR according to the model parameter

Table 3. Test and treatment costs (10)

	Costs (USD)
Anti-HCV	3.84 (10)
HCV-RNA test/PCR	53.83 (10)
FibroScan®	105.73 (10)
Treatment cost by disease stage	
F0-F4	1,622 (10)
Cirrhosis	2,916 (10)
Decompensated cirrhosis	27,216 (10)
Hepatocellular carcinoma	35,980 (10)
DAA	31,470 (10)

HCV: Hepatitis C virus, PCR: Polymerase chain reaction, DAA: Direct acting agents

Table 4. QALYs by disease stage (37,38)

Input	**QALY**
Acute HCV infection	1*
On treatment for all heath states	0.95 (37)
F0-F1	0.93 (38)
F2-F3	0.83 (38)
F4 (cirrhosis)	0.81 (38)
Decompensated cirrhosis	0.70 (38)
Hepatocellular carcinoma	0.67 (38)
Recovered	1

*: Expert opinion, HCV: Hepatitis C virus, QALYs: Quality-adjusted life years

γ; those who do not achieve SVR continue to progress through the natural history of disease.

For each scenario, the model projected the annual changes in HCV prevalence and HCV-related mortality, as well as the corresponding healthcare costs and QALYs, over a 10-year time horizon. The outputs of these scenario analyses were compared to evaluate the relative epidemiological and economic implications of expanding diagnosis-and-treatment coverage among the target population.

Cost-Effectiveness Analysis

To evaluate the impact of diagnosis-and-treatment on HCV prevention, we conducted a cost-effectiveness analysis by estimating the incremental cost per QALY gained and per infection averted compared with the no diagnosis-and-treatment scenario. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs by the difference in health outcomes between each scenario and the next best alternative. To assess the sensitivity of the results to discounting assumptions, we repeated the analysis using discount rates of 0% and 5%, in addition to the base case of 3%.

Sensitivity Analysis

We conducted a one-way sensitivity analysis to assess the impact of parameter uncertainty on model outcomes. The parameter ranges used are presented in Table 2. Where available, ranges were derived from published literature; in the absence of empirical data, a ±20% variation from the base value was assumed. The analysis quantified the relative influence of each parameter on the projected number of HCV cases in 2029, using the medium diagnosis-and-treatment scenario as the reference case. Results were visualized using a tornado diagram to illustrate the parameters with the greatest impact on model outcomes.

Results

We present total number of HCV cases and HCV-related deaths under each scenario over 10-years period in Figure 2. Under the "no diagnosis" scenario, the number of HCV infections doubles in 10-years from around 180,000 cases in 2019 to 280,000 cases in 2029. A similar trend could be observed in the number of HCV-related deaths with an average increase of up to 26-fold in the absence of testing and treatment. While this case is unrealistic, it provides us with an upper limit on what could happen without any testing and treatment efforts. The low diagnosis-and-treatment scenario shows that total infected cases could decrease by 61% while the medium and high- diagnosis-and-treatment scenarios yield substantially larger reductions of 91% and 98%, respectively, highlighting the potential for disease elimination. For liver-related mortality, model projections represent cumulative outcomes; therefore, comparisons are made relative to the no-treatment scenario to better capture the impact on mortality. Over a 10-year horizon, low, medium, and high diagnosis-and-treatment scenarios are projected to reduce total HCV-related deaths by 58%, 78%, and 86%, respectively.

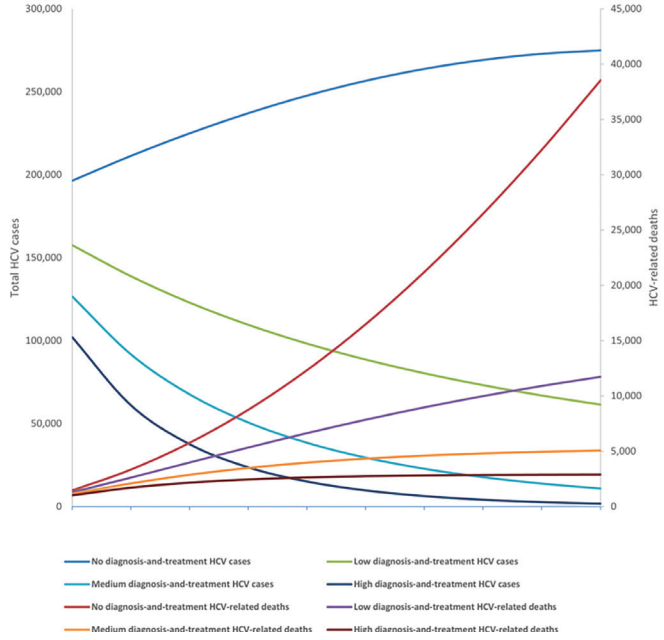

Figure 2. Estimated number of HCV cases and HCV-related deaths for no, low, medium and high diagnosis-and-treatment scenarios, 2020-2029
HCV: Hepatitis C virus

Figure 3 presents projections of acute infections and infections in F0-F4 stages across diagnosis-and-treatment scenarios. Consistent with the trends described above, the no diagnosis-and-treatment scenario shows persistently high levels of transmission and a growing chronic burden over time. In contrast, increasing diagnosis leads to a clear and progressive decline in both acute infections and total cases, with the steepest reductions observed under the high-diagnosis-and-treatment scenario.

This pattern is further reflected in the projected number of HCC and decompensated cirrhosis cases (Figure 4). The no diagnosis-and-treatment scenario results in the highest disease burden, whereas the low diagnosis-and-treatment scenario yields a 72% reduction in cases. Additional reductions of 17% and 5% are observed under the medium and high diagnosis-and-treatment scenarios, respectively, with HCC cases approaching near-zero levels under high diagnosis.

Cost-Effectiveness Analysis

Table 5 presents the cost-effectiveness results of improving diagnosis and treatment, with both costs and health outcomes discounted at an annual rate of 3%. In the base case, the no-treatment scenario represents an unrealistic benchmark with no treatment and, consequently, no treatment-related costs. The low diagnosis-and-treatment scenario results in $7.4 billion in testing and treatment costs, with an additional $400 million incurred when diagnosis is improved to the medium level. However, total costs decrease by approximately $300 million under the high diagnosis-and-treatment scenario, rendering it cost-saving relative to the medium scenario.

Although the pairwise comparisons presented in Table 5 evaluate the incremental effects of increasing diagnosis-and-treatment coverage between consecutive scenarios, construction of the cost-effectiveness frontier (Supplementary Table A1) indicates that the medium diagnosis-and-treatment strategy is strictly dominated by the high diagnosis-and-treatment strategy, which achieves greater health gains at a lower total cost.

Total QALYs increase from 3.2 million in the no diagnosis-and-treatment scenario to 3.7 million under high diagnosis-and-treatment. The cost per infection prevented, compared to the next best alternative, is $5,092 for the low scenario and $880 for the medium scenario, while the high scenario is cost-saving. Similarly, the ICERs per QALY gained are $25,653 and $4,715 for the low and medium scenarios, respectively, with the high scenario again being cost-saving and dominates the medium scenarios.

Using Türkiye's gross domestic product per capita (USD 8,798 in 2020) as the cost-effectiveness threshold, all scenarios except the low diagnosis-and-treatment scenario are cost-effective when evaluated in terms of QALYs, and the high diagnosis-and-treatment scenario is cost-saving compared with the medium scenario.

Cost-effectiveness results with 0% and 5% discounting is reported in the Supplemental Appendix (Tables A2 and A3).

Sensitivity Results

We conducted a one-way sensitivity analysis to assess the robustness of the model and identify key drivers of the results. The top 15 most influential parameters are presented in Figure 5. The model is most sensitive to the SVR rate and the transmission contact rate. The SVR rate directly affects treatment success and indirectly reduces transmission, as successfully treated individuals no longer contribute to onward transmission. The transmission contact rate, a key component of the force of infection, determines the rate at which susceptible individuals become infected and therefore strongly influences overall disease dynamics. The duration of the acute phase and the proportion of spontaneous clearance were identified as the next most influential parameters in the analysis.

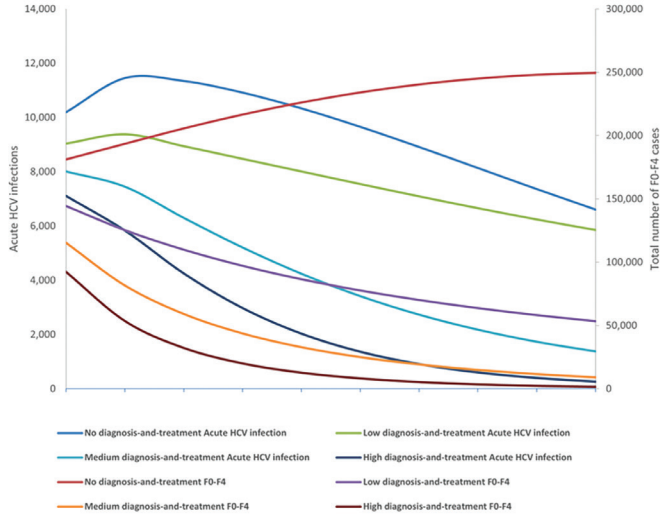

Figure 3. Estimated number of acute infections and infections in stages F0-F4 for no, low, medium and high diagnosis-and-treatment scenarios, 2020-2029
HCV: Hepatitis C virus

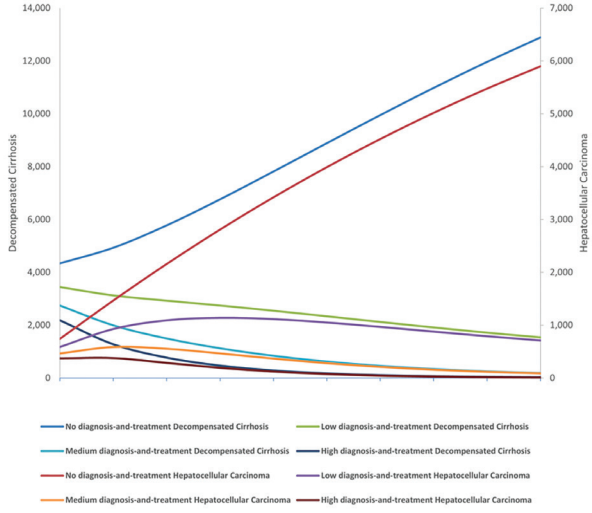

Figure 4. Estimated number of decompensated cirrhosis and hepacellullar carcinoma for no, low, medium and high diagnosis-and-treatment scenarios, 2020-2029

Table 5. Cost-effectiveness of diagnosis-and-treatment coverage strategies among people who inject drugs (PWID) in Türkiye (2020-2029)

	Total infections (2020-2029)	Total QALYs (2020-2029)	Total cost (2020-2029), $	Incremental cost prevented, $	Infections prevented	Incremental QALYs prevented	ICER infections prevented, $	ICER QALY, $
No diagnosis-and-treatment	2,454,480	2,906,867	0					
Low (25%)	997,403	3,196,115	7,420,163,380	7,420,163,380	1,457,077	289,248	5,092	25,653
Medium (50%)	469,632	3,294,669	7,884,851,199	464,687,819	527,772	98,553	880	4,715
High (75%)	264,366	3,335,426	7,578,245,318	Cost-saving	205,266	40,757	Cost-saving	Cost-saving

QALYs: Quality-adjusted life years, ICER: Incremental cost-effectiveness ratios

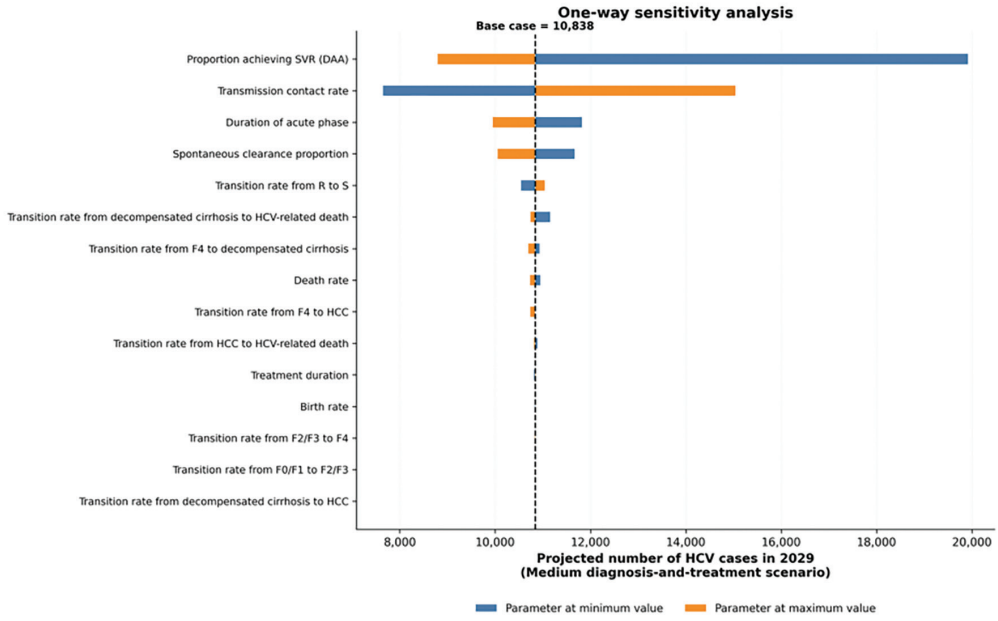

Figure 5. One-way sensitivity analysis of the projected number of HCV cases in 2029 under the medium diagnosis-and-treatment scenario. The vertical reference line represents the base-case estimate (10,838 projected HCV cases). Each parameter was varied individually between its minimum and maximum values reported in Table 2 while all remaining parameters were held at their base-case values

SVR: Sustained virologic response, DAA: Direct acting agents, HCC: Hepatocellular carcinoma, HCV: Hepatitis C virus

Discussion

In this study, we developed a mathematical model of HCV transmission and disease progression among PWID in Türkiye and analyzed the potential impact of increasing diagnosis-and-treatment rates on future disease spread. Our results show that, in the absence of diagnosis and treatment, HCV prevalence and HCV-related mortality could increase substantially. Although this no diagnosis-and-treatment scenario is unrealistic, it provides a useful benchmark for demonstrating the critical role of diagnosis and treatment as prevention strategies. Increasing diagnosis-and-treatment rates led to substantial reductions in both HCV prevalence and HCV-related deaths. In particular, the high diagnosis-and-treatment scenario resulted in a 98% reduction in HCV prevalence, suggesting that expanded diagnosis and treatment among PWID could make an important contribution to achieving WHO elimination goals.

Our findings also suggest that HCV diagnosis and treatment among PWID are cost-effective and may even become cost-saving, given the high transmission risk in this population. Although treatment costs remain considerable, diagnosis is relatively inexpensive, and the prevention of secondary infections can reduce the overall costs of diagnosis and treatment under higher-coverage scenarios. In terms of infections prevented and QALYs gained, the ICERs for the low, medium, and high diagnosis-and-treatment scenarios indicate that expanded diagnosis and treatment are either cost-effective or cost-saving, highlighting their value as both clinical and public health interventions.

Our results are comparable with those of previously published studies. Although none of the studies conducted in Türkiye specifically focused on PWID, and direct numerical comparisons are difficult because of differences in time horizons and diagnosis/treatment coverage scenarios, the overall conclusions are consistent. For example, Örmeci et al. (10) and Idilman et al. (11) suggested that increasing diagnosis and treatment rates could markedly reduce the number of HCV cases, and that achieving WHO targets for diagnosis (90%) and mortality reduction (65%) could decrease HCV prevalence by approximately 80% by 2030. Similarly, the high diagnosis-and-treatment scenarios in both previous studies and our model suggest major reductions in HCV prevalence and mortality. However, despite these improvements, the results also indicate that increasing diagnosis and treatment alone may not be sufficient to fully eliminate the disease.

Çekin et al. (9) reported that active screening and treatment programs are cost-effective for PWID, refugees, and prisoners, and recommended prioritizing PWID and refugees for targeted screening interventions. Although our study does not explicitly model an active screening and treatment program, improving diagnosis-and-treatment rates among PWID would likely require similar public health interventions and additional resource allocation. While the current diagnosis rate among PWID in Türkiye is not well established, achieving even a 50% diagnosis-and-treatment rate among infected individuals would likely require targeted screening efforts in this high-risk and vulnerable population.

Potential strategies to improve diagnosis rates include routine HCV screening within harm reduction programs such as AMATEM, integrated human immunodeficiency virus and HCV testing in voluntary counseling and testing centers, and prison-based

screening programs, given the substantial overlap between PWID and incarcerated HCV-positive populations. Community-based outreach, peer-supported testing initiatives, and simplified linkage-to-care pathways may also help improve engagement with diagnosis and treatment services among PWID.

Study Limitatons

Our study has several limitations. One of the key model parameters, the size of the PWID population in Türkiye, is subject to considerable uncertainty because of the limited availability of real-world epidemiological data. Therefore, the parameter values used in the model were informed by expert opinion and available estimates.

Another important limitation is that we did not incorporate the additional costs associated with increasing diagnosis rates. Achieving higher diagnosis-and-treatment coverage beyond the current status quo would likely require targeted public health interventions, such as screening, counseling, outreach, and linkage-to-care programs specifically designed for PWID. These interventions would increase the overall costs of diagnosis and treatment and could consequently increase the ICERs per infection prevented and per QALY gained. However, because there is currently no large-scale real-world implementation of such programs for PWID in Türkiye, reliable cost data for these interventions are not available. As a result, these costs were not included in our analysis.

Finally, uncertainty was assessed using one-way sensitivity analysis only, and a probabilistic sensitivity analysis was not performed. Although the one-way analysis identified the SVR rate and transmission contact rate as the most influential parameters, it does not capture the joint uncertainty across all model inputs. Therefore, the economic results should be interpreted with appropriate caution. Future studies should incorporate probabilistic sensitivity analysis when sufficient data are available to specify parameter distributions and correlations reliably.

Conclusion

In conclusion, HCV has the potential to become a major public health and economic burden, and the number of cases among PWID could increase considerably in the absence of improved diagnosis and treatment in this high-risk population. Using the best available data, our findings suggest that increasing diagnosis-and-treatment rates among PWID could be cost-effective, and potentially even cost-saving, while contributing substantially toward achieving WHO elimination targets. However, improving HCV control among PWID in Türkiye will require better surveillance data, more accurate estimates of the PWID population, and improved access to high-risk and hard-to-reach populations through targeted public health interventions.

Ethics

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of İstanbul University-Cerrahpaşa (approval no: 59491012-604.01.02, date: March 07, 2017).

Informed Consent: Verbal consent was obtained from all participants.

Acknowledgments

For transparency, the authors note that an artificial intelligence-assisted language model (ChatGPT, OpenAI) was utilized to support text editing and language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Concept: E.Y., Ş.Ü., Ü.Ü., F.T., Design: E.Y., Ş.Ü., Ü.Ü., F.T., Data Collection or Processing: Ş.Ü., Ü.Ü., F.T., Analysis or Interpretation: E.Y., Ş.Ü., Literature Search: Ş.Ü., Writing: E.Y.

Conflict of Interest: Fehmi Tabak is associate editor in Viral Hepatitis Journal. He had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

Financial Disclosure: The authors declare no financial support.

Supplemental Appendix: https://d2v96fxpocvxx.cloudfront.net/87200e80-fa4b-4309-8816-eff4c4e638c8/content-images/15f66aa1-4344-4e5e-8b44-d828178f75d2.pdf

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DOI: 10.4274/vhd.galenos.2026.2026-8-3
Viral Hepat J 2026;32(2):76-82

Pan-Immune-Inflammation Value and Functional Cure in Patients with Chronic Hepatitis B Receiving Long-Term Nucleos(t)ide Analogue Therapy

Uzun Süreli Nükleoz(t)id Analog Tedavisi Alan Kronik Hepatit B Hastalarında Pan-İmmün-Enflamasyon Değeri ve Fonksiyonel Kür

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ABSTRACT

Objectives: Functional cure, defined by hepatitis B surface antigen loss, is the preferred therapeutic endpoint in chronic hepatitis B (CHB). The pan-immune-inflammation value (PIV) is an inflammation-based index derived from routine complete blood count parameters. This study investigated the association between PIV and functional cure in patients with CHB receiving nucleos(t)ide analogue (NA) therapy.

Materials and Methods: This retrospective case-control study included 48 patients who achieved functional cure during NA therapy and 150 patients without functional cure as controls. PIV was evaluated at baseline and month-12. Receiver operating characteristic (ROC) analysis assessed the discriminatory performance of month-12 PIV, and multivariable logistic regression was used to identify factors independently associated with functional cure.

Results: Baseline PIV was comparable between groups, whereas month-12 PIV was significantly lower in the functional cure group (p=0.007). The area under the ROC curve for month-12 PIV was 0.629 [95% confidence interval (CI), 0.535-0.720]. A cut-off value of 148.4 provided 47.9% sensitivity and 73.9% specificity. After adjustment for age, hepatitis B e antigen status, baseline hepatitis B virus-DNA level, and fibrosis score, month-12 PIV≤148.4 remained independently associated with functional cure [adjusted odds ratio (OR), 2.66; 95% CI, 1.29-5.47; p=0.008]. Older age was also independently associated with functional cure (adjusted OR per year, 1.05; 95% CI, 1.02-1.08; p=0.003).

Conclusion: Lower month-12 PIV was independently associated with functional cure during NA therapy. Although its discriminatory ability

ÖZ

Amaç: Fonksiyonel kür, kronik hepatit B (KHB) tedavisinde hepatit B yüzey antijeni kaybı ile tanımlanan tercih edilen tedavi hedefidir. Pan-immün-enflamasyon değeri (PIV), rutin tam kan sayımı parametrelerinden hesaplanan enflamasyon temelli bir indekstir. Bu çalışmada, nükleoz(t)id analoğu (NA) tedavisi alan KHB hastalarında PIV ile fonksiyonel kür arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu retrospektif olgu-kontrol çalışmasına, NA tedavisi sırasında fonksiyonel kür gelişen 48 hasta ile fonksiyonel kür gelişmeyen 150 kontrol dahil edildi. PIV başlangıçta ve tedavinin 12. ayında değerlendirildi. On ikinci ay PIV değerinin ayırt edici performansı alıcı işletim karakteristiği (ROC) analizi ile incelendi ve fonksiyonel kür ile bağımsız olarak ilişkili faktörlerin belirlenmesi için çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Başlangıç PIV değerleri gruplar arasında benzerken, 12. ay PIV değeri fonksiyonel kür grubunda anlamlı olarak daha düşüktü (p=0,007). On ikinci ay PIV için ROC eğrisi altında kalan alan 0,629 [%95 güven aralığı (GA), 0,535-0,720] idi. 148,4 eşik değeri %47,9 duyarlılık ve %73,9 özgüllük sağladı. Yaş, hepatit B e antijeni durumu, başlangıç hepatit B virüs-DNA düzeyi ve fibrozis skoruna göre düzeltme yapıldıktan sonra, 12. ay PIV≤148,4 fonksiyonel kür ile bağımsız olarak ilişkili bulundu [düzeltilmiş olasılık oranı (OO), 2,66; %95 GA, 1,29-5,47; p=0,008]. İleri yaş da fonksiyonel kür ile bağımsız olarak ilişkiliydi (her bir yıllık yaş artışı için düzeltilmiş OO, 1,05; %95 GA, 1,02-1,08; p=0,003).

Sonuç: Daha düşük 12. ay PIV değeri, NA tedavisi sırasında fonksiyonel kür ile bağımsız olarak ilişkili bulundu. Ayırt edici gücü sınırlı olmakla birlikte

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Received: 13.08.2026 **Accepted:** 24.08.2026 **Publication Date:** 01.09.2026

Cite this article as: Vatan A. Pan-immune-inflammation value and functional cure in patients with chronic hepatitis B receiving long-term nucleos(t)ide analogue therapy. Viral Hepat J. 2026;32(2):76-82

was modest, PIV may provide a simple and inexpensive marker that could complement clinical and virological factors in the assessment of functional cure.
Keywords: Chronic hepatitis B, functional cure, hepatitis B surface antigen loss, pan-immune-inflammation value, nucleos(t)ide analogue therapy

PIV, fonksiyonel kürün değerlendirilmesinde klinik ve virolojik faktörleri tamamlayabilecek basit ve düşük maliyetli bir belirteç olabilir.
Anahtar Kelimeler: Kronik hepatit B, fonksiyonel kür, hepatit B yüzey antijeni kaybı, pan-immün-enflamasyon değeri, nükleoz(t)id analoğu

Introduction

Despite major advances in antiviral therapy, chronic hepatitis B (CHB) continues to impose a substantial burden through cirrhosis, hepatocellular carcinoma, and liver-related death worldwide (1). Extended treatment with nucleos(t)ide analogs (NAs) effectively suppresses hepatitis B virus (HBV) replication and reduces disease progression. Nevertheless, currently available NAs have little effect on intrahepatic covalently closed circular DNA, making prolonged or lifelong therapy necessary for most patients. Consequently, loss of HBV surface antigen (HBsAg), generally accepted as a functional cure, has become the preferred therapeutic endpoint in CHB (1,2). However, HBsAg clearance remains uncommon during long-term NA therapy, highlighting the need to identify factors associated with functional cure (3,4,5).

Several clinical and virological markers have been evaluated as potential predictors of functional cure. Quantitative HBsAg, HBcrAg, serum HBV-RNA, HBV-DNA, and HBeAg status are among the most extensively studied biomarkers (6). However, several of these assays are not routinely available, limiting their widespread applicability. Long-term NA therapy may also modulate host immune responses, supporting interest in accessible biomarkers of immune-inflammatory changes during treatment (3,7). Inflammation-based indices derived from routine hematological parameters have therefore gained interest as inexpensive biomarkers in CHB (8). The pan-immune-inflammation value (PIV), derived from neutrophil, monocyte, platelet, and lymphocyte counts, was initially developed as a prognostic biomarker in oncology and has subsequently been evaluated in chronic liver disease (9,10). Although several hemogram-derived inflammatory indices have been investigated in CHB, evidence regarding the association between PIV and functional cure remains limited. Therefore, we investigated the association of baseline and month-12 PIV with functional cure in patients with CHB receiving NA therapy.

Materials and Methods

Study Design

This retrospective case-control study included adults with chronic HBV infection receiving nucleos(t)ide analogue (NA) therapy. Patients who achieved functional cure during follow-up constituted the case group, whereas patients who did not achieve functional cure constituted the control group. Patients with human immunodeficiency virus, hepatitis C virus, or hepatitis D virus coinfection, acute infections unrelated to HBV, hematological disorders, malignancy, autoimmune disease, pregnancy, immunosuppressive therapy, or missing clinical or laboratory data were excluded.

Demographic characteristics, antiviral treatment, treatment and follow-up durations, biochemical and virological parameters, complete blood count results, and histological findings were extracted from the hospital electronic database. Laboratory parameters included alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, platelet count, white blood cell count, neutrophil count, lymphocyte count, and monocyte count. Virological parameters included HBeAg status, serum HBV-DNA, and HBsAg status. Histological activity index (HAI) and fibrosis scores were recorded when available. AST to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) were calculated from the relevant laboratory and clinical parameters. Serum HBsAg was assessed annually as part of routine follow-up.

Functional cure was defined as sustained HBsAg loss during antiviral therapy, continuation of NA treatment for at least 12 months after HBsAg loss, subsequent treatment discontinuation, persistent HBsAg negativity for at least 24 weeks after treatment withdrawal, and undetectable serum HBV-DNA throughout post-treatment follow-up. Anti-HBs seroconversion was not required.

PIV was the primary study variable and was evaluated at baseline and month 12, when laboratory data were available for all participants. In patients who achieved functional cure, laboratory results from the visit documenting HBsAg loss and the final post-treatment follow-up were also reviewed to confirm the outcome.

The study protocol was approved by the Sakarya University Health Sciences Scientific Research Ethics Committee (approval no: E-43012747-050.04-596826-561, date: 17.06.2026). The requirement for informed consent was waived because of the retrospective design of the study.

Laboratory Assessment

Complete blood count parameters were measured using an automated hematology analyzer. PIV was calculated as follows:

PIV = neutrophil count × monocyte count × platelet count / lymphocyte count

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Kolmogorov-Smirnov test. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, and categorical variables as counts and percentages.

Continuous variables were compared using the independent-samples t-test or Mann-Whitney U test, and categorical variables using the chi-square test or Fisher's exact test, as appropriate.

The discriminatory performance of baseline and month-12 PIV for functional cure was assessed using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC), with the optimal cutoff determined by the Youden index.

Logistic regression was used to identify factors independently associated with functional cure. Variables included in the adjusted analysis were selected a priori based on clinical importance, prior evidence, and the number of outcome events to minimize model overfitting. Because neutrophil, monocyte, lymphocyte, and platelet counts are mathematical components of the PIV equation, these variables were excluded from the multivariable analysis to avoid multicollinearity. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. Statistical significance was defined as a two-sided p-value <0.05.

Results

Baseline Characteristics

The study included 48 patients who achieved functional cure during NA therapy and 150 patients without functional cure who constituted the control group. Baseline demographic, clinical, and laboratory characteristics of the two groups are presented in Table 1.

Patients in the functional cure group were significantly older than those in the non-functional cure group (56.4±11.9 vs. 49.4±12.1 years, p<0.001). The baseline fibrosis score was also significantly higher in the functional cure group (p<0.001). Neutrophil counts were significantly lower in the functional cure group (p<0.001), as were lymphocyte counts (p=0.030). No significant differences were observed between the groups in sex, HBeAg positivity, baseline HBV-DNA level, HAI score, treatment or follow-up duration, ALT, AST, albumin, platelet count, monocyte count, or baseline PIV.

Laboratory Findings at Month 12

The laboratory findings at month 12 are summarized in Table 2. Compared with the non-functional cure group, patients in the functional cure group had significantly lower AST levels, white blood cell counts, neutrophil counts, lymphocyte counts, platelet counts, serum albumin levels, and PIV values. Total bilirubin levels were significantly higher in the functional cure group. No significant differences were observed in ALT, monocyte count, APRI, or FIB-4. Among the inflammatory indices evaluated, month-12 PIV was significantly lower in the functional cure group [167.80 (97.89-239.80) vs. 209.37 (146.88-304.36), p=0.007].

Receiver Operating Characteristic Analysis

ROC curve analysis was performed to evaluate the ability of month-12 PIV to discriminate between patients with and without functional cure. The AUC was 0.629 (95% CI, 0.535-0.720). The optimal cut-off value determined using the Youden index was 148.4, with a sensitivity of 47.9% and a specificity of 73.9% (Figure 1).

Logistic Regression Analysis

Variables with established clinical relevance were included in the multivariable logistic regression model (Table 3). In the univariable analysis, increasing age, higher fibrosis score, and low month-12 PIV (≤148.4) were significantly associated with functional cure. After adjustment for age, HBeAg status, baseline HBV-DNA level, and fibrosis score, low month-12 PIV remained independently associated with functional cure (adjusted OR, 2.66; 95% CI, 1.29-5.47; p=0.008).

Table 1. Baseline demographic, clinical, and laboratory characteristics according to functional cure status

Variable	Functional cure group (n=48)	Non-functional cure group (n=150)	p-value
Age (years)	56.4±11.9	49.4±12.1	<0.001
Male sex, n (%)	28 (58.3)	95 (63.3)	0.609
HBeAg positivity, n (%)	8 (16.7)	22 (15.2)	0.820
Baseline HBV-DNA (IU/mL)	12,490.5 (2,995.8-463,791.8)	40,206.5 (3,502.5-3,533,199.8)	0.36
HAI score	6 (6-9)	7 (6-8.8)	0.985
Fibrosis score	2 (2-3)	2 (1-2.75)	<0.001
Treatment duration (months)	96 (72-126)	92 (68-121)	0.48
Follow-up duration (months)	118 (90-144)	114 (88-140)	0.57
ALT (U/L)	30.5 (19.0-68.3)	37.5 (20.0-69.5)	0.958
AST (U/L)	25.5 (19.0-55.0)	31.0 (22.0-48.8)	0.545
Albumin (g/dL)	4.2 (3.95-4.40)	4.2 (4.0-4.4)	0.737
Platelet count (×10^3/μL)	197 (146.8-259.3)	220.5 (183.8-258.5)	0.062
Neutrophil count (×10^3/μL)	3.55 (2.40-4.03)	4.04 (3.26-5.18)	<0.001
Lymphocyte count (×10^3/μL)	1.91±0.71	2.17±0.74	0.03
Monocyte count (×10^3/μL)	0.50 (0.36-0.60)	0.47 (0.38-0.60)	0.961
Pan-immune-inflammation value	185.7 (91.2-254.7)	201.3 (134.3-279.3)	0.083

Data are presented as mean ± standard deviation for normally distributed continuous variables, median (interquartile range) for non-normally distributed continuous variables, and n (%) for categorical variables, as appropriate. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HAI: Histological activity index, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus

Table 2. Laboratory findings at month 12 according to functional cure status

Variable	Functional cure group (n=48)	Non-functional cure group (n=150)	p-value
ALT (U/L)	20.50 (15.00-32.50)	21.00 (16.00-32.00)	0.757
AST (U/L)	22.00 (18.00-27.00)	25.00 (20.00-32.00)	0.014
Total bilirubin (mg/dL)	0.70 (0.52-0.99)	0.60 (0.44-0.77)	0.011
Albumin (g/dL)	4.20 (3.90-4.40)	4.40 (4.10-4.50)	0.013
White blood cell count (×10³/μL)	5.88 (4.88-7.97)	6.84 (5.69-8.21)	0.021
Neutrophil count (×10³/μL)	3.51 (2.51-4.46)	4.11 (3.20-4.96)	0.010
Lymphocyte count (×10³/μL)	1.88±0.68	2.20±0.76	0.010
Monocyte count (×10³/μL)	0.45 (0.33-0.56)	0.44 (0.38-0.56)	0.838
Platelet count (×10³/μL)	197.40±59.10	251.22±67.63	<0.001
APRI	0.21 (0.18-0.32)	0.20 (0.16-0.27)	0.154
FIB-4	0.16 (0.08-0.26)	0.10 (0.07-0.19)	0.118
PIV	167.80 (97.89-239.80)	209.37 (146.88-304.36)	0.007

Data are presented as mean ± standard deviation for normally distributed continuous variables and median (interquartile range) for non-normally distributed continuous variables, as appropriate. PIV: Pan-immune-inflammation value, APRI: Aspartate aminotransferase-to-platelet ratio index, FIB-4: Fibrosis-4 index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Table 3. Univariable and multivariable logistic regression analyses for factors associated with functional cure

Variable	Univariable OR (95% CI)	p-value	Multivariable OR (95% CI)	p-value
Age, per 1-year increase	1.048 (1.019-1.077)	<0.001	1.047 (1.015-1.079)	0.003
Sex, female vs male	1.234 (0.636-2.394)	0.535	—	—
HBeAg positivity	1.118 (0.462-2.708)	0.804	1.559 (0.576-4.222)	0.382
Baseline HBV-DNA, per 1-log10 IU/mL increase	0.888 (0.735-1.074)	0.221	0.926 (0.749-1.145)	0.479
Fibrosis score, per 1-point increase	1.517 (1.106-2.081)	0.010	1.316 (0.923-1.875)	0.129
Low month-12 PIV (≤148.4)	2.611 (1.324-5.149)	0.006	2.659 (1.292-5.469)	0.008

OR: Odds ratio, CI: Confidence interval, PIV: Pan-immune-inflammation value, HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen

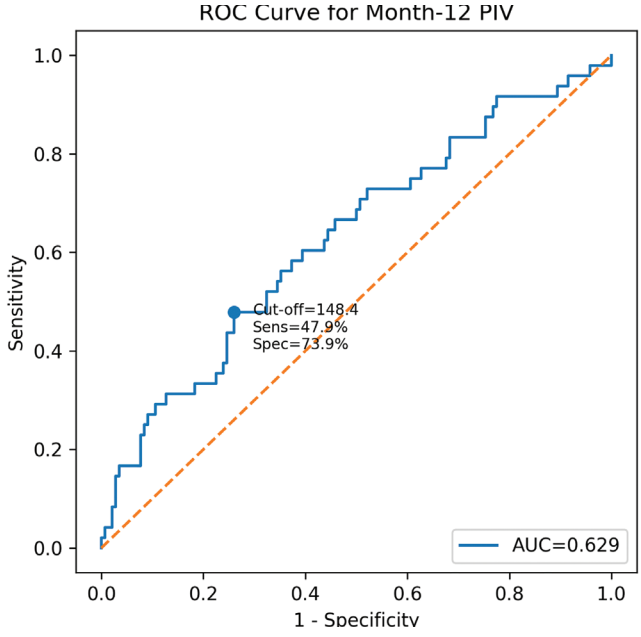

Figure 1. Receiver operating characteristic (ROC) curve for month-12 pan-immune-inflammation value (PIV) in discriminating patients with and without functional cure

AUC: Area under the curve

Increasing age was also independently associated with functional cure (adjusted OR, 1.05 per year; 95% CI, 1.02-1.08; p=0.003). HBeAg status, baseline HBV-DNA level, and fibrosis score were not independently associated with functional cure.

Discussion

Functional cure has emerged as the preferred therapeutic goal in CHB because of its well-established association with improved long-term clinical outcomes. Nevertheless, despite persistent inhibition of HBV replication during NA therapy, HBsAg loss remains an infrequent event (3). As a result, considerable attention has been directed toward identifying factors that may predict functional cure. Most previous studies have focused on virological biomarkers, particularly quantitative HBsAg, HBcrAg, and serum HBV-RNA (11,12). Although these biomarkers have demonstrated prognostic value, their incorporation into routine clinical practice remains limited because the required assays are not universally available.

PIV was initially introduced as a composite index based on neutrophil, monocyte, platelet, and lymphocyte counts (9). By integrating several circulating cell populations rather than relying on a single-cell count or a two-cell ratio, PIV may provide a broader representation of systemic immune-inflammatory status.

Its clinical relevance has subsequently been explored in cancer, metabolic disorders, and chronic liver diseases (13). Because chronic HBV infection is characterized by persistent immune dysregulation involving both innate and adaptive immune responses, a composite index incorporating multiple peripheral immune-cell populations may offer a more informative view of the immune milieu than indices derived from fewer cell types (14).

Patients who achieved functional cure during long-term NA therapy exhibited significantly lower month-12 PIV values than those who did not achieve functional cure. This association persisted after adjustment for age, HBeAg status, baseline HBV-DNA level, and fibrosis score, indicating that month-12 PIV was independently associated with functional cure. Given that PIV is calculated from routinely available complete blood count parameters, it may serve as a simple, inexpensive indicator of the peripheral immune-inflammatory milieu associated with functional cure during antiviral treatment.

ROC analysis showed that month-12 PIV had modest discriminatory ability for functional cure, with an AUC of 0.629. The identified cut-off value of 148.4 had a specificity of 73.9% but a relatively low sensitivity of 47.9%. These findings suggest that PIV alone is unlikely to be sufficient as a predictive marker for functional cure, but it may have value as part of a broader assessment together with virological and clinical factors.

Several complementary biological mechanisms likely explain the association between lower PIV values and functional cure. Current evidence indicates that functional cure reflects not only durable suppression of HBV replication but also progressive recovery of antiviral immune function during prolonged NA therapy (3,15). Although complete restoration of HBV-specific immunity is rarely achieved, sustained viral suppression has been shown to partially reverse T-cell dysfunction and alleviate the chronic immune dysregulation characteristic of persistent HBV infection (8,14). Growing evidence indicates that long-term antiviral therapy is accompanied by dynamic remodeling of both innate and adaptive immune-cell compartments, a process that parallels improved virological control and the eventual achievement of functional cure (16,17). These observations provide a biological basis for evaluating composite blood-cell indices such as PIV as indirect indicators of the evolving immune-inflammatory environment, while recognizing that they do not directly quantify HBV-specific immune responses.

The biological significance of PIV in chronic HBV infection can be better appreciated by considering the immunological functions of its cellular components. Neutrophils are an essential part of the innate immune response; however, chronic HBV infection has been shown to compromise their antimicrobial activity by suppressing neutrophil extracellular trap formation through alterations in reactive oxygen species generation and autophagy (18,19). Monocytes serve as an important interface between innate and adaptive immunity by contributing to antigen presentation and cytokine production. Exposure to HBV antigens may promote both inflammatory cytokine release and the development of immunoregulatory monocyte phenotypes that attenuate responses mediated by HBV-specific T-cells, B cells, and natural killer cells (16,20). Beyond their established function in hemostasis, platelets actively modulate hepatic immune responses by facilitating the recruitment of virus-specific $CD8^+$ T-cells and other inflammatory leukocytes to the liver (21,22). At the same time, circulating platelet counts may also reflect the presence of hepatic fibrosis, cirrhosis, and the overall severity of chronic liver disease (23). In our study, neutrophil and platelet counts were significantly lower in the functional cure group at month 12, whereas monocyte counts did not differ between groups. Lymphocyte counts were also lower despite forming the denominator of the PIV equation. These findings suggest that the lower PIV observed in the functional cure group reflects the combined behavior of its cellular components rather than a uniform change in any single cell population. The lower lymphocyte count observed in the functional cure group should be interpreted cautiously. Peripheral lymphocyte counts provide only a broad measure of the adaptive immune compartment and do not directly reflect HBV-specific immune activity. Functional cure is thought to depend primarily on effective HBV-specific $CD8^+$ cytotoxic T-cell activity, while $CD4^+$ T-cells provide the helper signals required for the generation, maintenance, and coordination of antiviral immunity (14,24). Therefore, a lower total peripheral lymphocyte count should not necessarily be interpreted as evidence of a weaker HBV-specific immune response.

The rationale for PIV is to integrate neutrophils, monocytes, and platelets in the numerator with lymphocytes in the denominator, providing an integrated, although non-specific, measure of the interplay between peripheral innate inflammatory activity and adaptive immune function. Although this measure does not directly assess HBV-specific antiviral immunity, the lower month-12 PIV observed in patients who subsequently achieved functional cure is biologically consistent with a more favorable immune-inflammatory environment during prolonged antiviral therapy. This concept is further supported by recent single-cell studies demonstrating coordinated remodeling of innate and adaptive immune cell populations in individuals who achieve a functional cure (17). To our knowledge, evidence linking PIV to functional cure in patients undergoing long-term NA therapy for CHB has not been reported previously.

Fibrosis scores were statistically different between the groups; however, this finding should be interpreted cautiously. Although the median fibrosis score was 2 in both groups, the distribution of fibrosis stages differed, with fibrosis scores in the functional cure group predominantly clustered at F2-F3. Moreover, controls were not individually matched to cases according to fibrosis stage. Thus, the observed difference may partly reflect differences in the distribution of fibrosis stages and the case-control sampling structure rather than a direct association between fibrosis severity and functional cure. For this reason, fibrosis score was included as an adjustment variable in the multivariable analysis.

Study Limitations

Several limitations should be considered when interpreting these findings. Because this was a retrospective study conducted at a single tertiary referral center, the applicability of the results to other populations may be limited. In addition, the observational design precludes any conclusions regarding causality. Although the multivariable analyses accounted for major clinical confounders, residual confounding cannot be entirely excluded. In addition, because PIV is calculated from routine peripheral blood cell counts, it provides only an indirect estimate of the peripheral immune-inflammatory milieu rather than HBV-specific immune function. Consequently, HBV-specific $CD4^+$ and $CD8^+$ T-cell responses, immune-cell phenotypes, cytokine profiles, and other immunological markers that might further explain the observed association were not available for analysis. Moreover, the present study evaluated PIV only at month 12, and longitudinal changes throughout antiviral treatment were not investigated. Nevertheless, the relatively large number of patients who achieved functional cure, along with adjustment for major clinically relevant confounders, enhances the robustness of our findings.

Conclusion

Lower month-12 PIV was independently associated with functional cure among patients with CHB managed with long-term NA therapy. This study identified an independent association between PIV and HBsAg loss in this clinical setting. As PIV is derived from routinely available complete blood count parameters at no additional cost, it may serve as a practical biomarker associated with functional cure. However, PIV should be interpreted as an indirect indicator of the peripheral immune-inflammatory milieu rather than a direct measure of HBV-specific immune restoration. Further prospective multicenter studies incorporating serial PIV measurements and detailed immunological profiling are warranted to confirm these findings and better define the role of PIV in patients receiving NA therapy.

Ethics

Ethics Committee Approval: The study protocol was approved by the Sakarya University Health Sciences Scientific Research Ethics Committee (approval no: E-43012747-050.04-596826-561, date: 17.06.2026).

Informed Consent: The requirement for informed consent was waived because of the retrospective design of the study.

Footnotes

Financial Disclosure: The author declares no financial support.

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Erratum

DOI: 10.4274/vhd.galenos.2026.e001
Viral Hepat J
Viral Hepat J 2026;32(2):83

DOI: 10.4274/vhd.galenos.2024.2024-7-4

Aydın NN, Aydın M. Potential drug-drug interactions between oral antiviral agents used for hepatitis B treatment and concomitant systemic medications. Viral Hepat J. 2024;30(3):59-64

The mistake has been made inadvertently by the author.

The date range information on which the study was carried out, located under the Materials and Methods heading of the article, has been corrected by the author as follows.

Between **01.07.2022-01.10.2022**, patients over the age of 18 who applied to the infectious diseases outpatient clinic of our hospital and were receiving antivirals (TDF, ETV, TAF) were included in the study.

The study's date range has been corrected.

Between **01.07.2021-01.10.2021**, patients over the age of 18 who applied to the infectious diseases outpatient clinic of our hospital and were receiving antivirals (TDF, ETV, TAF) were included in the study.