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AIM AND SCOPE

Viral Hepatitis Journal (Formerly Viral Hepatit Dergisi) is the regular publishing organ of the Viral Hepatitis Society. This periodical journal covers diagnosis, treatment, epidemiology, prevention and information of hepatitis.

Viral Hepatitis Journal is an open-access journal published 3 times per year (April, August and December). In addition, the special issues are published in some periods. It is a periodic national/international journal, published in English language with abstract and title published also in Turkish language and its editorial policies are based on independent peer-review principles.

The aim of Viral Hepatitis Journal is to continuously publish original research papers of the highest scientific and clinical values specifically on hepatitis, on an international level. Additionally, reviews on basic developments in education, editorial short notes, case reports, original views, letters from a wide range of medical personal containing experiences and comments as well as social subjects are published.

For general practitioners giving first line medical service who are interested in hepatitis, specialists in internal medicine, gastroenterology, microbiology, family physician, public health and hepatology, 'things that must be known' subjects will ensure to involve in Viral Hepatitis Journal.

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Viral Hepatitis Journal is a scientific journal that publishes retrospective, prospective or experimental research articles, review articles, case reports, editorial comment/discussion, letter to the editor, surgical technique, differential diagnosis, medical book reviews, questions-answers and also current issues of medical agenda from all fields of medicine and aims to reach all national/international institutions and individuals.

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The author(s) undertake(s) all scientific responsibility for the manuscript. All the authors must actively participate in the study. The author(s) guarantee(s) that the manuscript itself or any substantially similar content of the manuscript has not been published or is being considered for publication elsewhere. If the manuscript had been presented in a meeting before; the name, date and the province of the meeting should be noted.

Experimental, clinical and drug studies requiring approval by an ethics committee must be submitted to the Viral Hepatitis Journal with an ethics committee approval report confirming that the study was conducted in accordance with international agreements and the Declaration of Helsinki (revised in 2013) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). The approval of the ethics committee and the fact that informed consent was given by the patients should be indicated in the Materials and Methods section (including approval number). All papers reporting experiments using animals must include a statement in the Material and Methods section giving assurance that all animals have received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (www.nap.edu/catalog/5140.html) and indicating approval by the institutional ethical review board.

The content of the submitted manuscripts should conform to the criteria stated in "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals" published by International Committee of Medical Journal Editors and updated in 2016 (available at http://www.icmje.org/).

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The articles sent to be published in the journal shouldn't have been published anywhere else previously or submitted and accepted to be published. However, a complete report that follows publication of a preliminary report, such as an abstract can be submitted. If authors intend to discard any part of the manuscript, a written application should be sent to the Editor.

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Preparation of research articles and systematic reviews meta-analyses must comply with study design guidelines: CONSORT statement for randomized controlled trials (Moher D, Schultz KF, Altman D, for the CONSORT Group. The CONSORT statement revised recommendations for improving the quality of reports of parallel group randomized trials. JAMA 2001; 285: 1987-91) (http://www.consort-statement.org/),

PRISMA for preferred reporting items for systematic reviews and meta-analyses (Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(7): e1000097.) (http://www.prisma-statement.org/),

STARD checklist for the reporting of studies of diagnostic accuracy (Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al, for the STARD Group. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Ann Intern Med 2003;138:40-4.) (http://www.stard-statement.org/),

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Authors are encouraged to follow the following principles before submitting their article:

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Short Announcements

i. Turkish title, English title, author(s)' name(s) and institution(s) (Turkish and English)
ii. Turkish and English Abstract (max 300 words)
iii. Turkish and English Keywords
iv. Introduction (max 300 words)
v. Materials and Methods (max 400 words)
vi. Results (max 400 words)
vii. Discussion (max 700 words)
viii. Referances (should not exceed 15), all words 2000 not exceed.

• Author number for review articles should not exceed three.

• Author number for case report presentations should not exceed four.

• Articles should be written with double line space in 10 font size and right, left, upper and lower margins should all be 2.5 cm. Writing style should be Arial.

Manuscripts should have double-line spacing, leaving sufficient margin on both sides.

Manuscripts should be written with Microsoft Word and the main text should not exceed 2000 words.

Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

Cover Letter: Cover letter should include statements about manuscript category designation, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipments (if so), approval for language for articles in English and approval for statistical analysis for original research articles.

Title Page: Title should be concise and informative (in Turkish and English). The title page should include a list of all contributing authors and all of their affiliations. Positions of authors and names of departments and institutions to which they are attached and the province should be written. Supply full correspondence details for the corresponding author, including phone, mobile phone, fax number and e-mail address.

ARTICLE SECTIONS

The text file should include the title in Turkish, keywords, the title in English, keywords in English, the text of the article, references, tables (only one table for one page) and figure

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legends (if any), respectively. Within the text file, the names of the authors, any information about the institutions, the figures and images should be excluded.

Abstract: Turkish and English abstracts should be given together with the article title. It should be divided into four sections in the following order: Objectives, Materials and Methods, Results and Conclusion. Abstracts should not exceed 250 words. Abstracts for case reports should be unstructured and shorter (average 100-150 words; without structural divisions in Turkish and English).

Objectives: The aim of the study should be clearly stated.

Materials and Methods: **The study and standard criteria used should be defined; it should also** be indicated whether the study is randomized or not, whether it is retrospective or prospective, and the statistical methods applied should be indicated, if applicable.

Results: The detailed results of the study should be given and the statistical significance level should be indicated.

Conclusion: Should summarize the results of the study, the clinical applicability of the results should be defined, and the favorable and unfavorable aspects should be declared.

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• They should be minimally 3 and maximally 6 and should be written in Turkish and English.

• The words should be separated by semicolon (;) from each other.

• English keywords should be appropriate to "Medical Subject Headings (MESH)" (www.nlm.nih.gov/mesh/MBrowser.html).

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Results: The results of the study should be stated, with tables/figures given in numerical order; the results should be evaluated according to the statistical analysis methods applied. See General Guidelines for details about the preparation of visual material.

Discussion: The study results should be discussed in terms of their favorable and unfavorable aspects and they should be compared with the literature.

Study Limitations: Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion: The conclusion of the study should be highlighted.

Acknowledgements: Any technical or financial support or editorial contributions (statistical analysis, English/Turkish evaluation) towards the study should appear at the end of the article. Only acknowledge persons and institutions who have made substantial contributions to the study, but was not a writer of the paper.

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Case reports should present cases which are rarely seen, feature novelty in diagnosis and treatment, and contribute to our current knowledge. The first page should include the title in Turkish and English, an unstructured summary not exceeding 150 words, and keywords. The main text should consist of introduction, case report, discussion, acknowledgment, conclusion and references. The entire text should not exceed 5 pages (A4, formatted as specified above).

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Review articles can address any aspect of viral hepatitis Review articles must provide critical analyses of contemporary evidence and provide directions of or future research. Most review articles are commissioned, but other review submissions are also welcome. Before sending a review, discussion with the editor is recommended.

Reviews articles analyze topics in depth, independently and objectively. The first chapter should include the title in Turkish and English, an unstructured summary and keywords. Source of all citations should be indicated. The entire text should not exceed 25 pages (A4, formatted as specified above).

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Letters to the Editor should be short commentaries related to current developments in viral hepatitis and their scientific and social aspects, or may be submitted to ask questions or offer further contributions in response to work that has been published in the Viral Hepatitis Journal. Letters do not include a title or an abstract; they should not exceed 1000 words and can have up to 5 references.

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Follow the styles shown in examples below (please give attention to punctuation):

In reference section of the article, there should be no writing in languages other than English. The text language of the article should be indicated in parenthesis at the end of each reference (e.g. Yoldaş O, Bulut A, Altındiş M. The Current Approach of Hepatitis A Infections. Viral Hepatitis J 2012;18:81-86. (Turkish).

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Acknowledgment: Only acknowledge persons and institutions who have made substantial contributions to the study, but was not a writer of the paper.

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• Turkish and English titles

• Abstract (250 words) (Turkish and English)

• Keywords (minimum 3; maximum 6)

• Article divided into appropriate sections

• Complete and accurate references and citations

• List of references styled according to "journal requirements"

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Review

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The Problem of Access to Hepatitis B Treatment in the Balkan Country of North Macedonia

Balkan Ülkesi Kuzey Makedonya'da Hepatit B Tedavisine Erişim Sorunu

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ABSTRACT

Chronic hepatitis B (CHB) virus infection represents a global public health threat that causes considerable liver-related morbidity and mortality. In chronically infected patients, an elevated serum hepatitis B virus (HBV)-DNA concentration is the main risk factor for disease progression, although other clinical and viral characteristics can influence disease outcomes. At present, curing HBV infection is challenging in most patients and they need long-term antiviral treatment. The first-line treatments are nucleos(t)ide analogs (NAs) with a high barrier to resistance: tenofovir and entecavir, while in highly selected patients, an alternative treatment option is regulated interferon. Long-term therapy with NAs is safe and well tolerated, achieves potent viral suppression, and reduces the incidence of liver-related complications. For the majority of patients with CHB in North Macedonia, the current anti-HBV treatment is lamivudine with a low genetic barrier, which leads to compensatory mutations and resistance. With current vaccine strategy, applying therapies with effective high genetic barrier to resistance drugs, and improved linkage to care we should improve the treatment for patients with CHB and strive toward the World Health Organization goal of eliminating HBV as a global health threat by 2030.

Keywords: Hepatitis B virus, chronic hepatitis B, nucleos(t)ide analogs, pegylated interferon, lamivudine, entecavir, tenofovir

ÖZ

Kronik hepatit B (KHB) virüsü enfeksiyonu, önemli ölçüde karaciğerle ilişkili morbidite ve mortaliteye neden olan küresel halk sağlığı tehdidini temsil eder. Kronik olarak enfekte hastalarda, yüksek serum hepatit B virüsü (HBV)-DNA konsantrasyonu, hastalığın ilerlemesi için ana risk faktörüdür, ancak diğer klinik ve viral özellikler hastalık sonuçlarını etkileyebilir. Şu anda, HBV enfeksiyonunu iyileştirmek çoğu hastada zordur ve bu hastaların uzun süreli antiviral tedaviye ihtiyaçları vardır. Birinci basamak tedaviler, yüksek direnç bariyeri olan nükleos(t)id analoglarıdır (NAs): Tenofovir ve entecavir, çok seçilmiş hastalarda alternatif tedavi seçeneği pegile interferondur. NAs uzun süreli tedavi güvenlidir ve iyi tolere edilir, güçlü viral baskılama sağlar ve karaciğerle ilişkili komplikasyonların insidansını azaltır. KHB bulunan hastaların çoğunluğu için mevcut anti-HBV tedavisi, telafi edici mutasyonlara ve dirence yol açan düşük genetik bariyerli lamivudindir. Mevcut aşı stratejisi, dirençli ilaçlara karşı etkili, yüksek genetik bariyeri olan tedaviler ve bakım bağlantısının iyileştirilmesi ile KHB hastalarının tedavisini iyileştirmeli ve Dünya Sağlık Örgütü'nün HBV'yi 2030 yılına kadar küresel bir sağlık tehdidi olarak ortadan kaldırma hedefine doğru çaba göstermeliyiz.

Anahtar Kelimeler: Hepatit B virüsü, kronik hepatit B, nükleoz(t)id analogları, pegile interferon, lamivudin, entekavir, tenofovir

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Introduction

Chronic infection with hepatitis B virus (HBV) represents a global health problem with over 296 million people being chronic HBV surface antigen (HBsAg) carriers, with 1,2 million new infections every year. According to the World Health Organization (WHO) in 2019, hepatitis B resulted in estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma. At the same time, it has been estimated that 3.8% of the world population is living with chronic hepatitis HBV infection (1,2). Regardless of the vaccines, chronic hepatitis B (CHB) remains the predominant cause

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of chronic liver disease and liverrelated morbidity worldwide due to different vaccination policies and migration. CHB is considered to be the major risk factor for cirrhosis, endstage liver disease, and hepatocellular carcinoma (HCC), depending on host and viral factors (3). The natural history of CHB is complex and represents an interplay of virological, environmental, and host factors, and the infected patients can go through different phases during their disease. These phases differ between each other in terms of HBV-DNA serum levels, extent of liver diseases and disease progression toward liver fibrosis, which can be gradual, accelerated and sporadic. Schematically, the natural history of chronic HBV infection can be divided into five phases, taking into account the presence of hepatitis B e antigen (HBeAg), HBV-DNA levels, alanine aminotransferase (ALT) values and eventually the presence or absence of liver inflammation (4,5) (Figure 1).

The new nomenclature is based on the description of two main characteristics of chronicity: infection vs. hepatitis. The first phase is considered to represent a state of immune tolerance when HBeAg is positive, serum HBV-DNA levels are very high, HBV infectivity is high with normal ALT levels, and there is little if any liver damage. Vertical HBV transmission in neonates is very high in this phase, but horizontal HBV transmission can also occur. The second immune-reactive phase is associated with liver necroinflammation and fibrosis and is referred to as HBeAg-positive CHB, but the terms immune reactive, immune active, or HBeAg clearance phase are also used. HBeAg is positive, HBV-DNA levels are usually high but can vary, ALT levels are increased, and liver histology shows necroinflammation with variable stages of fibrosis. The phase of HBeAg-positive CHB may end not only in HBeAg seroconversion but also in HBsAg clearance and seroconversion to anti-HBs. However, in some patients, HBV replication continues despite HBeAg loss and the development of hepatitis B e antibodies (anti-HBe), and there is little if any residual viral replication, the so-called "inactive HBsAg carrier state" or the third phase. The majority of patients remain for a lifetime in an inactive carrier state, spontaneous clearance of HBsAg can occur in 1-3% of cases per year. The fourth

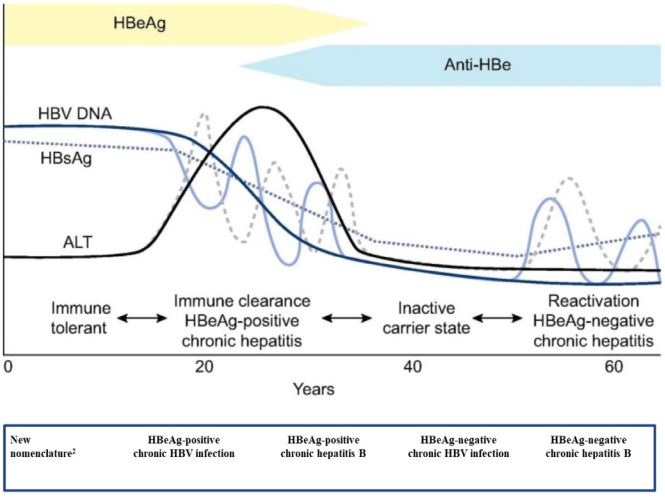

Figure 1. Phases of chronic HBV infection (4)

HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, HBsAG: Hepatitis B surface antigen, ALT: Alanine aminotransferase, anti-HBe: Hepatitis B e antibody

phase is so called HBeAg-negative CHB, characterized by the lack of serum HBeAg usually with detectable anti-HBe and persistent or fluctuating moderate to high levels of serum HBV-DNA, mostly lower than in HBeAg-positive patients; fluctuating or persistently elevated ALT values with hepatic necroinflammation and fibrosis. There are very low rates of spontaneous disease remission in this phase. In the fifth HBsAg- negative phase, the resolution of CHB is characterized by negative HBsAg, with or without detectible anti-HBs antibodies in the patients serum. Immunosuppression might lead to HBV reactivation in these patients, hence the term "occult HBV infection" (4).

The Epidemiology of Chronic HBV Infection in the Republic of North Macedonia

According to the prevalence of chronic HBsAg carriers, different geographic areas in the world are designated as areas with low (2%), intermediate (2-8%) and high (8%) endemicity levels (6,7,8). In the Euro-Mediterranean countries, current median HBV endemicity levels are below 3% (9,10). There are insufficient data for the prevalence of chronic HBV infection in the Republic of North Macedonia (11). According to the data from the North Macedonian National Institute of Health, the modeled prevalence for chronic HBsAg carriers in the general population is 0.81% (12) but according to the European Centre for Disease Prevention and Control technical report (13) on the epidemiological assessment of hepatitis B and C among migrants in the European Union/European Economic Area countries, the HBsAg prevalence in migrants from North Macedonia is 3,29%. Mandatory vaccination against hepatitis B in children was introduced in the national immunization protocol of North Macedonia in 2004, and this vaccination has a high coverage of 91.3% with three doses. According the data from the registry of the patients with CHB infection that are being followed-up and treated at the university clinic for infectious diseases and febrile conditions, in Skopje, part of the medical faculty of the state university, and one of the two national centers for treatment of patients with chronic hepatitis, the majority of patients with chronic HBV infection have HBeAg-negative CHB, and only 9,7% of patients have HBeAg-positive CHB. Genotyping has not been done in patients with CHB in North Macedonia, but according to Hadziyannis (14), in the countries in the Mediterranean Basin and in the neighboring countries there is an overall predominance of HBV genotype D in more than 80% and even 90% of HBV infections (Figure 2). HBV genotype D characterizes with predominance of HBeAg-negative precore mutant CHB, which develops during the course of chronic HBV infection thus preventing the formation of HBeAg (15,16,17). Patients with HBeAg-negative CHB have periods of reactivation with a pattern of fluctuating HBV-DNA and aminotransferase levels and histologic signs of active hepatitis and may have a potentially severe and progressive course toward cirrhosis and development of HCC (14,16,18). Long-term prognosis is poorer among patients with HBeAg-negative CHB compared to patients with HBeAg-positive CHB (18,19). Sustained off-therapy responses are rare with interferon-based therapies (19), only in a small proportion of patients, and the majority of patients with HBeAg-negative CHB necessitate long-term oral antiviral therapy, mostly lifelong therapy, which improves patients' outcome but is associated with progressively increasing rates of viral resistance.

Therefore, appropriate use of effective therapy is an important issue in the management of this group of patients.

The Therapy of Patients with Chronic HBV Infection

In 2021, WHO estimated that 12% to 25% of people with CHB infection will require treatment, depending on the setting and eligibility criteria (2). Antiviral therapy improves survival and quality of life by preventing liver disease progression to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, and death (4,5,20,21). The main endpoint of current treatment strategies is the induction of long-term suppression of HBV replication, and the loss of HBsAg is considered to be an optimal endpoint. Currently approved treatment options for CHB, peginterferon alpha-(PegIFN-α) and nucleos(t)ide analogues-NAs, do not offer a "complete cure"- clearance of covalently closed circular DNA and integrated HBV-DNA and rarely achieve a "functional cure" i.e. HBsAg loss. Eight NAs have been approved against HBV, of which the current recommended ones are entecavir and the two tenofovir prodrugs, disoproxil and alafenamide, with a high barrier to resistance, while in highly selected patients, an alternative treatment option is PegIFN (4,5,20,22,23).

The main advantage of PegIFN is the fixed duration of therapy and the chance for HBsAg seroconversion, but genotype D HBV patients have the lowest response rates, with only 20% achieving sustained control of viral replication (19,20,24). NAs inhibit HBV reverse transcriptase activity and therefore block HBV-DNA replication; they suppress viremia at clinically undetectable levels in up to 76% of HBeAg-positive and 93% of HBeAg-negative patients after one year of treatment. Their use is essentially lifelong for most patients, particularly those with HBeAg-negative CHB (20). Long-lasting, treatment-maintained suppression of HBV-DNA without resistance is achievable in most patients treated with entecavir or tenofovir (4,5,20,25).

Lamivudine, an oral NAs the first approved NA effective against HBV has very few side effects (25), but prolonged therapy results in high rates of viral resistance occurring in 14-32% of patients after 1 year of therapy, and in 60-70% of patients after 5 years, hence it is no longer widely used (26,27,28). Adefovir, an acyclic nucleotide analog initially used as monotherapy in patients with lamivudine resistance, but the development of resistance to adefovir was common, with inadequate control of viral replication (29).

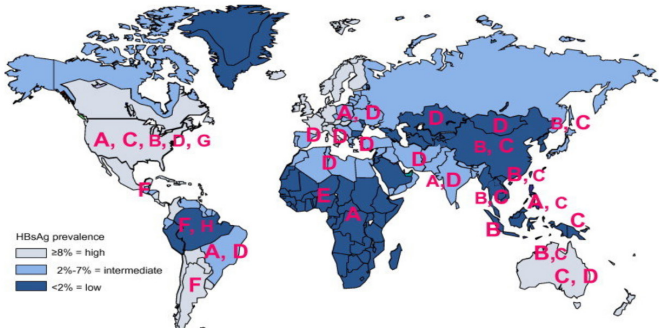

Figure 2. Geographical map displaying the levels of HBV endemicity in the world and the areas of predominance of the various HBV genotypes (14,17)

HBsAg: Hepatitis B surface antigen

Telbivudine is also a highly effective antiviral agent but has a very rapid emergence of resistance variants of HBV, 30% in 3 years. Lamivudine, adefovir, and telbivudine are no longer recommended as first-line therapies; however, they may still be widely prescribed in lower-middle income countries (4,5,20,25,26). Entecavir, a purine-derived NAs is a highly effective inhibitor of viral replication with few side effects. Long-term, minimum 3 years of entecavir therapy appears to result in the reversal of fibrosis and cirrhosis with improvement in liver histology. HBV drug resistance to entavir is extremely uncommon; it has been reported in only 1.2% of cases after 5 years. Entecavir is not the best choice of therapy for patients with established lamivudine resistance due to partial cross-resistance between lamivudine and entecavir and even given in a higher dose, 50% of such patients will develop entecavir resistance in 5 years (26). Entecavir is contraindicated in pregnancy and is not a good choice in young women who might be planning to or may accidentally become pregnant (30,31). Tenofovir disoproxil fumarate is an acyclic adenine nucleotide with potent activity against HBV and even after 8 years of follow-up of the patients, there was no tenofovir resistance registered (32). Tenofovir is the agent of choice for patients with lamivudine resistance because lamivudine and tenofovir have different mutational pathways to resistance and are highly effective in patients with prior adefovir resistance despite their similar resistance pathways, with 60-90% of patients receiving tenofovir having undetectable HBV-DNA after 1 year of therapy (29,33). Tenofovir alafenamide is a novel tenofovir prodrug with an improved safety profile. Tenofovir alafenamide is non-inferior to tenofovir disoproxil fumarate in both HBeAg-positive and HBeAg-negative CHB, and people treated with tenofovir alafenamide experienced smaller changes in bone mineral density and smaller declines in estimated glomerular filtration rate (34,35).

The Therapy of Patients with Chronic HBV Infection in North Macedonia

Republic of North Macedonia (Macedonia before 2019) is a country in Southeast Europe. It gained its independence in 1992 as one of the successor states of Yugoslavia and has a total area of 25,713 km^2 (9,928 sq mi). As of 2005 North Macedonia's unemployment rate was 37.2% and as of 2006, its poverty rate was 22% (36). The country's unemployment rate in the first quarter of 2015 decreased to 27.3% (37). North Macedonia has one of the highest shares of people struggling financially, with 72% of its citizens stating that they could manage on their household's income only "with difficulty" or "with great difficulty" (38). Census data from the last 2021 census show a population of 1,836,713 inhabitants (39) and North Macedonia Annual Household Income per Capita reached 2,627,562 USD in December 2021, compared with the previous value of 2,394.441 USD in Dec 2020 (40). The average monthly income in North Macedonia is 516.00 US Dollar per capita. In the USA, the figure is 5,911 US Dollar. However, the prices of consumer goods are also around 57.6% lower than in the USA, so when income and price levels are compared, the result is a more expensive life in North Macedonia than in the United States (41). The Republic of North Macedonia has a compulsory insurance-based health system with near universal coverage, and the current benefits package is considered to be very comprehensive. The Government and

the Ministry of Health provide the framework for operation and stewardship, and the Health Insurance Fund of North Macedonia is responsible for the collection of contributions, allocation of funds, and the supervision and contracting of providers. In the compulsory health insurance system, the funds generated by collecting contributions represent the main source of financing for the health sector. Co-payments by insured people and transfers from the state budget constitute additional sources of revenue, though rather small. Co-payments must be made by insured people for using health services and drugs (specified on a list) at all levels of care (42). The Health Insurance Fund established the Reference Price System for Positive Drug List (PDL) in 2008. This PDL has not been revised and expanded since 2011, and on this PDL only lamivudine is available through the co-payment system for people with CHB.

According to the data from one single center hospital, university clinic for infectious disease, from the registry of our patients with CHB, most patients are treated with NAs, namely with the first ever approved drug lamivudine, being the only drug on the PDL from the Insurance Fund of North Macedonia. A very small portion of patients, mostly with HBeAg-positive CHB that were treated with PegIFN, but except for very few who achieved HBeAg serotonversion and even fewer who achieved functional cure, the majority had to be treated with NAs. There is an increasing number of patients with CHB who have developed lamivudine resistance because of treatment longevity. Less than 15% of the patients with CHB are receiving tenofovir disoproxil fumarate mainly due to financial constraints. Namely, tenofovir is registered in North Macedonia, but it is not on the PDL, and the price for 1-month supply of the drug costs around 27% of the average monthly income in North Macedonia. Entecavir is also not on the PDL, and it has been registered only recently, the price for the drug has not been formed, and it is still not available on the market. Other drugs approved for the treatment of CHB such as adefovir and tenofovir alafanamid are not registered and therefore not available in North Macedonia.

A particular problem arises for patients who have developed resistance to lamivudine and who necessitate therapy with high barrier to resistance NAs. The drug resistance of entecavir is only 1% over 5 years in treatment-naive patients (4,5,43), but the rate of entecavir resistance could increase to 51% in lamivudine resistant patients because if primary lamivudine resistance mutations occur, compensatory resistance mutations to entecavir may arise even if primary lamivudine treatment is stopped (44). Therefore, entecavir is not the best treatment option after the development of lamivudine resistance in our patients because the majority of patients with CHB in North Macedonia are being or have been treated with lamivudine. Given the economic milieu of the country, it is more than obvious that therapy with tenofovir for the patients who have to be treated with this drug due to lamivudine resistance and have to buy it represents a significant monetary issue that undermines their already burdened domestic budget. Hence, it is necessary to raise the public, governmental, and policymakers' awareness about the management of patients with CHB and to put NAs with high resistance barriers on the PDL and to be covered by the North Macedonian Insurance Fund.

Conclusion

Republic of North Macedonia belongs to the countries with intermediate prevalence of chronic HBsAg carriage according to pooled data, and although routine immunization against hepatitis B has been implemented in the country since 2004 it has not shown its effect yet, seen by decreasing incidence and prevalence of both the acute and chronic form of HBV infection. Predominately, the patients in North Macedonia have HBeAg-negative CHB, and the only available drug which is on the PDL is lamivudine. According to the guidelines, treatment of patients with chronic HBV infection should be started with NAs with high resistance barrier to reduce the progression of the liver disease, but the prescription of tenofovir and entecavir, not being on the PDL, is limited due to financial constraints, whereas tenofovir alafenamide is not registered in North Macedonia. Entecavir resistance might be a clinical problem in antiviral treatment-experienced patients as are our patients, and if available, it should be reserved for treatment naïve patients. In our lamivudine - resistant patients, tenofovir is the agent of choice because lamivudine and tenofovir have different mutational pathways to resistance. Tenofovir monotherapy might be the optimal strategy for CHB patients in the Republic of North Macedonia, either treatment naïve or treatment experienced, and since cure rates are low, most patients will require therapy indefinitely. Effective antiviral treatment with universal vaccination should be implemented continuously to decrease the prevalence of chronic HBV infection in North Macedonia.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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References

1. World Health Organization. Combating Hepatitis B and C to reach elimination by 2030. 2016.
2. World Health Organization. Global hepatitis report 2022. Available from: https://cdn.who.int/media/docs/default-source/hq-hiv-hepatitis-and-stis-library/full-final-who-ghss-hiv-vh-sti_1-june2022.pdf?sfvrsn=7c074b36_13
3. Cox AL, El-Sayed MH, Kao JH, Lazarus JV, Lemoine M, Lok AS, Zoulim F. Progress towards elimination goals for viral hepatitis. Nat Rev Gastroenterol Hepatol. 2020;17:533-542.
4. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370-398.
5. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-1599.

6. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. Lancet. 2015;386:1546-1555.
7. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30:2212-2219.
8. Liaw YF, Brunetto MR, Hadziyannis S. The natural history of chronic HBV infection and geographical differences. Antivir Ther. 2010;15 Suppl 3:25-33.
9. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3:383-403.
10. Kao JH, Chen DS. Global control of hepatitis B virus infection. Lancet Infect Dis 2002;2:395-403.
11. www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/TER_100914_Hep_B_C%20_EU_neighbourhood.pdf
12. https://www.globalhep.org/country-progress/macedonia-former-yugoslav-republic
13. https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/epidemiological-assessment-hepatitis-B-and-C-among-migrants-EU-EEA.pdf
14. Hadziyannis SJ, Vassilopoulos D. Hepatitis B e antigen-negative chronic hepatitis B. Hepatology. 2001;34:617-624.
15. Brunetto MR, Stemler M, Schodel F, Will H, Ottobrelli A, Rizzetto M, Verme G, Bonino H, Raffel H. Identification of HBV variants which cannot produce precore derived HBeAg and may be responsible for severe hepatitis. Ital J Gastroenterol. 1989;21:151-154.
16. Funk ML, Rosenberg DM, Lok AS. World-wide epidemiology of HBeAg-negative chronic hepatitis B and associated precore and core promoter variants. J Viral Hepat. 2002;9:52-61.
17. Norder H, Couroucé AM, Coursaget P, Echevarria JM, Lee SD, Mushahwar IK, Robertson BH, Locarnini S, Magnius LO. Genetic diversity of hepatitis B virus strains derived worldwide: genotypes, subgenotypes, and HBsAg subtypes. Intervirology. 2004;47:289-309.
18. Guardiola Arévalo A, Gómez Rodríguez R, Romero Gutiérrez M, Gómez Moreno AZ, García Vela A, Sánchez Simón R, Gómez Hernando C, Andrés Esteban EM. Characteristics and course of chronic hepatitis B e antigen-negative infection. Gastroenterol Hepatol. 2017;40:59-69.
19. Marcellin P, Lau KKG, Bonino F, Farci P, Hadziyannis S, Piratvisuth T, Germanidis G, Yurdaydin C, Lai MY, Pluck N. Sustained response to peginterferon alfa-2a (40kD) (PEGASYS®) in HBeAg-negative chronic hepatitis B. One-year follow-up data from a large, randomised multinational study. J Hepatol. 2005;42(Suppl 2):185-186.
20. Prifti GM, Moianos D, Giannakopoulou E, Pardali V, Tavis JE, Zoidis G. Recent Advances in Hepatitis B Treatment. Pharmaceuticals (Basel). 2021;14:417.
21. Liaw YF. Reduction of cirrhosis and hepatocellular carcinoma with antiviral therapy in chronic hepatitis B. Hepatology. 2013;58:1856.
22. Sonneveld MJ, Hansen BE, Piratvisuth T, Jia JD, Zeuzem S, Gane E, Liaw YF, Xie Q, Heathcote EJ, Chan HL, Janssen HL. Response-guided peginterferon therapy in hepatitis B e antigen-positive chronic hepatitis B using serum hepatitis B surface antigen levels. Hepatology. 2013;58:872-880.
23. Lampertico P, Viganò M, Colombo M. Why do I treat HBeAg-negative chronic hepatitis B patients with pegylated interferon? Liver Int. 2013;33(Suppl 1):157-163.
24. Buster EH, Schalm SW, Janssen HL. Peginterferon for the treatment of chronic hepatitis B in the era of nucleos(t)ide analogues. Best Pract Res Clin Gastroenterol. 2008;22:1093-1108.
25. Pierra Rouviere C, Dousson CB, Tavis JE. HBV Replication Inhibitors. Antivir Res. 2020;179:104815.
26. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology. 2009;137:1593-608.e1-2.
27. Abd El Aziz MA, Sacco R, Facciorusso A. Nucleos(t)ide analogues and Hepatitis B virus-related hepatocellular carcinoma: A literature review. Antivir Chem Chemother. 2020;28:2040206620921331.
28. Su MH, Lu AL, Li SH, Zhong SH, Wang BJ, Wu XL, Mo YY, Liang P, Liu ZH, Xie R, He LX, Fu WD, Jiang JN. Long-term lamivudine for chronic hepatitis B and cirrhosis: A real-life cohort study. World J Gastroenterol. 2015;21:13087-94.
29. Lampertico P, Viganò M, Manenti E, Iavarone M, Lunghi G, Colombo M. Adefovir rapidly suppresses hepatitis B in HBeAg-negative patients developing genotypic resistance to lamivudine. Hepatology. 2005;42:1414-1419.
30. Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kobayashi M, Kumada H. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology. 2013;58:98-107.
31. Lok AS, Trinh H, Carosi G, Akarca US, Gadano A, Habersetzer F, Sievert W, Wong D, Lovegren M, Cohen D, Llamoso C. Efficacy of entecavir with or without tenofovir disoproxil fumarate for nucleos(t)ide-naïve patients with chronic hepatitis B. Gastroenterology. 2012;143:619-628.
32. Liu Y, Corsa AC, Buti M, Cathcart AL, Flaherty JF, Miller MD, Kitrinos KM, Marcellin P, Gane EJ. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. J Viral Hepat. 2017;24:68-74.
33. Svarovskaia ES, Curtis M, Zhu Y, Borroto-Esoda K, Miller MD, Berg T, Lavocat F, Zoulim F, Kitrinos KM. Hepatitis B virus wild-type and rtN236T populations show similar early HBV DNA decline in adefovir refractory patients on a tenofovir-based regimen. J Viral Hepat. 2013;20:131-140.
34. Buti M, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, Hui AJ, Lim YS, Mehta R, Janssen HL, Acharya SK, Flaherty JF, Massetto B, Cathcart AL, Kim K, Gaggar A, Subramanian GM, McHutchison JG, Pan CQ, Brunetto M, Izumi N, Marcellin P; GS-US-320-0108 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:196-206.
35. Chen YC, Hsu CW, Chien RN, Tai DI. One-year efficacy of tenofovir alafenamide in patients with chronic hepatitis B: An observational study. Medicine (Baltimore). 2022;101:e29269.
36. Macedonian unemployment rate. Worldbank.org.mk. Retrieved: 28 April 2010.
37. State Statistical Office Active population-Unemployment data.
38. Gallup Balkan Monitor, 2010 Archived 27 December 2012 at the Wayback Machine.
39. "Macedonia – State Statistical Office". Stat.gov.mk. Retrieved: 10 February 2016.
40. www.ceicdata.com/en/indicator/macedonia/annual-household-income-per-capital
41. www.worlddata.info/europe/northmacedonia/economy.php
42. https://eurohealthobservatory.who.int/countries/north-macedonia#
43. Sarin SK, Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1-98.
44. Tenney DJ, Rose RE, Baldick CJ, Levine SM, Pokornowski KA, Walsh AW, Fang J, Yu CF, Zhang S, Mazzucco CE, Eggers B, Hsu M, Plym MJ, Poundstone P, Yang J, Colonno RJ. Two-year assessment of entecavir resistance in Lamivudine-refractory hepatitis B virus patients reveals different clinical outcomes depending on the resistance substitutions present. Antimicrob Agents Chemother. 2007;51:902-911.

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Safety and Effectiveness of Tenofovir Alafenamide in the Turkish Population: A Systematic Review

Tenofovir Alafenamidin Türk Popülasyonunda Güvenliği ve Etkinliği: Sistematik İnceleme

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ABSTRACT

Hepatitis B virus infection is an important public health problem in the world and in Turkey. Nucleoside analogues and pegylated interferon-α are used as therapeutic agents in the management of chronic hepatitis B (CHB) infection. With current treatments, the disease is at a controllable point. Unfortunately, although cure studies continue, the cure treatments in the near future will not be an alternative. Tenofovir disoproxil fumarate (TDF) has been used for the treatment of CHB infection since 2008. Beside its high antiviral activity and lack of resistance, long-term use of TDF may lead to a decline in renal functions and bone mineral density. As a prodrug, tenofovir alafamide (TAF) provides considerable reduction (%90) in systemic exposure to tenofovir and has a better safety profile. TAF was used in some special cases (osteoporosis and decreased renal functions) in Turkey. In 2020, TAF was reimbursed for naive and treatment-experienced patients CHB patients. Evidence for the efficacy and safety of TAF continues to accumulate at an accelerating rate, especially following removal of reimbursement restrictions in 2020. In this review, we aim to summarize the real-world evidence obtained about TAF treatment in the last two years in Turkey.

Keywords: Chronic HBV infection, efficacy, tenofovir alafenamide

ÖZ

Hepatit B virüsü enfeksiyonu dünyada ve Türkiye'de önemli bir halk sağlığı sorunudur. Nükleosid analogları ve pegile interferon-α, kronik hepatit B (KHB) enfeksiyonunun tedavisinde terapötik ajanlar olarak kullanılır. Mevcut tedavilerle hastalık kontrol edilebilir bir noktaya geldi. Ne yazık ki kür çalışmaları devam etse de yakın gelecekte kür tedavileri alternatif olamayacaktır. Tenofovir disoproksil fumarat (TDF), 2008'den beri KHB enfeksiyonunun tedavisinde kullanılmaktadır. Yüksek antiviral aktivitesi ve direnç eksikliğinin yanı sıra TDF'nin uzun süreli kullanımı böbrek fonksiyonlarında ve kemik mineral yoğunluğunda azalmaya neden olabilir. Bir ön ilaç olarak tenofovir alafamid (TAF), tenofovire sistemik maruziyette önemli ölçüde azalma (%90) sağlar ve daha iyi bir güvenlik profiline sahiptir. Türkiye'de bazı özel durumlarda (osteoporoz ve böbrek fonksiyonlarında azalma) TAF kullanılmıştır. 2020 yılında TAF'ye, daha önce tedavi görmemiş ve tedavi deneyimi olan KHB hastaları için geri ödeme yapılmıştır. TAF'nin etkinliği ve güvenliğine ilişkin kanıtlar, özellikle 2020'de geri ödeme kısıtlamalarının kaldırılmasının ardından artan bir hızla birikmeye devam ediyor. Bu derlemede Türkiye'de son iki yılda TAF tedavisine ilişkin elde edilen gerçek dünya kanıtlarını özetlemeyi amaçladık.

Anahtar Kelimeler: Kronik HBV enfeksiyonu, etkililik, tenofovir alafenamid

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Introduction

Hepatitis B virus (HBV) infection remains a healthcare challenge affecting more than 250 million people worldwide (1). Turkey has a significant HBV burden with a prevalence of 4.57% (2,3). The main goals of HBV therapy are to prevent the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma, and death from HBV-related liver disease through the suppression of viral replication (4). Nucleoside analogues (NAs) and pegylated interferon-α are used as therapeutic agents in the management of chronic hepatitis B (CHB) infection (1).

NAs suppress viral replication in the longterm and improve liver-related outcomes. Tenofovir disoproxil fumarate (TDF) has been used for the treatment of CHB infection since 2008. In addition to its high antiviral activity and lack of resistance, TDF may have a negative impact on renal and bone metabolism (1,5). As a prodrug, tenofovir tenofovir alafenamide (TAF) provides considerable reduction (90%) in systemic exposure to tenofovir and has a better safety profile (6).

TAF was first included in the reimbursement list with a restriction on its use for the treatment of CHB patients with renal and bone conditions or with other comorbidities in Turkey in 2018 (7). Evidence for the efficacy and safety of TAF continues to accumulate at an accelerating rate, especially following the removal of reimbursement restrictions in 2020. In this review, we summarize the real-world evidence obtained regarding TAF treatment in the last two years in Turkey.

Materials and Methods

Search Strategy

The search strategy consisted of searching PubMed, Scopus, Web of Science, Google Scholar, and abstracts from five major liver meetings and congresses (The National Viral Hepatitis Congress, The National Hepatology Congress, The Gastroenterology Week, and AASLD-TASL Digital Hepatology Connect and AASLD Liver Meeting) between January 1, 2020 and December 30, 2021. Because the restrictions of TAF use only in patients with renal and/or bone issues were omitted in 2020, data from 2020 and 2021 were used. Reports describing the use of TAF were included. The titles and abstracts were screened to detect the relevance of the study, and the full texts of the relevant studies were obtained and reviewed. Search strings for hepatitis, HBV, tenofovir alafenamide, TAF, Turkey, and Türkiye were used. The references of the cited articles were searched for additional articles that may have been missed. The data in this review are reported according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (8) (Figure 1).

Results

A search of medical literature yielded 11 studies from Turkey (9, 10,11,12,13,14,15,16,17,18,19,20).

Treatment-naive Cases

Three studies presented treatment effectiveness and/or safety characteristics of treatment-naive patients given TAF (9,10,11) (Table 1).

Biological and chemical response: Clinical effectiveness in treatment-naive cases was examined in only two meeting abstracts. Tabak et al. (9) presented the percentage of cases with undetectable HBV-DNA (<20 IU/mL) and normal alanine transaminase (ALT) levels (<35 IU/L for men, <25 IU/L for women) in three consecutive moments (baseline, 3rd, and 6th month). The percentage of cases with normal ALT levels rose from approximately 40% to approximately 80%. In addition, HBV-DNA became undetectable in 89.1% of cases. Türker et al. (10) reported 89.1% and 80% virologic and biochemical responses.

Safety outcomes: Three studies reported safety outcomes (9,10,11) (Table 2). Tabak et al. (9) and Türker et al. (10) reported no significant difference in renal function. Karasahin et al. (11) showed a significant increase in estimated glomerular filtration rate (eGFR) in the 3rd month and then regressed to its baseline level in the 6th month.

The lipid profile was examined in two studies (9,10). Total cholesterol, low-density lipoprotein (LDL) and high-density lipoprotein cholesterol, and triglyceride levels did not change significantly.

Treatment-experienced Cases

In treatment-experienced cases, TDF was the leading agent in their treatment history. Investigators reported that approximately 70-80% of cases switched to TAF from TDF. In Table 3, 4, baseline characteristics and efficacy and safety endpoints of TAF cases are given, respectively.

Biological and chemical response: Although investigators did not share the statistical significance, it could be observed in the numerical increase in viral suppression and ALT normalization. Virologic response increased from approximately 70% to 80% 12 months after switching to TAF.

Safety outcomes: Renal function remained stable in three studies (9,12,13). Kalkan et al. (15) reported a marked statistically significant improvement in renal function.

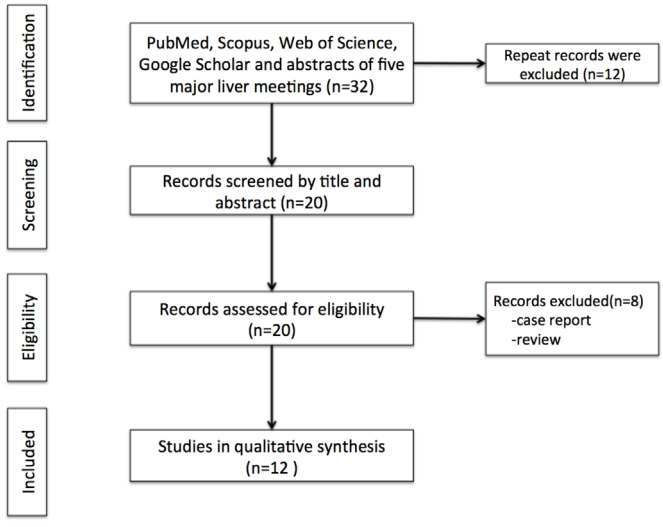

Figure 1. PRISMA flow diagram of literature review process for the studies of tenofovir alafenamide use in Turkey

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1. Baseline characteristics and treatment effectiveness of the treatment-naive patients given tenofovir alafenamide

References	Baseline characteristics							Treatment effectiveness							
								HBV-DNA <20 IU/mL, %				Normal ALT (%)**			
	n	Median age (years)	Gender (male, n,%)	ALT (IU/L, median)	HBeAg-negative (n, %)	Fibrosis (median)	HAI (median)	Baseline	6th months	12th months	p	Baseline	6th months	12th months	p
Tabak et al. (9)	71	48	35 (48.5)	33	43 (84.3)	2	7		79.4	84.7		45.9	76.3	77.8	
Türker et al. (10)	202	50	122 (60.4)	40	118 (80.3)	2	7		74.7	89.1		38.2	73.2	80.0***	<0.05
Karasahin et al. (11)	105	58	68(64.8)												

*Based on Ishak's scoring, **<35 IU/L for male, <25 IU/L for female. ***p<0.05, HAI: Histologic activity index

Table 2. Safety outcomes of the treatment-naive patients given tenofovir alafenamide*

References	Parameter	Baseline	3rd months	6th months	12th months	p
Tabak et al. (9)	HDL, mg/dL, median (SD)	65 (35.0)		110 (37.1)	96 (26.9)	>0.05
	LDL, mg/dL, median (SD)	99 (39.9)		90 (29.9)	88 (24.7)	>0.05
	Cholesterol, mg/dL, median (SD)	202 (46.1)		226 (28.0)	212 (67.2)	>0.05
	Triglyceride, mg/dL, median (SD)	134.5 (88.3)		184 (56.4)	156 (48.8)	>0.05
	Creatinine, mg/dL	0.80		0.97	0.78	
	eGFR, mL/min	90.5		89.5	101	
Türker et al. (10)	HDL, mg/dL, median (SD)	53 (27.3)		52 (32.2)	56 (34.6)	>0.05
	LDL, mg/dL, median (SD)	107 (37.3)		100 (37.2)	97 (31.1)	>0.05
	Cholesterol, mg/dL, median (SD)	189 (59.1)		208 (41.7)	166 (28.2)	>0.05
	Triglyceride, mg/dL, median (SD)	103 (66.2)		142.5 (75.3)	146 (63.4)	>0.05
	Creatinine, mg/dL	0.80		0.89	0.85	
	eGFR, mL/min	99		95	94	
Karasahin et al. (11)**	eGFR, mL/min, (n=5)	67.60 (41.04)	76.40 (41.04)	67.20 (40.64)		<0.001
	Phosporus, mg/dL, (n=4)	3.68 (1.83)		3.59 (1.73)		0.115
	T-score, hip, (n=1)	-1.2		NA		
	T-score, spine, (n=1)	-2.6		NA		

*Baseline characteristics of these patients were given in Table 1. **This study includes 105 patients: median age 58 years, male 68 (64.8%), osteoporosis 11 (12.6%), cirrhosis 48 (49.5%), haemodialysis 5 (4.9%), solid organ transplantation 48 (49%), steroid use 78 (74.3%). HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation, eGFR: Estimated glomerular filtration rate, NA: Not available

Table 3. Baseline characteristics and treatment effectiveness of the treatment-experienced patients switched to tenofovir alafenamide

Referefences	Baseline characteristics										Treatment effectiveness							
											Normal ALT (%)**				Undetectable HBV-DNA (%)			
	n	Age (years, median)	Gender (male, n, %)	ALT (U/L, median)	HBeAg positive (n,%)	Fibrosis*	HAI*	Previous treatment (%)	Duration of previous treatment (months, median)	Reason to switch	Baseline	6 months	12 months	p	Baseline	6 months	12 months	p
Sarı et al. (12)	391	44	235 (60)	23	238 (85)	2	7	TDF: 81.6, ETV: 8.2, LAM: 6.1, TEL: 2.9, ADV: 1.1			71.6	81.5	83.9		80.7	79.4	84.7	
Tabak et al. (9)	504	54	288 (59.1)	22.5	345 (86.5)	2	7	TDF: 83.9, ETV: 6.9, LAM: 5.6, TEL: 2.8, ADV: 0.8	52	GFR 61 (12.1), proteinuria/ albuminuria 49 (9.7), transplantation 11 (2.2), steroids 6 (1.2), fractures 2 (0.4), hemodialysis 2 (0.4)	72.3	79.1	80.0		79.4	90.2	87.0	
Sürme et al. (13)	565	53	336 (59.5)					TDF 83.9, ETV: 7.6, LAM: 5.1, TEL: 2.7, ADV: 0.7	12		71.9	79.1	79.6		78.6	87.8	85.4	
Akar (14)	27	48	16 (59)	51	3 (11)	3	8				7		0		7		0	
Kalkan et al. (15)	237	38	160 (67.5)	33							43.2			48.3	97.2		98.2	1

*Based on Ishak's scoring, **<35 IU/L for male, <25 IU/L for female. ***p<0.05, ALT: Alanine transaminase, HBeAg: Hepatitis B e antigen, HBV: Hepatitis B virus, HAI: Histologic activity index, TDF: Tenofovir disoproxil fumarate, ETV: Entecavir, LAM: Lamivudine, TEL: Telbivudine, ADV: Adefovir

Table 4. Safety characteristics and treatment effectiveness of the treatment-experienced patients switched to tenofovir alafenamide*

Reference	Feature	Baseline	6th months	12th months
Sarı et al. (12)	HDL, mg/dL median (SD)	44.5 (19.1)	44.5 (18.2)	51 (15.3)
	LDL, mg/dL median (SD)	114 (54.5)	132.5 (33.2)	136 (44.1)
	Cholesterol, mg/dL, median (SD)	176 (52.7)	206 (39.1)	199 (52.7)
	Triglyceride, mg/dL, median (SD)	102 (65.4)	125.5 (77.7)	113 (50.9)
	Creatinine, mg/dL	0.86	0.86	0.88
	eGFR, mL/min	92	84.2	87.2
Tabak et al. (9)	Creatinine, mg/dL	0.83	0.86	0.85
	eGFR, mL/min	94	90	86.9
Sürme et al. (13)	Creatinine, mg/dL	0.80	0.89	0.85
	eGFR, mL/min	99.0	95	94
Karasahin et al. (11)*	eGFR, mL/min, (n=105)	99.21 (20.56)	103.41 (19.11)	
	Phosphorus, mg/dL, (n=117)	2.82 (0.44)	2.90 (0.44)	
	T-score hip, (n=78)	-1.57 (0.65)	-1.46 (0.72)	
	T-score, spine, (n=78)	-1.77 (0.83)	-1.50 (1.05)	
Akar (14)	GFR (mL/min), mean ± SD	100 (14)		102 (5)
	Phosphorus (mg/dL), mean ± SD	2.3 (0.4)		2.9 (0.6)
Kalkan et al. (15)	GFR (mL/min), mean,	102.27		**<0.001**
	Phosphorus (mg/dL), mean,	2.82		0.226
	Creatinine (mg/dL), mean	0.90		**0.011**
	T-score hip, mean	-1.74		**0.001**
	T-score, spine, mean	-1.56		0.608
	LDL (mg/dL), mean	101.3		107.9
	HDL (mg/dL), mean	58.6		60.2
	Cholesterol (mg/dL), mean	196.9		204.2
	TG (mg/dL), mean	196.3		196.4

*Baseline characteristics of these patients were given in Table 3. HDL: High-density lipoprotein, LDL: Low-density lipoprotein, eGFR: Estimated glomerular filtration rate, SD: Standard deviation, TG: Triglyceride

Sarı et al. (12) reported a numerical increase in LDL and total cholesterol levels compared with the basal level with no statistical significance.

Cases with Special Health Conditions

Data in this category were reported in six studies (9,16,17,18,19,20) (Table 5).

Biological and chemical response: Three studies (9,16,17) reported TAF prophylaxis in immunosuppressed patients, and no reactivation at 12th month was reported (Table 5).

Similarly, the effectiveness data revealed a high virologic response in patients undergoing chronic hemodialysis and renal transplant.

Safety outcomes: Studies by Gokcan et al. (18) and Yapalı et al. (19) reported no change in lipid profile or renal function.

Discussion

Clinical practice guidelines have proposed the preference of TAF or entecavir (ETV) over TDF in elderly patients and those with a current bone mineral density (BMD) and renal condition (21,22). Recent evidence showed its superiority to ETV in terms of both virological and biochemical responses (23). TAF has been widely used in both treatment-naive and experienced patients, most likely because of its better safety and efficiency profiles.

In treatment-naive patients, the virologic response (having lower HBV-DNA levels, <29 IU/mL) was reported as 94% in hepatitis B e antigen (HBeAg)-negative (24) and 93% in HBeAg-positive cases (25) in phase III studies at the 48th week. In the cohort of Türker et al. (10), the virologic response rate (defined as having lower HBV-DNA levels <20 IU/mL) was reported as 89.1% at the same time point. The proportion of HBeAg-negative cases was 80.3% in this cohort. In these phase III studies, the ALT normalization rate (<30 for men, 19 for women) was reported as 50% in HBeAg-negative and 45% in HBeAg-positive cases. Normalization rate cases having normal ALT levels at the end of the study were reported to be approximately 78-80% (9,10). The observed ALT normalization rate might be considered as a sign of additional benefit of TAF treatment according to the results of studies indicating decreased rates of hepatocellular carcinoma, encephalopathy, and ascites in cases with normal ALT levels (26).

A pooled analysis of phase III studies reported signs of worsening of the lipid profile with TAF, with respect to the observed scores in TDF treatments (6% vs. 1% for LDL >190 mg/dL, 1% vs

Table 5. Characteristics of patients in special groups given tenofovir alafenamide

References	Special group	Indication	n	Age (mean, years)	Male (n, %)	Baseline characteristics	Effectiveness outcome	Safety outcome
Tabak et al. (9)	Immunosuppressed	Prophylaxis	58	57	24 (41.4%),	HBeAg (-) 90.3%, HBsAg (-) 64.3%, median ALT: 20 U/L.	Normal ALT: baseline 74.5%, 6th months 73.5%, 12th months 72%	Cr (mg/dL): baseline 0.97, 6th months 0.85, 12th months 0.77. eGFR (mL/min): baseline 58, 6th months 96, 12th months 92.5
Yörük et al. (16)	Immunosuppressed	Prophylaxis	145	58	67 (46.2%)	HBeAg (-) 92.9%, HBsAg (-) 55.3%,	No reactivation on 12th months Normal ALT: baseline 69%, 6th months 78%, 12th months 72.7%	Cr (mg/dL): baseline 0.97, 6th months 0.89, 12th months 0.77. eGFR (mL/min): baseline 90.5, 6th months 96, 12th months 92.7
Gündüz et al (17)	Immunosuppressed	Prophylaxis	171	60.7	84 (49%)	HBsAg (-) 38%	No reactivation during follow up of 6 months (mean)	The renal function tests and lipid profiles did not significantly change. No serious adverse events were reported at the follow-up.
Gokcan et al. (18)	HBV Cirrhosis	Treatment	34	64	50%	Median ALT: 29 IU/L, median HBV-DNA 6,200 IU/L, 11.8% TAF-naive, 19.7% decompensated	ALT normalized in all cases between 3-12 months. No reactivation. No HBV-related death	TAF was well-tolerated
	Post-transplant HBV	Treatment	76	57	80	Median ALT: 22 IU/L. Tacrolimus use, 90%, everolimus 47%. TAF-naive 22.4%	The virologic and biochemical response was observed in all patients	Renal function tests and lipid profiles remained stable during the treatment. No serious adverse effects were reported.
Yapalı et al. (19)	HBV Cirrhosis	Treatment	72	64	54	Median ALT: 29 IU/L, median HBV-DNA 6,200 IU/L, decompensated cirrhosis 21%, treatment naive 21%, most common indications for TAF: Renal dysfunction, osteoporosis	On 4 months (median) follow up, ALT normalized (>40 IU/L) 90%. No reactivation, no HBV-related death.	Lipid profile and renal functions did not change.
	Post-transplant HBV	Treatment	125	57	78	Median ALT: 23 IU/L, median HBV-DNA 6,200 IU/L, tacrolimus use 78%, everolimus use 38%	On 6 months (median) follow up, no HBV reactivation	Lipid profile and renal functions did not change.
Adanır et al. (20)	HBV Cirrhosis	Treatment	16	54.6	63	Treatment-naive (n=25), TAF-naive (n=12)	Follow up 10.4 months (mean). Among treatment-naive patients, viral and biochemical responses at 12 months: 92% and 96%.	No reactivation
	Post-transplant HBV	Treatment	61	11	31	Tacrolimus use 82%, cyclosporine 23%, everolimus 15%	Follow-up 7 months (mean). In all patients, viral and biochemical responses were obtained on 3 to 12 months.	

HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, HBsAg: Hepatitis B surface antigen, ALT: Alanine transaminase, TAF: Tenofovir alafamide, Cr: Creatinine eGFR: Estimated glomerular filtration rate

0% for total cholesterol more than 300 mg/dL) (27). This difference could be a result of high plasma tenofovir levels in TDF-treated patients. In contrast to the relative lowering effect of TDF, Jeong et al. (28) reported no difference in lipid profiles between TAF-treated and non-HBV-infected controls. In addition, in the cohort of Tabak et al. (9), no significant change was reported in total cholesterol and its subfractions over 48 weeks. It could be inferred that these findings support the opinion that changes in lipid levels after TAF switching represents "returning to normal"(6).

While Tabak et al. (9) reported a numerical decrease in serum creatinine level at the 48th week; phase III studies reported serum creatinine level increase as 0.01 mg/dL (0.00 to 0.02) at the same time-point (24,25). In addition, in contrast to findings in phase III studies (-1.8 and-5.4 mL/min median change in GFR, respectively), Tabak et al. (9) reported a numerical increase in GFR at the 48th week compared with baseline (101 vs 90.5). Additionally, Karasahin et al. (11) reported that an emerging numerical increase in GFR (76.40 mL/min) at the 24th week regressed to baseline level at the 48th week (67.60 mL/min vs 67.60 mL/min).

In treatment-experienced patients, according to the reported results from the cohort of Sarı et al. (12), the ALT normalization rate was 83.9% at the 48th week and comparable to that reported (79%) by Lampertico et al. (29) at the same time point. Lampertico et al. (29) and Kalkan et al. (15) reported similar ALT normalization rates at 24th week (48.3%) and 48th week (50%) respectively. ALT normalization rates at the 48th week after switching to TAF were reported from the data of two non-interventional studies as 70.2% (30) and 83% (31).

Changes in renal function have been reported in these cohorts. Karasahin et al. (11), Akar (14) and Kalkan et al. (15) reported an increase in GFR (2-7 mL/min) at different time points. Additionally, Kalkan et al. (15) reported a reduction in creatinine levels (0.05 mg/dL). These findings were similar to those of Lampertico et al. (29) and Byun et al. (32), who reported increases in GFR of +0.94 and +7.3 mL/min, respectively. Interestingly, Lee et al. (33) reported a reduction in GFR (-0.6% at the 24th week, -5.2% at the 72nd week). The majority of data from clinical trials and real-life studies suggest that TAF would be an advantageous choice for treating people with the potential of having or getting renal conditions.

BMD was evaluated as another safety issue by Karasahin et al. (11) and Kalkan et al. (15). Both authors reported improvement in hip and spine T-scores over treatment, and their findings reached statistical significance, except for spine T-scores in the cohort of Kalkan et al. (15). TAF use may be safer in patients with bone disease, especially considering that chronic hepatitis patients are elderly and will get older over a long treatment period.

In the cohort of Sarı et al. (12), a numerical increase in total and subfractions was observed between before and after treatment, but the changes were reported as insignificant. However, Kalkan et al. (15) reported that the observed increase in LDL and total cholesterol reached statistical significance.

As a serious event, HBV reactivation can be prevented by prophylaxis (34). However, the risk of reactivation is overlooked because patients are followed by different clinical departments (35,36). The efficacy of TAF prophylaxis was compared with that of ETV by Inada et al. (37). They found no difference in the HBV-DNA decreasing rate. In addition, they reported no difference in eGFR as a renal safety indicator. Yörük et al. (16) and Gündüz et al. (17) reported no reactivation among immunosuppressed individuals administered TAF for prophylaxis at 12 and 6 months, respectively.

Three studies reported the results of TAF use in post-transplant patients (18,19,20). Gokcan et al. (18) and Adanır et al. (20) reported virologic and biochemical responses in all liver transplant patients within one year. Yapalı et al. (19) described no HBV reactivation at 6 months' follow-up as a response.

Three studies have reported the results of TAF use in cirrhotic patients (18,19,20). Gokcan et al. (18) reported ALT normalization in all cases between 3 -12 months with no reactivation and no HBV-related death. Yapalı et al. (19) reported ALT normalization in 90% of patients in a median follow-up period of 4 months with no reactivation and no HBV-related death, while Adanır et al. (20) described viral and biochemical responses in all patients at 3 to 12 months.

Conclusion

As a prodrug, TAF provides effective viral suppression and ALT normalization. Beyond its antiviral effectiveness, ALT normalization could result in decreased risk of delayed complications, including development of hepatocellular carcinoma, encephalopathy, and esophageal varices. Safety outcomes on bone metabolism and renal functions are encouraging for TAF use in naive cases for chronic use considering the advanced/advancing age of the patients. Real-life efficiency and safety data on its prophylactic or therapeutic use in special groups, including immunosuppressed individuals, post-transplant patients, and cirrhotic patients, support its use.

Ethics

Peer-review: Internally peer reviewed.

Authorship Contributions

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

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References

1. Buti M, Marcos-Fosch C, Esteban R, Valenti L. Nucleos(t)ide analogue therapy: The role of tenofovir alafenamide. Liver Int. 2021;41:9-14.
2. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, Kaymakoglu S, Ergonul O. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clinical Microbiol Infect. 2015;21:1020-1026.
3. Toy M, Önder FO, Wörmann T, Bozdayi AM, Schalm SW, Borsboom GJ, van Rosmalen J, Richardus JH, Yurdaydin C. Age- and region-specific hepatitis B prevalence in Turkey estimated using generalized linear mixed models: a systematic review. BMC Infect Dis. 2011;11:337.

4. Idilman R. The summarized of EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Turk J Gastroenterol. 2017;28:412-416.
5. Marcellin P, Wong DK, Sievert W, Buggisch P, Petersen J, Flisiak R, Manns M, Kaita K, Krastev Z, Lee SS, Cathcart AL, Crans G, Op den Brouw M, Jump B, Gaggar A, Flaherty J, Buti M. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int. 2019;39:1868-1875.
6. Lim YS, Seto WK, Kurosaki M, Fung S, Kao JH, Hou J, Gordon SC, Flaherty JF, Yee LJ, Zhao Y, Agarwal K, Lampertico P. Review article: switching patients with chronic hepatitis B to tenofovir alafenamide-a review of current data. Aliment Pharmacol Ther. 2022;55:921-943.
7. Sosyal Güvenlik Kurumu Sağlık Uygulama Tebliğinde Değişiklik Yapılmasına Dair Tebliğ [Internet]. 2018 [cited 2022 Sep 15]. Available from: https://www.resmigazete.gov.tr/eskiler/2018/12/20181228M1-1.pdf
8. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339.
9. Tabak F, Yörük G, Köksal İ, Erdem H, Yıldız D, İnce N, Güner R, HEPB Study Group. Tenofovir alafenamide in HBV: Real life data from Turkey. AASLD TASL Digital Hepatology Connect, Nov 12-15, 2021. Hepatology Forum 2021;2(Suppl 1):22.
10. Türker K, Yörük G, Karabay O, et al., Hep B Çalışma Grubu. Tenofovir Alafenamid ile tedavi edilen naif KHB hastaları: Gerçek Yaşam Verileri. Oral presentation-0015, 15th National Viral Hepatitis Congress, 7-10 October 2021, Dalaman, Turkey.
11. Karasahin O, Akdemir Kalkan I, Dal T, Altunısık Toplu S, Harputoğlu M, Mete AO, Kömür S, Sarigül F, Yildiz Y, Esmer F, Kandemir O, Nazik S, İnan D, Akgul F, Kaya S, Tunc N, Balin ŞÖ, Bayindir Y, Taşova Y, Akar F, Oren MM, Ayhan M, Demir Y, Çelen MK. Real-life data for tenofovir alafenamide fumarate treatment of hepatitis B: the Pythagoras Cohort. Hepat Mon. 2021;21:e104943.
12. Sarı ND, Köksal İ, Erdem H, et al. Hep B Study Group. Changes in lipid profile among HBV patients treated with tenofovir alafenamide: Turkey's experience of real life setting. AASLD TASL Digital Hepatology Connect, Nov 12-15, 2021. Hepatology Forum 2021;2(Suppl 1):15-16.
13. Sürme S, Yörük G, Karabay, O, et al. Hep B Çalışma Grubu. Tedavi DeneyimLi Hastalarda Kronik Hepatit B Tedavisinde Tenofovir Alafenamid: Gerçek Yaşam Verileri. Oral presentation-0016, 15th National Viral Hepatitis Congress, 7-10 October 2021, Dalaman, Turkey.
14. Akar M. Real-life data of tenofovir disoproxil fumarate and tenofovir alafenamide fumarate in the patients with chronic hepatitis B: a single-center experience. Anatolian Cur Med J. 2021;3:239-245.
15. Kalkan İA, Karaşahin Ö, Sarıgül F, Altunışık Toplu S, Aladag M, Mete AO, Golbol A, Nazik S, Kömür S, Ören MM, Yıldız Y, Demir Y, Ayhan M, Tosova Y, Bayındır Y, Dal T, Celen MK. Comparison of tenofovir alafenamide and entecavir therapy in patients with chronic hepatitis B initially treated with tenofovir disoproxil: A retrospective observational survey. Hepat Mon. 2021;21:e118721.
16. Yörük G, Karabay O, Yamazhan N, et al. Hep B Çalışma Grubu. İmmünsüpresif Hastalarda Profilakside Tenofovir Alafenamid'in Yeri: Gerçek Yaşam Verileri. Oral presentation-0017, 15th National Viral Hepatitis Congress, 7-10 October 2021, Dalaman, Turkey.
17. Gündüz F, Durak S, Ünsal Y, et al. Kemoterapi ve İmmünosüpresif Tedavi Alan Hastalarda Hepatit B Reaktivasyon Profilaksisinde Tenofovir Alafenamid Fumaratın Etkinliği ve Güvenliği: Çok Merkezli-Gözlemsel Çalışmanın ilk Sonuçları. National Hepatology Week, 28-30 May 2021, Turkey.
18. Gokcan H, Yapali S, Ellik ZM, et al. Real-life efficacy and tolerability of tenofovir alafenamide fumarate (TAF) in special groups of Hepatitis B patients: Liver transplant recipients and cirrhosis. AASLD TASL Digital Hepatology Connect, Nov 12-15, 2021. Hepatology Forum 2021;2(Suppl 1):18.
19. Yapalı S, Gökcan H, Harputluoğlu MMM, et al. Tenofovir Alafenamid fumarat'ın hepatit B özel hasta gruplarında gerçek yaşam etkinliği ve tolere edilebilirliğinin ön sonuçları: HBV-ilişkili siroz ve post-transplant hastalar (PS-43). 13.Ulusal Hepatoloji Kongresi, Sanal Kongre, Antalya, Turkey, 2021.
20. Adanır H, Etik DÖ, Yıldırım AE, et al. Tenofovir Alafenamid'in Kronik Hemodializ Hastası Veya Böbrek Nakli Olmuş Hepatit B Virüs İle Enfekte Hastalarda Etkinliği Ve Güvenirliği: Ön sonuçlar. 38th National Gastroenterology Week, Nov 16-21, 2021, Antalya, Turkey. Turkish J Gastroenterol 2021;32(Suppl 1) PP-242.
21. Roade L, Loglio A, Borghi M, Riveiro-Barciela M, Soffredini R, Facchetti F, di Paolo D, Tabernero D, Lunghi G, Esteban R, Buti M, Lampertico P. Dig Liver Dis. 2020;52:1164-1169.
22. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560-1599.
23. Li ZB, Li L, Niu XX, Chen SH, Fu YM, Wang CY, Liu Y, Shao Q, Chen G, Ji D. Switching from entecavir to tenofovir alafenamide for chronic hepatitis B patients with low-level viraemia. Liver Int. 2021;41:1254-1264.
24. Buti M, Gane E, Seto WK, Chan HL, Chuang WL, Stepanova T, Hui AJ, Lim YS, Mehta R, Janssen HL, Acharya SK, Flaherty JF, Massetto B, Cathcart AL, Kim K, Gaggar A, Subramanian GM, McHutchison JG, Pan CQ, Brunetto M, Izumi N, Marcellin P; GS-US-320-0108 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:196-206.
25. Chan HL, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, Hui AJ, Janssen HL, Chowdhury A, Tsang TY, Mehta R, Gane E, Flaherty JF, Massetto B, Gaggar A, Kitrinos KM, Lin L, Subramanian GM, McHutchison JG, Lim YS, Acharya SK, Agarwal K; GS-US-320-0110 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:185-195.
26. Yuen MF. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. Gut. 2005;54:1610-1614.
27. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, Ahn SH, Izumi N, Chuang WL, Bae H, Sharma M, Janssen HLA, Pan CQ, Çelen MK, Furusyo N, Shalimar D, Yoon KT, Trinh H, Flaherty JF, Gaggar A, Lau AH, Cathcart AL, Lin L, Bhardwaj N, Suri V, Mani Subramanian G, Gane EJ, Buti M, Chan HLY; GS-US-320-0110; GS-US-320-0108 Investigators. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68:672-681.
28. Jeong J, Shin JW, Jung SW, Park EJ, Park NH. Tenofovir alafenamide treatment may not worsen the lipid profile of chronic hepatitis B patients: A propensity score-matched analysis. Clin Mol Hepatol. 2022;28:254-264.
29. Lampertico P, Buti M, Fung S, Ahn SH, Chuang WL, Tak WY, Ramji A, Chen CY, Tam E, Bae H, Ma X, Flaherty JF, Gaggar A, Lau A, Liu Y, Wu G, Suri V, Tan SK, Subramanian GM, Trinh H, Yoon SK, Agarwal K, Lim YS, Chan HLY. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol. 2020;5:441-453.
30. Yeh ML, Trinh S, Huang CF, et al. Improvement in virologic, biochemical and renal outcomes in chronic hepatitis B (CHB) patients swichted to tenofovir alafenamide (TAF) in routine clinical practice. Hepatology. 2019;70:295A-296A.
31. Reddy R, CUrry M, Bae H, Dieterich D. Longer-term experience with tenofovir alafenamide (TAF) in HBV-infected patients; changes in eGFR, FIB4, ALT, and DNA suppression. J Hepatol. 2019;70:S309A.
32. Byun KS, Choi J, Kim JH, Lee YS, Lee HC, Kim YJ, Yoo BC, Kwon SY, Gwak GY, Lim YS. Tenofovir alafenamide for drug-resistant hepatitis B: A randomized trial for switching from tenofovir disoproxil fumarate. Clin Gastroenterol Hepatol. 2022;20:427-437.e5.

33. Lee BT, Chang M, Lim C, Bae HS, Fong TL. Bone and renal safety profile at 72 week after switching to tenofovir alafenamide in chronic hepatitis B patients. JGH Open. 2020;5:258-263.
34. Papatheodoridis GV, Lekakis V, Voulgaris T, Lampertico P, Berg T, Chan HLY, Kao JH, Terrault N, Lok AS, Reddy KR. Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: A systematic review, meta-analysis, and expert opinion. J Hepatol. 2022;77:1670-1689.
35. Balaban HY, Aslan AT, Ayar ŞN, Dağ O, Alp A, Şimşek C, Vahabov C, Yıldırım T, Göker H, Büyükaşık Y, Şimşek H. Lack of awareness of Hepatitis B screening and vaccination in high-risk groups. Turk J Med Sci. 2021;51:1229-1233.
36. Türe Z. Overlooked prophylaxis of Hepatitis B in patients undergoing hematopoietic stem cell transplantation. Erciyes Med J. 2020;43:31-36.
37. Inada K, Kaneko S, Kurosaki M, Yamashita K, Kirino S, Osawa L, Hayakawa Y, Sekiguchi S, Higuchi M, Takaura K, Maeyashiki C, Tamaki N, Yasui Y, Itakura J, Takahashi Y, Tsuchiya K, Nakanishi H, Okamoto R, Izumi N. Tenofovir alafenamide for prevention and treatment of hepatitis B virus reactivation and de novo hepatitis. JGH Open. 2021;5:1085-1091.

Research Article

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The Effect of HCV-RNA, HCV-Genotype 1b, and Anti-HCV Positivity on Laboratory Parameters

HCV-RNA, HCV-Genotip 1b ve Anti-HCV Pozitifliğinin Laboratuvar Parametrelerine Etkisi

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ABSTRACT

Objectives: We aimed to compare the effect of hepatitis C virus (HCV)-RNA, HCV-genotype 1b, and anti-HCV positivity on laboratory parameters in our study.

Materials and Methods: HCV-RNA and anti-HCV tests were analyzed from 500 patients and the HCV genotyping test was applied to 100 patients between January 2018 and September 2020. Hemoglobin, white blood cell, platelet (PLT), mean platelet volume (MPV), platelet distribution width, the volume of platelet of total blood volume-plateletcrit, mean corpuscular volume, red cell distribution width, alpha-fetoprotein (AFP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), albumin, prothrombin time, partial thromboplastin time (PTT), International Normalized Ratio values were analyzed simultaneously.

Results: Age, AFP levels, AST, ALT, GGT, ALP, PTT, and MPV values were detected to be significantly higher in HCV-RNA positive patients than in HCV-RNA negative patients. Anti-HCV titer, PLT, and albumin values were found to be lower in HCV-RNA positive patients compared with HCV-RNA negative patients. HCV-RNA, AST, ALP, and GGT values were higher in anti-HCV positive patients compared to anti-HCV negative patients. Albumin values were lower in anti-HCV positive patients than in anti-HCV negative patients. The average age of patients with HCV-genotype 1b was determined to be higher than that of patients with non-HCV-genotype 1b.

Conclusion: HCV-RNA is the most important specific biomarker that affects other non-specific parameters used to evaluate HCV infection. The detection of genotype 1b in patients with HCV infection may be guiding in the treatment of older patients than non-genotype 1b.

Keywords: HCV-RNA, anti-HCV, HCV-genotype 1b

ÖZ

Amaç: Çalışmamızda hepatit C virüs (HCV)-RNA, HCV-genotip 1b ve anti-HCV pozitifliğinin laboratuvar parametrelerine etkisini karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmamıza Ocak 2018-Eylül 2020 tarihleri arasında hastanemize başvurup HCV-RNA, anti-HCV testleri yapılan 500 hasta ve HCV genotiplendirme testi yapılan 100 hasta dahil edildi. Hastaların eş zamanlı alınan kanlarından hemoglobin, beyaz kan hücresi, trombosit sayısı (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği, kandaki trombosit oranı, ortalama hücresel hacim, kırmızı hücre dağılım genişliği, alfa-fetoprotein (AFP), aspartat aminotransferaz (AST), alanin aminotransferaz (ALT), alkalen fosfataz (ALP), gama-glutamil transferaz (GGT), albümin, protrombin zamanı, parsiyel tromboplastin zamanı (PTT), Uluslararası Normalleştirilmiş Oran değerleri eş zamanlı, retrospektif olarak incelendi.

Bulgular: HCV-RNA pozitif hastalarda HCV-RNA negatif hastalara göre, yaş, AFP, AST, ALT, GGT, ALP, PTT ve MPV değerleri anlamlı yüksek saptandı ($p<0.01$). HCV-RNA pozitif hastalarda HCV-RNA negatif hastalara göre, anti-HCV titresi, PLT ve albümin değerleri düşük bulundu. Anti-HCV pozitif hastalarda anti-HCV negatif hastalara göre, HCV-RNA, AST, ALP ve GGT değerleri yüksek saptandı. Anti-HCV pozitif hastalarda, anti-HCV negatif hastalara göre albümin değerleri düşük belirlendi. HCV-genotip 1b saptanan hastaların yaş ortalaması, HCV-genotip 1b dışındaki genotip saptanan hastalara göre yüksek belirlendi.

Sonuç: HCV-RNA pozitifliği, HCV enfeksiyonunu değerlendirmek için kullanılan diğer spesifik olmayan parametreleri etkileyen en önemli spesifik biyobelirteçtir. HCV enfeksiyonu olan hastalarda genotip 1b'nin saptanması, genotip 1b olmayanlara göre daha yaşlı hastaların tedavisinde yol gösterici olabilir.

Anahtar Kelimeler: HCV-RNA, anti-HCV, HCV-genotip 1b

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Introduction

It is estimated that 71 million people worldwide are infected with the hepatitis C virus (HCV) (1,2). Acute HCV infection usually has an asymptomatic course and, if left untreated, becomes chronic and progresses to clinical conditions up to cirrhosis and hepatocellular cancer. The diagnosis of HCV infection is primarily based on an anti-HCV test that provides the detection of the HCV antibody. Anti-HCV tests may not be sufficient for the diagnosis of acute HCV infection because of the window period. Also, the establishment of false positivity and HCV-RNA negativity in low anti-HCV positive titrations may result in delays in the diagnosis and treatment of HCV infection (3). The polymerase chain reaction (PCR) test is based on viral RNA detection and is used more advantageously in the diagnosis of acute HCV infection, where serological tests are negative or false positivity should be evaluated with serological tests (4). The HCV-RNA test is used for scanning and diagnostic purposes, verification, monitoring, and treatment of active HCV infection. Another test used in HCV infection allows HCV genotyping testing to determine HCV subtypes and allows treatment response and disease prognosis to be evaluated (5,6,7). Different HCV genotypes show characteristic distributions in different parts of the world. Genotype 1 (subtype 1b) has the highest global prevalence (8,9,10,11). The persistence treatment of genotype 1b is more difficult than other genotypes, and therefore the requirement for HCV genotyping has been highlighted in many studies (12,13,14). In addition, non-specific biochemical and hematological parameters related to liver function are evaluated in the diagnosis and follow-up of HCV infection (15). Early diagnosis and effective management of HCV infection can prevent the progression of the disease (16,17).

In our study, we aimed to compare the effect of HCV-RNA, HCV-genotype 1b, and anti-HCV positivity on laboratory parameters.

Materials and Methods

Our study was conducted at University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital, which serves the South Marmara region with a population of approximately 5 million. The study protocol was approved by the Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2022/01-15, sate: 26.01.2022).

HCV-RNA and anti-HCV tests were analyzed from 500 patients and the HCV genotyping test was retrospectively applied to 100 patients between January 2018 and September 2020 hemoglobin (HGB), white blood cell (WBC), platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), the volume of platelet of total blood volume-plateletcrit (PCT), mean corpuscular volume (MCV), red cell distribution width (RDW), alpha-fetoprotein (AFP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), albumin, prothrombin time (PT), partial thromboplastin time (PTT), International Normalized Ratio (INR) values were analyzed simultaneously and retrospectively.

The anti-HCV test was performed in a fully automated COBAS e601 (Roche, Germany) device with the chemiluminescent method in the ELISA laboratory of our hospital. HCV-RNA and HCV genotyping tests were conducted at our hospital PCR laboratory. The HCV-RNA extraction was done in a Qiasympony RGQ (Qiagen, Germany) device with the fully automated system. HCV-RNA amplification was performed in a Rotor-Gene Q (Qiagen, Germany) device with the real-time PCR method. RNA extraction for HCV genotyping was performed in a Qiasympony RGQ (Qiagen, Germany) device with the fully automated system. The HCV genotyping assay was manually performed using the Qiagen HCV genotyping kit. HGB, WBC, PLT, MPV, PDW, PCT, MCV and RDW values were analyzed with the Hematology Analyzer (Mindray, BC-6000, China) device in the Hematology Laboratory of our hospital. AFP, AST, ALT, ALP, GGT, and albumin levels were studied with COBAS 8000 (Roche, Germany) in the Biochemistry Laboratory of our hospital. PT, PTT, and INR tests were performed with a SYSMEX C55160 (Siemens, Germany) device in the Biochemistry Laboratory of our hospital.

Statistical Analysis

Data were expressed as frequency or related percent values. Normality analyzes were performed for data (n>50) with the Kolmogorov-Smirnov test. A comparison of the two groups was done with the Independent sample t-test for normally distributed parameters and the Mann-Whitney U test for non-normally distributed parameters. Comparison of more than two groups was done with Kruskal-Wallis tests for non-normally distributed parameters. Data were analyzed using SPSS Statistics for Windows, version 23.0 (IBM SPSS Statistics for Windows, version 23.0. Armonk, NY: IBM Corp). $P<0.05$ and $p<0.01$ were accepted as statistically significant.

Results

Biomarkers of patients were compared according to HCV-RNA positivity in Table 1. Age, AFP levels ($p<0.05$, $p<0.05$), and AST, ALT, GGT, ALP, PTT, and MPV values ($p<0.01$) were detected to be significantly higher in HCV-RNA positive patients than in HCV-RNA negative patients. Anti-HCV titer, PLT, and albumin values were found to be lower in HCV-RNA positive patients compared to HCV-RNA negative patients ($p<0.05$) ($p<0.01$) ($p<0.01$). There was no significant difference in the WBC, HGB, MCV, RDW, PT, INR, PDW, and PCT values of the patients according to HCV-RNA positivity.

Comparison of biomarkers of patients according to anti-HCV positivity is shown in Table 2. HCV-RNA, AST, ALP, and GGT values were higher in anti-HCV positive patients compared to anti-HCV negative patients ($p<0.05$) ($p<0.05$) ($p<0.01$) ($p<0.05$). Albumin values were lower in anti-HCV positive patients than in anti-HCV negative patients ($p<0.05$). There was no significant difference in age, WBC, HGB, PLT, MCV, RDW, AFP, ALT, PT, PTT, INR, MPV, PDW and PCT values according to anti-HCV positivity.

Comparison of biomarkers of patients with genotype 1b and genotypes other than HCV-genotype 1b detected is shown in Table 3. The average age of patients with HCV-genotype 1b was determined to be higher than that of patients with non-HCV-genotype 1b ($p<0.01$). HCV-RNA, anti-HCV titer, WBC, HGB, PLT, MCV, RDW, AFP, AST, ALT, ALP, GGT, albumin, PT, PTT, INR, MPV, PDW, and PCT values showed no significant difference in patients with HCV-genotype 1b according to genotypes other HCV-genotype 1b detected.

Discussion

Accurate determination of the presence of HCV infection and advanced description of the HCV with HCV-genotyping is essential for effective treatment (18). According to our study, there was no significant difference between HCV genotyping and HCV-RNA values, anti-HCV titration, and biochemical and hematological parameters, although the average age of patients was higher with genotype 1b than patients with non-genotype 1b genotype. According to studies, the effect of the HCV genotype on biochemical biomarkers is contradictory. In some studies, there is no relationship between viral genotypes and biomarkers, whereas in some studies, AST, ALT, and ALP values were higher in patients with genotype 1 (12). In addition, some studies showed that high viral load was associated with HCV genotype 1 or found no association with HCV genotype (8).

The HCV-RNA test must be studied for anti-HCV positive patients, and the genotype test should be studied for HCV-RNA positives, but the combined use of HCV-RNA and genotyping tests together to evaluate HCV infection has remained only 50% in the last 10 years in Turkey (19). Although some studies showed that anti-HCV antibody titration can be used to determine HCV viremia and indicates a positive correlation with HCV-RNA, some studies showed the opposite (2,20,21). According to our study, the detection of HCV-RNA and genotype 1b positivity without higher anti-HCV levels shows that HCV-RNA values are more valuable than anti-HCV values in assessing HCV acute infection and activation.

Hypoalbuminemia has been reported as an important prognostic factor in HCV infection (22,23). In our study, the determination of lower albumin values in patients with anti-HCV-positive and HCV-RNA-positive that the albumin values guide the evaluation of the prognosis of HCV infection in HCV-RNA- and anti-HCV -positive HCV patients regardless of genotype.

HCV viral load was found to be associated with lower PLT values, and the HCV-RNA viral load was identified as a biomarker of disease prognosis and treatment response (15,24,25). According to our study, the detection of lower PLT values in HCV-RNA positive patients shows that lower PLT values can provide information on disease behavior, regardless of anti-HCV and genotyping in HCV-RNA-positive patients.

MPV, which shows PLT function and activation, was associated with advanced fibrosis and disease severity in patients

Table 1. Comparison of biomarkers according to HCV-RNA positivity

	HCV-RNA negative	HCV-RNA positive	p
	Mean ± SD	Mean ± SD	
Age	51±19	55±19	**0.017**[a*]
HCV-RNA	0	4269331±5640479	**0.001**[b**]
Anti-HCV titer	48.8±52.0	45.9±25.4	**0.023**[b*]
WBC	7.6±2.5	8.1±6.2	0.236[a]
HGB	13.2±1.9	13.5±2.3	0.282[b]
PLT	247±81	224±92	**0.004**[a**]
MCV	87.1±6.4	87.5±7.0	0.579[a]
RDW	14.1±1.7	14.2±2.0	0.388[b]
Alpha-fetoprotein	5.5±13.1	46.5±306.6	**0.023**[b*]
AST	34±58	67±99	**0.001**[b**]
ALT	34±72	82±162	**0.001**[b**]
ALP	102±133	241±1070	**0.006**[b**]
GGT	34±54	101±181	**0.001**[b**]
Albumin	4.5±0.6	4.4±2.8	**0.001**[b**]
PT	13.6±2.5	13.6±2.0	0.887[a]
PTT	26.3±4.8	27.8±4.9	**0.006**[a**]
INR	1.2±2.0	1.0±0.1	0.345[b]
MPV	9.70±1.52	10.08±1.18	**0.002**[b**]
PDW	16.14±1.09	16.06±1.27	0.463[b]
PCT	0.24±0.13	0.22±0.09	0.089[b]

[a]: Independent t-test, [b]: Mann-Whitney U test, *p<0.05 **p<0.01, HCV: Hepatitis C virus, SD: Standard deviation, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Table 2. Comparison of biomarkers of patients according to anti-HCV positivity

	Anti-HCV negative	Anti -HCV positive	p
	Mean ± SD	Mean ± SD	
Age	44±18	52±19	0.174[a]
HCV-RNA	0	1825303±4403095	**0.008**[b]
Anti-HCV titer	0.3±0.5	49.0±43.0	**0.001**[b]
WBC	7.8±2.9	8.0±5.0	0.916[a]
HGB	12.7±1.8	13.3±2.1	0.328[b]
PLT	256±84	242±88	0.602[a]
MCV	86.9±4.6	86.9±6.9	0.984[a]
RDW	13.9±1.0	14.2±2.0	0.774[b]
Alpha-fetoprotein	2.0±1.1	32.0±248.6	0.109[b]
AST	18±7	51±88	**0.012**[b]
ALT	17±9	56±127	0.076[b]
ALP	52±15	139±204	**0.001**[b]
GGT	19±9	64±102	**0.027**[b]
Albumin	4.8±0.4	4.4±2.4	**0.016**[b]
PT	14.3±0.8	13.5±2.4	0.421[a]
PTT	28.9±3.2	26.5±5.1	0.266[a]
INR	1.0±0.0	1.2±1.7	0.452[b]
MPV	9.78±1.39	9.88±1.41	0.502[b]
PDW	16.25±0.44	16.06±1.31	0.128[b]
PCT	0.22±0.07	0.24±0.13	0.060[b]

[a]: Independent t-test, [b]: Mann-Whitney U test, HCV: Hepatitis C virus, SD: Standard deviation, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

Table 3. Comparison of biomarkers of patients with genotype 1b and genotypes other than HCV-genotype 1b detected

	HCV-genotype 1b	Genotypes other than HCV-genotype 1b	p
	Mean ± SD	Mean ± SD	
Age	61±15	46±18	**0.001**[a]
HCV-RNA	3524425±5254788	4109971±6109528	0.521[b]
Anti-HCV titer	46.9±21.2	41.4±27.7	0.245[b]
WBC	7.4±2.3	9.1±10.2	0.185[a]
HGB	13.5±2.1	13.6±1.9	0.901[b]
PLT	208±70	232±106	0.060[a]
MCV	88.3±7.2	87.6±6.5	0.488[a]
RDW	14.0±1.6	14.2±2.8	0.381[b]
Alpha-fetoprotein	69.6±397.2	16.3±47.6	0.425[b]
AST	62±99	56±78	0.802[b]
ALT	80±179	61±87	0.479[b]
ALP	124±142	390±1874	0.080[b]
GGT	81±99	94±258	0.230[b]
Albumin	4.6±3.4	4.3±0.6	0.529[b]
PT	13.6±1.9	13.5±2.0	0.706[a]
PTT	26.8±5.2	27.5±5.0	0.442[a]
INR	1.3±2.4	1.0±0.1	0.963[b]
MPV	10.20±1.15	10.08±1.23	0.500[b]
PDW	16.14±0.44	16.16±0.50	0.723[b]
PCT	0.21±0.07	0.26±0.26	0.102[b]

[a]: Independent t-test [b]: Mann-Whitney U tests, HCV: Hepatitis C virus, SD: Standard deviation, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, RDW: Red cell distribution width, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International Normalized Ratio, MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit

with chronic hepatitis C (26,27,28,29,30). Our study shows that higher MPV values in HCV-RNA-positive patients regardless of anti-HCV and genotype 1b positivity can be a non-invasive guide in evaluating the severity of liver disease in HCV infection.

Elevated AFP values have been accepted as cautionary biomarkers for advanced fibrosis, end-stage liver disease, and hepatocellular cancer in chronic HCV infection (31). Although higher AFP levels were correlated with lower albumin levels in studies, its association with genotype 1b and HCV-RNA positivity is unclear (32,33). In our study, the detection of higher AFP values in HCV-RNA-positive patients except for anti-HCV and genotype 1b positivity shows that determination of higher AFP values with HCV-RNA positivity together is more useful in assessing serious liver damage.

According to studies, higher GGT values, which are a non-invasive significant marker of advanced severe liver disease in chronic hepatitis C, can indicate the effectiveness of interferon therapy (34,35). In our study, the higher GGT values in HCV-RNA-positive patients, irrespective of anti-HCV and genotype 1b positivity, illustrate the importance of higher GGT values in HCV-RNA-positive patients for diagnosis and treatment of advanced liver disease.

According to the studies conducted, HCV viral load and higher ALT values are clinically related parameters that indicate treatment activity, especially in chronic HCV patients (36,37). In addition, Ijaz et al. (38) demonstrated that the evaluation of ALP levels with viral load independent of the genotype determination can help to estimate disease progression in patients with hepatitis C.

Doğan et al. (39) showed that albumin, AST, ALT, GGT, and AFP values in compensated cirrhosis patients with genotype 1b after treatment and ALT, AST, GGT, ALP, and AFP values in non-cirrhosis patients after treatment were significantly changed. In our study, higher AST, ALT, and GGT values were determined in anti-HCV and HCV-RNA-positive patients, in addition to higher ALP values in HCV-RNA-positive patients. According to our study, higher AST, ALT, and GGT values in HCV-RNA and anti-HCV positive patients and higher ALP values with HCV-RNA positivity are the guiding factors for the diagnosis and treatment evaluation of advanced HCV infection, regardless of genotype 1b positivity.

Study Limitations

The limitations of our study were the inability to evaluate the clinical data of the patients and the inability to evaluate the development of hepatocellular cancer and mortality due to advanced HCV infection.

Conclusion

In conclusion, according to our study, HCV-RNA is the most important specific biomarker that affects other non-specific parameters used to evaluate HCV infection. The detection of genotype 1b in patients with HCV infection may be guiding in the treatment of older patients than non-genotype 1b.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital (approval number: 2011-KAEK-25 2022/01-15, sate: 26.01.2022).

Informed Consent: Retrospective study.

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Authorship Contributions

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References

1. Yu ML, Yeh ML, Tsai PC, Huang CI, Huang JF, Huang CF, Hsieh MH, Liang PC, Lin YH, Hsieh MY, Lin WY, Hou NJ, Lin ZY, Chen SC, Dai CY, Chuang WL, Chang WY. Huge gap between clinical efficacy and

community effectiveness in the treatment of chronic hepatitis C: a nationwide survey in Taiwan. Medicine (Baltimore). 2015;94:e690.

2. Liu HY, Lin YH, Lin PJ, Tsai PC, Liu SF, Huang YC, Tsai JJ, Huang CI, Yeh ML, Liang PC, Lin ZY, Dai CY, Huang JF, Chuang WL, Huang CF, Yu ML. Anti-HCV antibody titer highly predicts HCV viremia in patients with hepatitis B virus dual-infection. PLoS One. 2021;16:e0254028.
3. Aydın G, Adaleti R, Boz ES, Yücel FM, Özhan HK, Aksaray S. Investigation of Anti-HCV S/CO Value in Detecting Viremia in Patients with Hepatitis C Virus Infection. Mikrobiyol Bul. 2020;54:110-119.
4. Şanlıdağ T, Şanlıdağ T, Akçalı S, Ecemiş T, Süer K, Erbay Dündar P, Arıkan A, Güvenir M, Güler E. Investigation of the correlation between anti-HCV levels (S/Co) with HCV-RNA in the diagnosis of hepatitis C virus (HCV) infection. Mikrobiyol Bul. 2016;50:508-510.
5. Albertoni G, Arnoni CP, Araújo PR, Carvalho FO, Barreto JA. Signal to cut-off (S/CO) ratio and detection of HCV genotype 1 by real-time PCR one-step method: is there any direct relationship? Braz J Infect Dis. 2010;14:147-152.
6. Sreevatsan S, Bookout JB, Ringpsis FM. Algorithmic approach to high-throughput molecular screening for alpha interferon-resistant genotypes in hepatitis c patients. J Clin Microbiol. 1998;36:1895-1901.
7. Petruzziello A, Coppola N, Loquercio G, Marigliano S, Giordano M, Azzaro R, Diodato AM, Iervolino V, Di Costanzo G, Di Macchia CA, Di Meo T, Paradiso L, Ferro R, Giuliano P, Russo F, Pasquale G, Cacciapuoti C. Distribution pattern of hepatitis C virus genotypes and correlation with viral load and risk factors in chronic positive patients. Intervirology. 2014;57:311-318.
8. Castro GLC, Amoras EDGS, Araújo MSM, Conde SRSDS, Vallinoto ACR. Hepatitis C virus genotypes and associated risk factors in the state of Pará, Northern Brazil. Braz J Infect Dis. 2020;24:304-309.
9. Haldeda M, Baume J, Tamalet C, Bizhga M, Colson P. Hepatitis C virus genotypes in Tirana, Albania. Int J Infect Dis. 2014;18:90-93.
10. Oh DJ, Park YM, Seo YI, Lee JS, Lee JY. Prevalence of hepatitis C virus infections and distribution of hepatitis C virus genotypes among Korean blood donors. Ann Lab Med. 2012;32:210-215.
11. Üçbilek E, Abayli B, Koyuncu MB, Midikli D, Gözüküçük S, Akdağ A, Özdoğan O, Altintaş E, Sezgin O. Distribution of hepatitis C virus genotypes among intravenous drug users in the Çukurova region of Turkey. Turk J Med Sci. 2016;46:66-71.
12. Saravanan S, Velu V, Kumarasamy N, Shankar EM, Nandakumar S, Murugavel KG, Balakrishnan P, Solomon SS, Solomon S, Thyagarajan SP. The prevalence of hepatitis B virus and hepatitis C virus infection among patients with chronic liver disease in South India. Int J Infect Dis. 2008;12:513-518.
13. Podzorski RP. Molecular testing in the diagnosis and management of hepatitis C virus infection. Arch Pathol Lab Med. 2002;126:285-290.
14. Zein NN. Clinical significance of hepatitis c virus genotypes. Clin Microbiol Rev. 2000;13:223-235.
15. Basharkhah S, Sabet F, Ghezeldasht SA, Mosavat A, Jahantigh HR, Barati E, Shamsian K, Saleh-Moghaddam M, Sharebyani H, Hassannia T, Shamsian SAA. Prediction of HCV load using genotype, liver biomarkers, and clinical symptoms by a mathematical model in patients with HCV infection. Microbiol Immunol. 2019;63:449-457.
16. Cavalcante LN, Lyra AC. Predictive factors associated with hepatitis C antiviral therapy response. World J Hepatol. 2015;7:1617-1631.
17. Mukherjee R, Burns A, Rodden D, Chang F, Chaum M, Garcia N, Bollipalli N, Niemz A. Diagnosis and management of hepatitis C virus infection. J Lab Autom. 2015;20:519-538.
18. Kumar A, Rajput MK, Paliwal D, Yadav A, Chhabra R, Singh S. Genotyping & diagnostic methods for hepatitis C virus: A need of low-resource countries. Indian J Med Res. 2018;147:445-455.
19. Balaban HY, Dağ O, Alp A, Tseveldorj N, Vahabov C, Göktaş MA, Pürnak T, Hasçelik G, Demir H, Sivri B, Şimşek H. Retrospective Evaluation of Hepatitis C Awareness in Turkey Through Two Decades. Turk J Gastroenterol. 2021;32:88-96.
20. Ranjbar Kermani F, Sharifi Z, Ferdowsian F, Paz Z, Tavassoli F. The Usefulness of Anti-HCV Signal to Cut-off Ratio in Predicting Viremia in Anti-HCV in Patients With Hepatitis C Virus Infection. Jundishapur J Microbiol. 2015;8(4):e17841.
21. Li Y, Zhao L, Geng N, Zhu W, Liu H, Bai H. Prevalence and characteristics of hepatitis C virus infection in Shenyang City, Northeast China, and prediction of HCV RNA positivity according to serum anti-HCV level: retrospective review of hospital data. Virol J. 2020;17:36.
22. Nagao Y, Sata M. Serum albumin and mortality risk in a hyperendemic area of HCV infection in Japan. Virol J. 2010;7:375.
23. Erdal H, Bakır A, Güney M, Günal A, Erçin CN, Uygun A, Gülşen M. The relationship between histopathological stages of liver fibrosis and albumin–bilirubin score in chronic hepatitis C infection. The Turkish Journal of Academic Gastroenterology. 2020;19:25-30.
24. Gallotta A, Paneghetti L, Mrázová V, Bednárová A, Kružlicová D, Frecer V, Miertus S, Biasiolo A, Martini A, Pontisso P, Fassina G. Development of a novel diagnostic algorithm to predict NASH in HCV-positive patients. Int J Biol Markers. 2018;33:231-236.
25. Elbedewya TA, Ghazya MA, Mabroukb MM. Serum thrombopoietin and platelet antibodies in thrombocytopenic patients with chronic hepatitis C virus: clinical application of platelet indices. Egypt J Haematol. 2016;41:15-22.
26. Karaman H, Karakükcü C, Karaman A, Kayman T, Yalçın S, Taşdemir EA, Zararsız G, Poyrazoğlu O. Mean platelet volume as a fibrosis marker in patients with chronic hepatitis C. Turk J Med Sci. 2013;43:39-45.
27. Kosekli MA. Prediction of Fibrosis in Chronic Hepatitis C by Mean Platelet Volume and Platelet to Lymphocyte Ratio. Nat J Health Sci. 2021;6:48-52.
28. Karagöz E, Tanoğlu A, Ülçay A, Erdem H, Turhan V, Kara M, Yazgan Y. Mean platelet volume and red cell distribution width to platelet ratio for predicting the severity of hepatic fibrosis in patients with chronic hepatitis C. Eur J Gastroenterol Hepatol. 2016;28:744-748.
29. Purnak T, Olmez S, Torun S, Efe C, Sayilir A, Ozaslan E, Tenlik I, Kalkan IH, Beyazit Y, Yuksel O. Mean platelet volume is increased in chronic hepatitis C patients with advanced fibrosis. Clin Res Hepatol Gastroenterol. 2013;37:41-46.
30. Uslu AU, Aydin B, Balta S, Yonem O, Uncu T, Seven D. The effect of standard therapy on mean platelet volume in patients with chronic hepatitis C. Prz Gastroenterol. 2016;11:200-205.
31. Bruce MG, Bruden D, McMahon BJ, Christensen C, Homan C, Sullivan D, Deubner H, Williams J, Livingston SE, Gretch D. Clinical significance of elevated alpha-fetoprotein in Alaskan Native patients with chronic hepatitis C. J Viral Hepat 2008;15:179-187.
32. Chu CW, Hwang SJ, Luo JC, Lai CR, Tsay SH, Li CP, Wu JC, Chang FY, Lee SD. Clinical, virologic, and pathologic significance of elevated serum alpha-fetoprotein levels in patients with chronic hepatitis C. J Clin Gastroenterol. 2001;32:240-244.
33. Chen CH, Lin ST, Kuo CL, Nien CK. Clinical significance of elevated alpha-fetoprotein (AFP) in chronic hepatitis C without hepatocellular carcinoma. Hepatogastroenterology. 2008;55:1423-1427.
34. Silva IS, Ferraz ML, Perez RM, Lanzoni VP, Figueiredo VM, Silva AE. Role of gamma-glutamyl transferase activity in patients with chronic hepatitis C virus infection. J Gastroenterol Hepatol. 2004;19:314-318.
35. Hwang SJ, Luo JC, Lai CR, Chu CW, Tsay SH, Lu CL, Wu JC, Chang FY, Lee SD. Clinical, virologic and pathologic significance of elevated serum gamma-glutamyl transpeptidase in patients with chronic hepatitis C. Zhonghua Yi Xue Za Zhi (Taipei). 2000;63:527-535.
36. Akkaya O, Kiyici M, Yilmaz Y, Ulukaya E, Yerci O. Clinical significance of activity of ALT enzyme in patients with hepatitis C virus. World J Gastroenterol. 2007;13:5481-5485.
37. Beld M, Penning M, Mcmorrow M, Gorgels J, Van Den Hoek A, Goudsmit J. Different Hepatitis C Virus (HCV) RNA Load Profiles Following Seroconversion among Injecting Drug Users without Correlation with HCV Genotype and Serum Alanine Aminotransferase Levels. J Clin Microbiol. 1998;36:872-877.

38. Ijaz B, Ahmad W, Javed FT, Gull S, Sarwar MT, Kausar H, Asad S, Jahan S, Khaliq S, Shahid I, Sumrin A, Hassan S. Association of laboratory parameters with viral factors in patients with hepatitis C. Virol J. 2011;8:361.

39. Doğan M, Topçu B, Karaali R, Erdem I. Evaluation of Treatment Results with Direct Acting Antiviral Drugs of Cirrhotic/Non-cirrhotic Chronic Liver Disease Caused by Hepatitis C Virus Genotype 1b Infection. Viral Hepat J. 2020;26:43-48.

Research Article

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Sofosbuvir/Velpatasvir/Voxilaprevir Experience in Treatment-Naive Chronic Hepatitis C Patients: Preliminary Findings of Real World Data

Tedavi Naive Kronik Hepatit C Hastalarında Sofosbuvir/Velpatasvir/Voxilaprevir Gerçek Yaşam Verileri: Ön Sonuçlar

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ABSTRACT

Objectives: The aim of this study was to present the preliminary findings of real-world data of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in treatment-naive chronic hepatitis C (CHC) patients, which was approved for the first time in treatment-naive patients in Turkey.

Materials and Methods: This retrospective, cross-sectional, multicenter and national study comprised treatment-naive CHC patients receiving SOF/VEL/VOX between June-December 2022 in ten centers from Turkey. The sustained virological response (SVR) was defined as undetectable hepatitis C virus (HCV)-RNA after at least 12 weeks or more from the end of antiviral therapy.

Results: Forty one patients initiating SOF/VEL/VOX were included in the study; median age 55 [interquartile range (IQR): 34.5-61 years], 63.4% males, and median HCV-RNA 521,644 IU/mL. Genotype distribution ranged from 1 to 4 in 28 patients who underwent genotype analysis, and genotype-1 was detected in 24 (85.7%) patients. The most common risk factor was substance

ÖZ

Amaç: Bu çalışmada tedavi naive kronik hepatit C (KHC) hastalarında sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) gerçek yaşam verilerinin ön sonuçlarının sunulması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif, kesitsel, çok merkezli, ulusal çalışmaya Haziran-Aralık 2022 tarihleri arasında SOF/VEL/VOX tedavisi başlanmış tedavi naive KHC hastaları dahil edilmiştir. Kalıcı virolojik yanıt (SVR), antiviral tedavinin kesilmesinin ardından en az 12 hafta sonra saptanamayan hepatit C virüs (HCV)-RNA olarak tanımlanmıştır.

Bulgular: Çalışmaya SOF/VEL/VOX başlanan 41 tedavi naive KHC hastası dahil edildi. Hastaların medyan yaşı 55 [çeyrekler arası aralık (IQR) 34,5-61 yaş] olup, %63,4'ü erkekti. Medyan HCV-RNA 521.644 IU/mL saptandı. Genotip analizi yapılan 28 hastada genotip dağılımı 1 ile 4 arasında değişmekteydi ve hastaların 24'ünde (%85,7) genotip 1 saptandı. En sık görülen risk faktörü madde kullanımı (n=10, %24,4), en sık eşlik eden hastalık hipertansiyon (n=11, %26,8) idi. 3 (%7,3) hastada kompanse siroz ve 1 (%2,4)

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abuse (n=10, 24.4%) and the most common comorbidity was hypertension (n=111, 26.8%). 3 (7.3%) patients had compensated cirrhosis and one (2.4%) had hepatocellular carcinoma. While in the 1st month of treatment, HCV-RNA was negative in all patients except one patient, at the end of treatment all patients' viral load was negative. SVR12 results were available in 23 patients and SVR24 in 10 patients. SVR12 and SVR24 were achieved in all patients who could be evaluated (100%) (SVR12, 23/23; SVR24, 10/10). Adverse events were reported by two patients: Diarrhea (2.4%) and nausea (2.4%), but did not lead to a discontinuation of treatment.

Conclusion: The preliminary results of our study corroborated the efficacy and well tolerateability of SOF/VEL/VOX in treatment-naive CHC patients. High SVR rates were also observed across genotypes 1, 2, 3, 4 with the pangenotypic SOF/VEL/VOX.

Keywords: Hepatitis C treatment, sofosbuvir/velpatasvir/voxilaprevir, real-world data, direct acting antivirals

hastada hepatoselüler karsinom vardı. Tedavinin 1. ayında 1 hasta dışında tüm hastalarda HCV-RNA negatif iken, tedavi bitiminde tüm hastaların viral yükleri negatifti. SVR12 sonuçları 23 hastada ve SVR24 sonuçları 10 hastada mevcuttu. Değerlendirilebilen tüm hastalarda (%100) SVR12 ve SVR24 elde edildi (SVR12, 23/23; SVR24, 10/10). Hastaların birinde ishal (%2,4) ve birinde de mide bulantısı (%2,4) görüldü, ancak tedavinin kesilmesine neden olmadı.

Sonuç: Çalışmamızın ön sonuçları, daha önce tedavi görmemiş KHC hastalarında SOF/VEL/VOX'in etkin olduğunu ve iyi tolere edilebildiğini göstermektedir. Ayrıca pangenotipik SOF/VEL/VOX ile genotip 1, 2, 3, 4'te de yüksek SVR oranları gözlenmiştir.

Anahtar Kelimeler: Hepatit C tedavisi, sofosbuvir/velpatasvir/voxilaprevir, gerçek yaşam verileri, direkt etkili antiviraller

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Introduction

Hepatitis C virus (HCV) infection remains one of the most important public health problems worldwide, currently affecting 58 million people and 1.5 million newly infected patients each year (1). However, enhanced recognition of virus particles and understanding the pathophysiology of the disease, provided developments of direct-acting antivirals (DAA) pioneering improvements of therapy (2). After the first DAA was approved in 2011 by the US Food and Drug Administration, more than ten pharmaceuticals (including effective against all genotypes) are currently available for use (3). The World Health Organization proposes pan-genotypic DAAs for all adult patients infected with HCV (1).

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX); containing 400 mg sofosbuvir (NS5B polymerase inhibitor), 100 mg velpatasvir (NS5A inhibitor), and 100 mg voxilaprevir (NS3/4A protease inhibitor) is a pan-genotypic DAA introduced in treatment-experienced patients who were previously treated but failed with DAA-containing regimens. The product provides opportunity to patients using a single tablet once a day with good tolerability (4,5). Recently reported real-world data also endorses the effectiveness of SOF/VEL/VOX as a new option for treatment regimens for HCV patients who had previously experienced DAA failure (6,7).

Although the efficacy of the SOF/VEL/VOX combination is well established in treatment-naive patients in phase-3 trials, real world data is not available in the literature in such patients (8). SOF/VEL/VOX has been approved as a new option both in treatment-naive and prior experienced chronic hepatitis C (CHC) patients since June 2022 in Turkey (9). Thus, we were able to use SOF/VEL/VOX for the first time in real life in CHC patients who had not received any antiviral therapy previously.

In this study, we aimed to present the preliminary findings of real-world data of SOF/VEL/VOX in treatment-naive CHC patients, which was approved for the first time in treatment-naive patients in Turkey as well as in the world.

Materials and Methods

Patients and Study Design

This retrospective, cross-sectional, multicenter, and national study was conducted on patients who were administered SOF/VEL/VOX between June 2022 and December 2022 in ten centers from Turkey. The data of patients [sociodemographic features (age, sex, route of transmission), laboratory [viral load, HCV genotype-subtype, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama-glutamyl transferase (GGT), alkaline phosphatase, platelet, International Normalized Ratio, alpha-fetoprotein, total bilirubin and radiological findings before and during treatment, treatment-related side effects and comorbidities] were collected retrospectively.

Patients who were older than 18 years, were infected with any genotype and subtype of HCV for more than 6 months and had never received antiviral therapy for HCV (treatment-naive) were included in the study.

Patients who were pregnant or breastfeeding and those who had experienced prior CHC treatment were excluded.

All patients were treated with one tablet SOF/VEL/VOX per day for eight weeks in non-cirrhotic patients and 12 weeks in patients with compensated cirrhosis in accordance with the manufacturer's and Social Security Institution of Turkey's recommendations (5,9). Patients were examined for clinical, virological, and biochemical improvements at the fourth, eighth, and, if any, twelfth weeks of treatment. The follow-up of the patients whose treatment was completed was continued every three months to determine the sustained virological response (SVR).

SVR was defined as undetectable HCV-RNA after at least 12 weeks or more from the end of antiviral therapy. The primary endpoint was an achievement of SVR. The secondary endpoints were determined as virologic responses at week four and the end of treatment (eighth or twelfth week).

This study was approved by the Harran University Faculty of Medicine Ethics Committee Commission (approval number: HRÜ/23.02.29, date: 23.01.2023).

Statistical Analysis

Statistical analyzes were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies, distributions, and percentages, and continuous variables as medians [interquartile range (IQR)]. The Kolmogorov-Smirnov test was used to assess the normality of the samples distribution. Friedman test and Wilcoxon signed-rank test were used to analyze variation of the recurrent laboratory parameters at the beginning of treatment, the 1st month of treatment, and the end of treatment for dependent groups. A value of $p<0.05$ was accepted statistically significant.

Results

This study included 41 treatment-naive CHC patients who were initiated SOF/VEL/VOX. Baseline characteristics and pretreatment laboratory results of all patients are presented in Table 1. The median age of the patients was 55 (IQR: 34.5-61 years) and 26 (63.4%) were male. The most frequently identified risk factor for CHC was substance abuse (n=10, 24.4%), while the most common comorbidity was hypertension (n=11, 26.8%). Three (7.3%) patients had compensated cirrhosis and one (2.4%) had hepatocellular carcinoma (HCC). The HCV genotype was evaluated in 28 (68.3%) patients. Genotype distribution was; genotype 1 in 24 (85.7%), genotype 2 in one (3.6%), genotype 3 in two (7.1%), and genotype 4 in one (3.6%) patient.

Pre-treatment laboratory data and changes in parameters at the 1st month of treatment and at the end of treatment are presented in Table 2. The results of the patients whose laboratory parameters were recorded in all three time periods were analyzed. Changes in ALT, AST, GGT, and total bilirubin were found to be statistically significant at the beginning, 1st month, and the end of treatment. This significant difference in ALT, AST, and GGT changes was associated with a significant reduction in the 1st month of treatment compared to pre-treatment ($p<0.001$, $p= 0.001$ and $p=0.029$, respectively). A significant difference for the total bilirubin change was associated with a decrease in the 1st month of treatment compared with the end of treatment ($p=0.048$). The changes in ALT, AST, GGT and total bilirubin are shown in Figure 1. In the 1st month of treatment, HCV-RNA was negative in all patients except one patient; who had multiple preexisting diseases and had to use multiple medications and was also co-infected with syphilis and penicillin treatment had been administered concurrent with SOF/VEL/VOX. The patient's HCV-RNA at the end of treatment was negative.

The median pretreatment HCV-RNA of the patients was 521,644 IU/mL. HCV-RNA was evaluated in 35 patients in the 1st month of treatment and in 36 patients at the end of the treatment.

Table 1. Baseline characteristics of patients before treatment

	n=41
Age, year, median (IQR)	55 (34.5-61)
Sex, n (%)	
Male	26 (63.4)
Female	15 (36.6)
Risk factors, n (%)	
Substance abuse	10 (24.4)
Hemodialysis	1 (2.4)
Unknown	30 (73.2)
Comorbidities, n (%)	
Diabetes mellitus	4 (9.8)
Hypertension	11 (26.8)
Heart disease	8 (19.5)
Thyroid disease	1 (2.4)
Chronic renal failure	1 (2.4)
Asthma	3 (7.3)
Cirrhosis, n (%)	3 (7.3)
Hepatocellular carcinoma, n (%)	1 (2.4)
Splenomegaly, n (%)	1 (2.4)
Hepatosteatosis, n (%)	8 (19.5)
Pretreatment laboratory data	
HCV-RNA, IU/mL, median (IQR)	521,644 (177,630-2,668,048)
Platelets, x10^3/µL	248,000 (190,000-291,500)
Creatinin, mg/dL	0.82 (0.69-0.92)
Albumin, g/dL	4.2 (3.7-4.5)
ALT, U/L	58 (30-90)
AST, U/L	40 (27-61)
GGT, U/L	39 (26-77)
ALP, U/L	85 (62-111)
TB, mg/dL	0,60 (0.47-0.80)
AFP, IU/mL	3.0 (2.2-4.4)
INR	1.03 (1.00-1.10)
Genotype	
gp 1	24
Subtype 1a	4
Subtype 1b	14
Subtype unspecified	6
gp 2	1
gp 3	2
gp 4	1
Treatment duration	
8 weeks, n (%)	38 (92.7)
12 weeks, n (%)	3 (7.3)

IQR: Interquartile range, HCV: Hepatitis C virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase ALP: Alkaline phosphatase, TB: Total bilirubin, AFP: Alpha-fetoprotein, INR: International Normalized Ratio, gp: Genotype

Table 2. Pre-treatment, 1st month of treatment, and post-treatment laboratory data

Laboratory data, median (IQR)	n	Pre-treatment	Firstmonth of treatment	Post-treatment	p*
Platelets	24	237,500 (191,500-263,000)	230,500 (195,500-287,500)	240,500 (210,250-273,750)	0.284
Albumin	20	4.1 (3.7-4.4)	4.3 (3.9-4.4)	4.3 (3.7-4.7)	0.959
ALT	24	51 (27-83)	19 (14-26)	16 (11-26)	**<0.001**
AST	24	39 (27-57)	25 (17-30)	20 (17-29)	**<0.001**
GGT	16	34 (20-97)	26 (19-43)	27 (16-32)	**0.011**
ALP	15	85 (49-109)	78 (66-100)	78 (44-100)	0.526
TB	17	0.55 (0.35-0.93)	0.58 (0.40-0.95)	0.40 (0.27-0.80)	**0.014**
AFP	14	2.8 (2.0-3.3)	2.4 (1.7-3.2)	2.1 (1.8-3.3)	0.225
INR	17	1.03 (1.0-1.1)	1.0 (0.97-1.1)	1.0 (0.99-1.05)	0.167

IQR: Interquartile range, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamil transferaz, ALP: Alkaline phosphatase, TB: Total bilirubin, AFP: Alpha-fetoprotein, INR: International Normalized Ratio, *Friedman test

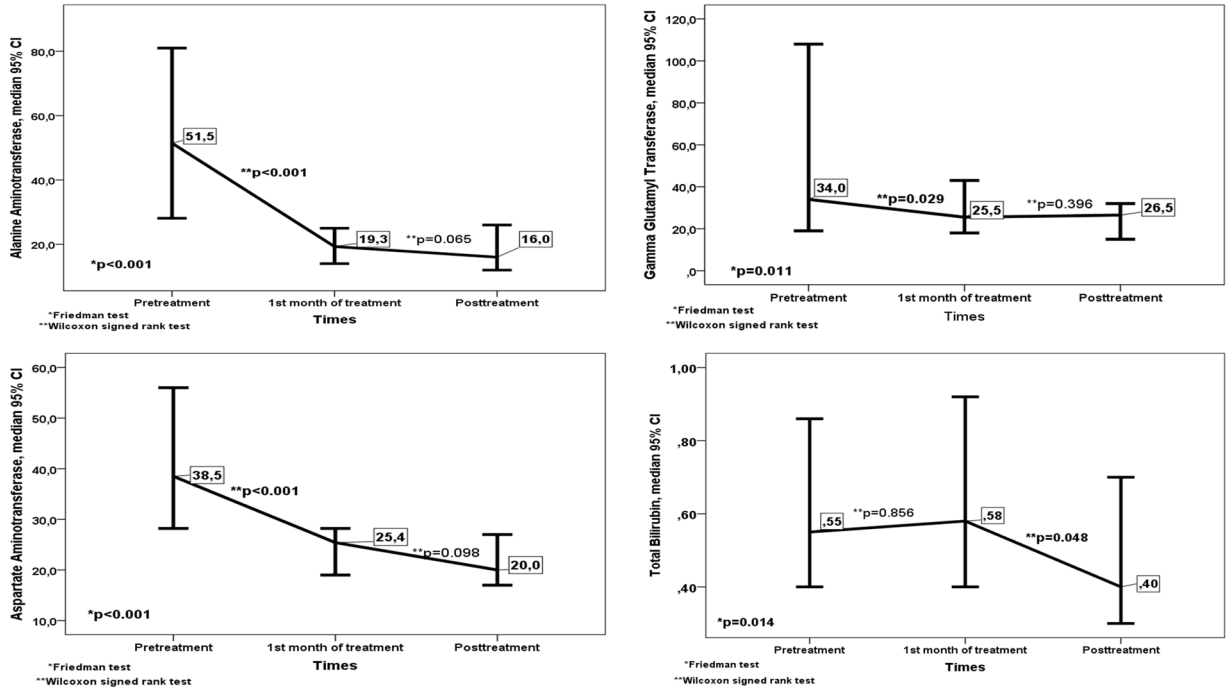

Figure 1. Change of laboratory parameters during treatment

While only one patient had detectable HCV-RNA (2375 IU/mL) in the 1st month of treatment, all patients were negative for HCV-RNA at the end of treatment. SVR12 results were available in 23 patients and SVR24 in 10 patients. SVR12 and SVR24 were achieved in all patients who could be evaluated (100%) (SVR12, 23/23; SVR24, 10/10). Diarrhea was detected in one patient (2.4%) and nausea in another patient (2.4%) in the first month of treatment. The complaints of the patient who had nausea continued throughout the treatment, but the treatment was completed successfully.

One patient who is cirrhotic died during treatment because of underlying disease pancreatic adenocancer, and thus could not be evaluated for SVR. Another patient developed novel HCC six months after the cessation of treatment while examining for SVR24. He achieved SVR24 and underwent transarterial chemotherapy (TACE).

Discussion

This study presented preliminary results of real-world data of treatment - naive CHC patients treated with SOF/VEL/VOX and supports that SOF/VEL/VOX is effective and tolerable in treatment-naive CHC patients. Also, limited data show that SVR rates are high, favoring the results of clinical trials.

SOF/VEL/VOX, the efficacy of which has been demonstrated in phase-3 trials, was introduced as a reliable salvage treatment option especially in patients nonresponding to DAA treatment. POLARIS-1 and POLARIS-4 phase-3 trials included DAA-experienced patients and consistent with these trials real world settings showed high SVR rates in patients who failed from DAA course (6,7,10,11,12). On the other hand, real-world data are scarce about the efficacy and safety of SOF/VEL/VOX in patients who have never received HCV therapy.

POLARIS-2 and POLARIS-3, phase-3 open-label trials, in which the efficacy of SOF/VEL/VOX was investigated primarily in DAA-naive CHC patients, comprised patients who had not received any antiviral therapy previously, besides interferon-based regimen experienced patients. Cirrhotic and noncirrhotic patients from all genotypes were included in the POLARIS-2 study, except genotype-3 cirrhotic patients. Genotype-3 cirrhotic patients who were excluded from POLARIS-2 were included in POLARIS-3. In the SOF/VEL/VOX treatment arm; 76% (n=383) of the patients included in the POLARIS-2 study and 68% (n=75) of the patients included in the POLARIS-3 study were treatment-naive patients who had never received any HCV therapy previously. In these trials, SOF/VEL/VOX for 8 weeks compared with SOF/VEL for 12 weeks. Albeit the SOF/VEL/VOX arm could not be shown to be non-inferior to the SOF/VEL arm in POLARIS-2, high overall SVR rates were obtained in both arms, 95% versus 98% (13). In the present study 41 treatment-naive CHC patients with genotype 1-4 were included, and the majority of our patients were noncirrhotic (92,7%); therefore, except three patients, they received SOF/VEL/VOX for 8 weeks. All patients' response to treatment was excellent and HCV-RNAs were negative at the 1st month of treatment except one patient. The patient who had detectable HCV-RNA in the first month of treatment had multiple preexisting diseases and had to use multiple medications concomitant with HCV treatment. Also, he was co-infected with syphilis and penicillin treatment had been administered in addition to SOF/VEL/VOX. However, the patient's viral load was negative at the end of treatment. SVR12 results were available in 23 patients during the article submission, and SVR rates were 100%.

In this evaluation, one patient with chronic renal failure who was on dialysis three times a week received SOF/VEL/VOX, despite the fact that it has not been studied in patients with end-stage renal disease (ESDR) requiring dialysis. Since the patient was a Syrian refugee and there was no HCV treatment approved for refugees in Turkey, SOF/VEL/VOX was used which obtained by the patient's own resources. SOF/VEL/VOX was used with no dose adjustment in accordance with the manufacturer's recommendation (5). The patient completed the treatment with no complications and achieved SVR. To the best of our knowledge, this is the first case of receiving SOF/VEL/VOX in a patient with ESDR requiring dialysis. SOF/VEL/VOX was given to a patient with HCC and viral load was negative at the first month of treatment. Follow-up continues for virological response.

Clinical studies and postmarketing experience revealed that the most common gastrointestinal adverse reactions related to SOF/VEL/VOX are diarrhea and nausea (4,11,12,13,14). In this study, diarrhea was detected in one patient (2.4%) and nausea in another patient (2.4%) in the first month of treatment. The complaints of the patient, who had nausea, continued throughout the eight weeks but did not lead to a discontinuation of treatment. Serious adverse events were determined in two patients. One patient developed current HCC six months after the cessation of treatment while examining for SVR24. He achieved SVR24 and underwent TACE for HCC. Another patient who was cirrhotic died during treatment because of underlying disease pancreatic adenocancer, which was not related to the SOF/VEL/VOX treatment.

Study Limitations

The strength of this study is that it is the first study examining SOF/VEL/VOX for the first time in treatment-naive CHC patients in a real-life setting. On the other hand, the major limitation of our study was the relatively small patient size. Also, the number of patients with cirrhosis was low. Another limitation is that data of if any resistance-associated substitutions of patients not be eligible due to the insufficient resources of our country.

Conclusion

The preliminary results of our study corroborated the efficacy and well tolerateability of SOF/VEL/VOX in treatment-naive CHC patients. We also observed high SVR rates across genotypes 1, 2, 3, 4 with the pangenotypic SOF/VEL/VOX. Consequently, SOF/VEL/VOX may be another choice with the easy-to-use (once-daily, fixed-dose combination and short-duration regimen) in all genotypes of treatment-naive CHC patients. Additional studies with high sample sizes are required to support our data.

Ethics

Ethics Committee Approval: This study was approved by the Harran University Faculty of Medicine Ethics Committee Commission (approval number: HRÜ/23.02.29, date: 23.01.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.D.Ç., Concept: T.D.Ç., T.Y., E.Y., F.A., B.K., Ö.K., O.K., G.Ü., İ.N.C., H.P., Y.T., S.K., Y.Y., Ç.M., Y.D., M.K.Ç., Design: T.D.Ç., T.Y., E.Y., F.A., B.K., Ö.K., O.K., G.Ü., İ.N.C., H.P., Y.T., S.K., Y.Y., Ç.M., Y.D., M.K.Ç., Data Collection or Processing: T.D.Ç., T.Y., E.Y., F.A., B.K., Ö.K., O.K., G.Ü., İ.N.C., H.P., Y.T., S.K., Y.Y., Ç.M., Y.D., M.K.Ç., Analysis or Interpretation: T.D.Ç., Literature Search: T.D.Ç., Writing: T.D.Ç.

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References

1. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69:461-511.
3. AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. Clin Infect Dis. 2018;67:1477-1492.
4. Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, Vierling JM, Tran TT, Pianko S, Bansal MB, de Lédinghen V, Hyland RH, Stamm LM, Dvory-Sobol H, Svarovskaia E, Zhang J, Huang KC, Subramanian GM, Brainard DM, McHutchison JG, Verna EC, Buggisch P, Landis CS, Younes ZH, Curry MP, Strasser SI, Schiff ER, Reddy KR, Manns MP, Kowdley KV, Zeuzem S; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med. 2017;376:2134-2146.
5. Vosevi [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2017.

6. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. J Viral Hepat. 2019;26:980-990.
7. Da BL, Lourdusamy V, Kushner T, Dieterich D, Saberi B. Efficacy of sofosbuvir/velpatasvir/voxilaprevir in direct-acting antiviral experienced patients with hepatitis C virus. Eur J Gastroenterol Hepatol. 2021;33:859-861.
8. Younossi ZM, Stepanova M, Jacobson IM, Asselah T, Gane EJ, Lawitz E, Foster GR, Roberts SK, Thompson AJ, Willems BE, Welzel TM, Pearlman B, Younossi I, Racila A, Henry L. Sofosbuvir and velpatasvir with or without voxilaprevir in direct-acting antiviral-naïve chronic hepatitis C: patient-reported outcomes from POLARIS 2 and 3. Aliment Pharmacol Ther. 2018;47:259-267.
9. https://www.sgk.gov.tr/Duyuru/Detay/01062022-SUT-Degisiklik-Tebligi-Islenmis-Guncel-2013-SUT-2022-06-16-10-29-43
10. Onofrio FQ, Cooper C, Borgia SM, Vachon ML, Ramji A, Lilly LB, Wong A, Booth J, Sattar I, Morales H, Lee S, Conway B, Feld JJ. Salvage Therapy with Sofosbuvir/Velpatasvir/Voxilaprevir in DAA-experienced Patients: Results from a Prospective Canadian Registry. Clin Infect Dis. 2021;72:e799-e805.
11. Degasperi E, Spinetti A, Lombardi A, Landonio S, Rossi MC, Pasulo L, Pozzoni P, Giorgini A, Fabris P, Romano A, Lomonaco L, Puoti M, Vinci M, Gatti F, Carolo G, Zoncada A, Bonfanti P, Russo FP, Aghemo A, Soria A, Centenaro R, Maggiolo F, Rovere P, Pasin F, Paon V, Faggiano G, Vario A, Grossi G, Soffredini R, Carriero C, Paolucci S, Noventa F, Alberti A, Lampertico P, Fagiuoli S; NAVIGATORE-Lombardia and Veneto Study Groups. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. J Hepatol. 2019;71:1106-1115.
12. Llaneras J, Riveiro-Barciela M, Lens S, Diago M, Cachero A, García-Samaniego J, Conde I, Arencibia A, Arenas J, Gea F, Torras X, Luis Calleja J, Antonio Carrión J, Fernández I, María Morillas R, Rosales JM, Carmona I, Fernández-Rodríguez C, Hernández-Guerra M, Llerena S, Bernal V, Turnes J, González-Santiago JM, Montoliu S, Figueruela B, Badia E, Delgado M, Fernández-Bermejo M, Iñarrairaegui M, Pascasio JM, Esteban R, Mariño Z, Buti M. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. J Hepatol. 2019;71:666-672.
13. Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, Borgia SM, Shafran SD, Workowski KA, Pearlman B, Hyland RH, Stamm LM, Svarovskaia E, Dvory-Sobol H, Zhu Y, Subramanian GM, Brainard DM, McHutchison JG, Bräu N, Berg T, Agarwal K, Bhandari BR, Davis M, Feld JJ, Dore GJ, Stedman CAM, Thompson AJ, Asselah T, Roberts SK, Foster GR. Efficacy of 8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. Gastroenterology. 2017;153:113-122.
14. Liu CH, Peng CY, Liu CJ, Chen CY, Lo CC, Tseng KC, Su PY, Kao WY, Tsai MC, Tung HD, Cheng HT, Lee FJ, Huang CS, Huang KJ, Shih YL, Yang SS, Wu JH, Lai HC, Fang YJ, Chen PY, Hwang JJ, Tseng CW, Su WW, Chang CC, Lee PL, Chen JJ, Chang CY, Hsieh TY, Chang CH, Huang YJ, Kao JH. Sofosbuvir/velpatasvir/voxilaprevir for patients with chronic hepatitis C virus infection previously treated with NS5A direct-acting antivirals: a real-world multicenter cohort in Taiwan. Hepatol Int. 2023;17:291-302.

Research Article

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Can We Accurately Assess Fibrosis in Chronic Hepatitis B Virus Patients?

Kronik Hepatitis B Virüs Hastalarında Fibrozu Doğru Bir Şekilde Değerlendirebiliyor muyuz?

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ABSTRACT

Objectives: To compare the efficacy of blood biochemical indicators with imaging techniques and biopsy data in detecting liver fibrosis in patients with chronic hepatitis B (CHB).

Materials and Methods: One hundred fifty-three CHB patients followed without treatment in the Infectious Diseases Hepatitis Outpatient Clinic between 2021 and 2023 at Ege University Medical Faculty Hospital. The aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, fibrosis-4 (FIB-4) score, aspartate aminotransferase - platelet ratio index (APRI) score, and platelet (PLT) count were all calculated at the same time as the International Normalized Ratio (INR) level and FIB-4 score. Hepatobiliary system ultrasonography (USG) findings, demographic characteristics, hepatitis B virus (HBV)-DNA levels, ultrasound-based elastographic imaging results, and liver biopsy results were assessed. With serum fibrosis markers, AST/ALT ratio, FIB-4 score, APRI score, INR level, PLT number and gender, age, HBV-DNA, liver damage levels via biopsy and ultrasound-based elastography and hepatobiliary system USG results and their relationship between each other were investigated.

Results: Of the patients, 73 (47.7%) were male. The average age was 47.11±13.47 years. Being female, the AST/ALT ratio of more than 1 and being >40 years were found to be statistically significant. The rate of AST/ALT >1 was found to be significantly higher in patients with normal USG findings. The PLT count was found to be higher in the group with HBV-DNA >2000 IU/mL. The FIB-4 score was found to be higher only in males. There was no statistically significant difference between the genders in the APRI score; however, it was found to be higher in patients aged >40 years.

Conclusion: To predict the progression to cirrhosis or hepatocellular carcinoma in CHB patients who do not match the treatment criteria per the Turkish CHB treatment reimbursement

ÖZ

Amaç: Kronik hepatit B'li (KHB) hastalarda karaciğer fibrozunu tespit etmede kullanılan serum biyokimyasal belirteçlerinin performanslarının, fibrozu saptamaya yönelik olarak kullanılan görüntüleme yöntemleri ve biyopsi sonuçları ile karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Ege Üniversitesi Tıp Fakültesi Hastanesi'nde Ocak 2021-Mart 2023 tarihleri arasında Enfeksiyon Hastalıkları Hepatit Polikliniği'nde tedavi almadan takip edilen 153 KHB hastasının fibrozis-4 (FIB-4) skoru, aspartat aminotransferaz - trombosit oranı indeksi (APRİ) skoru, aspartat aminotransferaz/alanin aminotransferaz oranı (AST/ALT) hesaplanmış, eş-zamanlı Uluslararası Normalleştirilmiş Oran (INR) seviyesi ve trombosit (PLT) sayılarına bakılmıştır. Bu serum belirteçlerinin hesaplanıp, kaydedildiği dönemde sistem kayıtlarından hastaların; demografik özellikleri, hepatit B virüs (HBV)-DNA düzeyleri, ultrason bazlı elastografik görüntüleme sonuçları, hepatobiliyer sistem ultrasonografi (USG) bulguları ve karaciğer biyopsi sonuçları değerlendirilmiştir. Serum fibroz belirteçleri olan; AST/ALT oranı, FIB-4 skoru, APRİ skoru, INR düzeyi, PLT sayısı ile cinsiyet, yaş, HBV-DNA, karaciğer biyopsi hasarı düzeyleri ile ultrason bazlı elastografi görüntüleme sonucu ve hepatobiliyer sistem USG sonuçlarının birbiri ile olan ilişkisi, istatistiksel analizler ile araştırılmıştır.

Bulgular: Hastaların 73'ü (47,7) erkek, 80'i (52,3) kadın olup; yaş ortalaması:47,11±13,479 yıl idi. AST/ALT oranın >1 olması, kadın cinsiyet ve >40 yaş bireylerde istatiksel anlamlı bulunmuştur. Normal USG bulgularına sahip hastalarda AST/ALT >1 olma oranı anlamlı oranda daha yüksek saptanmıştır. HBV-DNA >2000 IU/mL olan grupta PLT değeri daha yüksek bulunmuştur. FIB-4 skoru sadece erkeklerde daha yüksek saptanmış, APRİ skorunda cinsiyetler arasında istatistiksel anlamlı bir fark bulunmamış, ancak >40 yaş hastalarda daha yüksek bulunmuştur.

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guideline, fibrosis risk was assessed using biochemical markers and radiological imaging techniques. However, it was determined that radiological imaging using serum markers is not a reliable way to predict fibrosis in its early stages.
Keywords: Chronic HBV infection, liver fibrosis, non-invasive parameter, liver biopsy

Sonuç: Çalışmamızda Sağlık Uygulama Tebliği'ne göre tedavi kriterlerini sağlamayan KHB hastalarında siroza/hepatosellüler kansere ilerleyişi öngörmek için fibrozis riski, biyokimyasal belirteçler ve radyolojik görüntüleme yöntemleri ile değerlendirilmiştir. Ancak çalışmamızda serum belirteçleri ile radyolojik görüntülemenin, fibrozun erken göstergesi olmadığı sonucuna varılmıştır.
Anahtar Kelimeler: Kronik hepatit B, karaciğer fibrozisi, non-invaziv fibrosis göstergeleri, karaciğer biyopsisi

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Introduction

Detection of fibrosis in patients with chronic hepatitis B (CHB) has become an increasingly important issue in recent years in terms of evaluating the prognosis of the disease and quickly initiating antiviral treatment. The fact that hepatic fibrosis is not an irreversible process as it was accepted in the past, that the progression can be slowed and that it can be resolved to some extent with antiviral treatment has also accelerated the fibrosis diagnosis process (1).

The gold standard for staging hepatic fibrosis is the histopathological analysis of the liver biopsy specimen. Liver biopsy, however, has its own restrictions. The main drawbacks include the need for hospitalization, the difficulty of repeating it, the cost, the potential for deadly complications like hemorrhage and perforation, the capacity to sample just a limited portion of the liver, and the sampling variability and interobserver variability that come with these limitations (1,2,3). Due to these drawbacks, noninvasive techniques to detect hepatic fibrosis have been developed. Non-invasive fibrous testing can be used to determine the start of treatment in specific patient groups according to the 2017 viral hepatitis treatment guideline published by the European Association for the Study of the Liver [with hepatitis B virus (HBV)-DNA level >2000 IU\mL, alanine aminotransferase (ALT) levels normal and refusal to undergo biopsy] (4). These tests were evaluated in two separate groups as imaging and serum markers. In this study, early detection of fibrosis by serum markers and imaging methods and its statistical relationship with findings such as liver biopsy, age, gender, HBV-DNA level, and liver ultrasonography (USG) in CHB patients followed in our outpatient clinic and for whom treatment could not be initiated according to the Turkish CHB treatment reimbursement guideline were investigated.

Materials and Methods

The study included 153 CHB patients who did not receive treatment and were evaluated in the Infectious Diseases Hepatitis Outpatient Clinic at Ege University Hospital between January 2021 and March 2023. Demographic features, fibrosis-4 (FIB-4) (1.45-3.25) score, [aspartate aminotransferase - platelet ratio index (APRI) (0.5-2)] score, ratio of aspartate aminotransferase to alanine aminotransferase (AST/ALT >1) were calculated, International Normalized Ratio (INR), platelet (PLT) count, HBV-DNA levels [Cobas® 6800 (Roche Molecular Diagnostics, Switzerland)], ultrasound-based elastographyimaging, hepatobiliary system USG findings and liver biopsy results were recorded retrospectively. HBV-DNA levels were classified as having HBV-DNA >2000 IU/mL at some point in life or having all measurements. Liver biopsy results were grouped as mild, moderate, and severe according to grade and stage values in the Ishak fibrosis staging. USG findings were divided into normal and abnormal (additional adiposity, increase in paraenchymal echogenicity, increase in portal vein diameter, etc.) ≤2000. The AST/ALT ratio, FIB-4 score, APRI score, INR number, and PLT number values; age (>40, sex ≤40), HBV-DNA (>2000 ve ≤2000), liver biopsy result (mild, moderate, severe), ultrasound-based elastography imaging result (F0, F1, F2), and hepatobiliary system USG result (normal, abnormal) were statistically compared with each other and analyzed.

The study was planned in accordance with the Helsinki Declaration decisions and the patient rights regulation, and the Turkish CHB treatment reimbursement guideline (HBV-DNA >2000 IU/mL or $>10^4$ copy/mL and Ishak fibrosis score ≥2/6 or Histology Activity Index ≥6/18). Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: E-99166796-050.06.04-1197109, date: 27.03.2023).

Statistical Analysis

The SPSS statistical analysis program was used to evaluate the data. For numerical variables, first to fit the normal distribution Kolmogorow-Smirnov and Shaphiro-Wilk tests were performed. If the p (statistical significance) value was greater than 0.05 in both tests, it was accepted that the data had a normal distribution. T-test was used for the variables with a normal distribution, and the Mann-Whitney U test was used for those who did not. Statistically, $p<0.05$ was considered significant.

Results

When 153 CHB patients who were followed up between January 2021 and March 2023 and who did not receive treatment were analyzed 73 (47.7). Of the patients, 73 (47,7.3%) were

male and the mean age was 47.11±13.48 years. The mean ALT, AST, PLT, and INR values of the patients were, respectively; 24.06±25.42 U/L, 20.81±12.24 U/L, 240.91±53.97 10^3µL, and the INR value was 0.96±0.06. A serum marker AST/ALT ratio of more than 1 was found to be statistically significantly higher in females and individuals aged more than 40 years (p=0.00003, 0.0072, respectively). Contrary to expectations, the AST/ALT >1 rate was higher in patients with normal USG findings. (p=0.0146). When the PLT count was evaluated, there was no significant difference between the groups, but the platelet PLT was found to be higher in the group with HBV-DNA >2000 IU/mL (p=0.00154). The FIB-4 score was found to be higher only in males (p=0.0457), and no statistically significant difference was found in other parameters. There was no statistically significant difference between the genders in the APRI score, but it was found to be higher in patients aged more than 40 years (p=0.04). Contrary to expectations, the APRI score was found to be statistically significantly higher in patients with normal USG findings. The INR value was found to be high in patients aged 40 years (p=0.0055). Comparison data between groups are summarized in Table 1, 2.

Discussion

Liver biopsy is the gold standard method in the determination of fibrosis in CHB patients and is a necessary and mandatory practice in Turkey to initiate treatment for naive patients. In the last decade of hepatology, the determination of liver fibrosis by non-invasive diagnostic methods without biopsy and early initiation of treatment in certain groups by considering individual risk factors has been included in the guidelines and accepted internationally (4,5,6,7).

In this research, we did not encounter a patient in our chronic HBV patient group for whom we could not start treatment according to the Turkish CHB treatment reimbursement guideline, and we thought it necessary to start treatment with non-invasive serum fibrous markers and ultrasound-based elastography methods. This situation is mainly due to the analyzed patient group, we attribute ALT, AST, PLT, and INR values to the patients with mild disease according to their HBV-DNA mean. In addition, the young age and female gender predominance of the patient group were also effective in this result.

Williams and Hoofnagle (8) showed in a retrospective study that AST/ALT ≥1 is significant for cirrhosis in a population of patients with non-alcoholic liver disease. Reedy et al. (9), on the other hand, stated in their study that the AST/ALT ratio evaluated before the treatment of chronic HCV infection could not accurately predict the presence of cirrhosis and the need for liver biopsy continued. Although AST/ALT ratio more than 1 was found to be higher in the female gender and >40 age group in our study, it was unexpectedly found to be statistically higher in individuals with normal USG findings. The lack of a statistically significant relationship between biopsy and elastography results might be due to the insufficient number of the study group.

Low PLT count and especially recently prolonged INR have been mentioned in many publications as important markers of cirrhosis and advanced fibrosis (10,11). Gold standard liver biopsy and non-invasive serum fibrous markers were compared retrospectively in 464 patients who underwent surgical resection for hepatocellular cancer. Where ISHAK score and 10 different non-invasive fibrous markers were compared, no significant correlation was found between tests and biopsy scores (12). The fact that such a result was obtained even in the patient group with high fibrosis is supportive in terms of the accuracy of the results of our study, in which patients with mild fibrosis were predominant.

FIB-4 and APRI scoring systems have been routinely used in recent years to determine fibrosis. In this respect Shin et al. (13) showed that the APRI score is a reliable method for estimating fibrosis. Another study in patients with chronic HCV concluded that the APRI score was more reliable in predicting fibrosis in women than in men (14). Yilmaz et al. (15), in their study on 207 CHB, 108 CHC and 140 NAFLD patients, showed results that correlated with liver biopsy, with APRI score showing significant fibrosis in all three patient groups. In the study of Sayar et al. (16), the diagnostic performance of the FIB-4 index in determining cirrhosis was found to be good. Kaya et al. (17) found that the negative predictive value of FIB-4 index was high.

Wai et al. (18) compared the biopsy results with the APRI score in untreated patients with chronic HBV and demonstrated that the APRI score was successful in identifying patients with significant fibrosis and cirrhosis. In the study of Lin et al. (19), on the other hand, they found that APRI could identify fibrosis associated with CHB with moderate accuracy. At the latest, in a publication in which high patient data such as 69,106 were reviewed retrospectively, the diagnostic value of FIB-4 and APRI test results in determining fibrosis was found to be low. In this publication, it was reported that 86% and 67% of patients with fibrous F3-F4 scores, respectively, with FIB-4 and APRI scores were misdiagnosed as F1-F2 (20,21). Statistically significant in our study, in patients with APRI score >40 years; FIB-4 score was found to be higher in males; It was found to be compatible with some literature, but there are also studies reporting different results.

Imaging techniques, one of the noninvasive methods that detect fibrosis, have taken their place in the guides in terms of diagnosis (4). Studies have reported that fibroscan and serum biomarkers have similar performance in detecting fibrosis in hepatitis patients with significant fibrosis (22). Although the combination of fibroscan and serum biochemical markers is more effective than the combination of the two serum markers, its higher cost draws attention in studies (4,23,24). In our study, fibroscan and biopsy findings did not yield statistically significant results with non-invasive biochemical tests. We think that our patient group consisted of patients with m, and fibrosis and the comparison of fibroscan and biopsy results in a few patients is probably responsible for this situation.

In our study, the APRI score and AST/ALT ratio were found to be higher in individuals with normal USG findings, contrary to expectations. We think that the reason for this is that our patients are in the young age group with mild disease without advanced liver damage. Another problem is that USG evaluations were made at different times and by different radiologists. USG is the first preferred imaging method because it is inexpensive and easily accessible in detecting chronic liver damage (25). Demir et al.

(26) investigated the value of ultrasound in the diagnosis of early cirrhosis by comparing the histopathological findings of patients with chronic viral hepatitis with ultrasound changes in the liver. In this study, it was determined that the most sensitive finding in the diagnosis of early cirrhosis was the irregularity of the liver parenchyma. In another study, it was reported that ultrasound had a diagnostic accuracy of 84-87% for the diagnosis of significant fibrosis, 89-91% for the diagnosis of severe fibrosis, and 92-93% for the diagnosis of liver cirrhosis (27).

Table 1. Intergroup analysis of AST/ALT ratio, APRI score, and PLT count

Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
AST/ALT	Male	73	0.864	0.375	2,5	0.00003
	Female	80	1,071	0.455	2,625	
	<=40 years	54	0.915	0.375	2	0.0072
	>40 years	99	1,045	1,04545	2,625	
	HBV-DNA <=2000	73	One	0.455	2,625	0.645
	HBV-DNA >2000	80	One	0.375	1,889	
	Abnormal	49	0.888	0.375	2	0.014
	Normal	67	One	0.444	2,625	
	F0	24	0.968	0.571	1,615	0.975
	F1	4	0.974	0.714	1,429	
T-test biopsy		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
AST/ALT	Mild	24	1,015	0.3064		0.035
	Moderate	4	0.655	0.2334		
T-test		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
PLT (10^3µL)	Male	73	219.23	44.76		7,358
	Female	80	260.7	54,299		
	<=40 years	54	237.61	56.62		0.577
	>40 years	99	242.72	52,681		
	HBV-DNA <=2000	73	226.62	48,141		0.00154
	HBV-DNA >2000	80	253.96	55,961		
	Abnormal	49	250.45	55,238		0.1896
	Normal	67	237.3	51,341		
	F0	24	229	61,163		0.3144
	F1	4	264.75	86,102		
	Mild	24	255.92	56,083		0.693
	Moderate	4	244.25	37,322		
Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
APRI	Male	73	0.401	0.156	1,689	0.354
	Female	80	0.42	0.169	1,651	
	<=40 years	54	0.383	0.156	1,361	0.04
	>40 years	99	0.426	0.191	1,689	
	HBV-DNA <=2000	73	0.439	0.191	1,689	0.109
	HBV-DNA >2000	80	0.3885	0.156	1.05	
	Abnormal	49	0.375	0.156	0.922	0.01099
	Normal	67	0.439	0.169	1,689	
	F0	24	0.439	0.287	1.05	0.635
	F1	4	0.4125	0.209	0.611	
T-test	**Biopsy**	**n**	**Mean**	**SD**		**Sig. (2-tailed)**
APRI	Mild	24	0.43679	0.183567		0.092
	Moderate	4	0.271	0.091902		

AST/ALT: Aspartate aminotransferase/alanine aminotransferase, APRI: Aspartate aminotransferase - platelet ratio index, PLT: Platelet, HBV: Hepatitis B virus, SD: Standard deviation

Table 2. Intergroup analysis of FIB-4 score and INR value

Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
INR	Male	73	0.96	0.85	1.16	0.463
	Female	80	0.965	0.86	1.15	
	<=40 years	54	0.975	0.9	1.16	0.0055
	>40 years	99	0.95	0.85	1.15	
	HBV-DNA <=2000	73	0.97	0.88	1.16	0.79
	HBV-DNA >2000	80	0.96	0.85	1.1	
	Abnormal	49	0.955	0.86	1.1	0.157
T-test		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
INR	F0	23	0.97565	0.050075		0.741
	F1	4	0.985	0.061914		
	Mild	23	0.95826	0.051756		0.051
	Moderate	4	1,015	0.047958		
Mann-Whitney U test		**n**	**Median**	**Minimum**	**Maximum**	**Asymp. sig. (2-tailed)**
FIB-4	Male	73	0.83	0.37	3.25	0.0457
	Female	80	0.745	0.24	3.17	
	<=40 years	54	0.61	0.24	1.33	2,267
	>40 years	99	0.97	0.262	3.25	
	HBV-DNA <=2000	73	0.92	0.24	3.25	0.0647
	HBV-DNA >2000	80	0.74	0.262	2.05	
	Abnormal	49	0.94	0.262	1.95	0.801
	Normal	67	0.76	0.295	3.25	
T-test		**n**	**Mean**	**SD**		**Sig. (2-tailed)**
FIB-4	F0	24	0.89308	0.323162		0.114
	F1	4	0.62	0.161038		
	Mild	24	0.90133	0.40718		0.996
	Moderate	4	0.9025	0.422641		

FIB-4: Fibrosis-4, HBV: Hepatitis B virus, INR: International Normalized Ratio

Study Limitations

The limitations of our study are that we have biopsy and fibroscan results from a limited number of patients and that these results are not concurrent with serum fibrous markers.

Conclusion

We think that this study is an original study in terms of complicating the possibility of early treatment by comparing serum fibrous markers and imaging tests used to detect liver fibrosis with the factors of the patient.

The risk of fibrosis was assessed with noninvasive biochemical and radiological tests, and their superiority over liver biopsy was investigated in CHB patients who did not receive treatment because they did not meet the current treatment criteria in order to prevent progression to cirrhosis and hepatocellular cancer. We could not uncover any results in our study that supported our hypothesis that these technologies, which are affordable, simple, and accessible, can prevent both patients and doctors from an intrusive operation such as a biopsy. Our research has led us to believe that non-invasive fibrous indicators are not yet a viable substitute for liver biopsies, but they do have a negative predictive value when deciding whether to begin treatment.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval number: 2023-033623-3T/25, date: 16.02.2023).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: N.Y., H.P., T.Y., Concept: N.Y., H.P., T.Y., Design: N.Y., H.P., T.Y., Data Collection or Processing: N.Y., A.K., G.Ş.İ., M.M.V., H.P., T.Y., Analysis or Interpretation: N.Y., A.K., H.P., T.Y., Literature Search: N.Y., H.P., T.Y., Writing: N.Y., H.P., T.Y.

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References

1. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of

Gastroenterology and the Royal College of Physicians of London. Gut. 1995;36:437-441.

2. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, Feng ZZ, Reddy KR, Schiff ER. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol. 2002;97:2614-2618.
3. El-Zayadi AR, Badran HM, Saied A, Shawky S, Attia Mel-D, Zalata K. Evaluation of liver biopsy in Egyptian HBeAg-negative chronic hepatitis B patients at initial presentation: implications for therapy. Am J Gastroenterol. 2009;104:906-911.
4. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63:237-264.
5. Dhyani M, Anvari A, Samir AE. Ultrasound elastography: liver. Abdom Imaging. 2015;40:698-708.
6. Gheorghe G, Bungău S, Ceobanu G, Ilie M, Bacalbaşa N, Bratu OG, Vesa CM, Găman MA, Diaconu CC. The non-invasive assessment of hepatic fibrosis. J Formos Med Assoc. 2021;120:794-803.
7. Soresi M, Giannitrapani L, Cervello M, Licata A, Montalto G. Non invasive tools for the diagnosis of liver cirrhosis. World J Gastroenterol. 2014;20:18131-18150.
8. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology. 1988;95:734-739.
9. Reedy DW, Loo AT, Levine RA. AST/ALT ratio > or = 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. Dig Dis Sci. 1998;43:2156-2159.
10. Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, Ripoll C, Maurer R, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Makuch R, Rendon G; Portal Hypertension Collaborative Group. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol. 2009;7:689-695.
11. Wang Y, Dong F, Sun S, Wang X, Zheng X, Huang Y, Li B, Gao Y, Qian Z, Liu F, Lu X, Liu J, Ren H, Zheng Y, Yan H, Deng G, Qiao L, Zhang Y, Gu W, Xiang X, Zhou Y, Xu B, Hou Y, Zhang Q, Xiong Y, Zou C, Chen J, Huang Z, Jiang X, Qi T, Luo S, Chen Y, Gao N, Liu C, Yuan W, Mei X, Li J, Li T, Zheng R, Zhou X, Zhang W, Li H, Meng Z. Increased INR Values Predict Accelerating Deterioration and High Short-Term Mortality Among Patients Hospitalized With Cirrhosis or Advanced Fibrosis. Front Med (Lausanne). 2021;8:762291.
12. Ho SY, Liu PH, Hsu CY, Hsia CY, Su CW, He YJ, Lee YH, Huang YH, Hou MC, Huo TI. Current noninvasive liver reserve models do not predict histological fibrosis severity in hepatocellular carcinoma Sci Rep. 2018;8:15074.
13. Shin WG, Park SH, Jang MK, Hahn TH, Kim JB, Lee MS, Kim DJ, Jun SY, Park CK. Aspartate aminotransferase to platelet ratio index (APRI) can predict liver fibrosis in chronic hepatitis B. Dig Liver Dis. 2008;40:267-274.
14. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7:1104-1112.
15. Yilmaz Y, Yonal O, Kurt R, Bayrak M, Aktas B, Ozdogan O. Noninvasive assessment of liver fibrosis with the aspartate transaminase to platelet ratio index (APRI): Usefulness in patients with chronic liver disease: APRI in chronic liver disease. Hepat Mon. 2011;11:103-106.
16. Sayar S, Atalay R, Cakmak S, Ayrancı G, Kürbüz K, Kahraman R, Calışkan Z, Öztürk O, Demirdağ H, Adalı G, Özdil K, Doğanay HL. Diagnostic Performance of Non-invasive Fibrosis Indexes in Hepatitis B Related Fibrosis. Viral Hepat J. 2020;26:78-84 (Turkish).
17. Kaya O, Akçam FZ, Sönmez Y, Tığlı A, Çiriş M. Evaluation of Non-invasive Methods for Prediction of Fibrosis in Chronic Hepatitis B and C Infections. Viral Hepat J. 2009;14:91-97 (Turkish).
18. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38:518-526.
19. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, Sun Y, Xuan SY. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53:726-736.
20. Hashem A, Awad A, Shousha H, Alakel W, Salama A, Awad T, Mabrouk M. Validation of a machine learning approach using FIB-4 and APRI scores assessed by the metavir scoring system: A cohort study. Arab J Gastroenterol. 2021;22:88-92.
21. Kesimal U, Öztürk Durmaz Ş. (2021). Comparison of non-invasive fibrosis scoring methods with liver biopsy in chronic hepatitis B patients. Akd Med J. 2021;7:283-288 (Turkish).
22. Castéra L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology. 2005;128:343-350.
23. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62:932-954.
24. Köksal İ, Yılmaz G, Parlak M, Demirdal T, Kınıklı S, Candan M, Kaya A, Akhan S, Aydoğdu Ö, Turgut H, Gürbüz Y, Dağlı Ö, Gökal AA, Güner R, Kuruüzüm Z, Tarakçı H, Beslen N, Erdoğan S, Özdener F, Study Group TCHC. Diagnostic value of combined serum biomarkers for the evaluation of liver fibrosis in chronic hepatitis C infection: A multicenter, noninterventional, observational study. Turk J Gastroenterol. 2018;29:464-472.
25. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383:1749-1761.
26. Demir A, Akarca US, Yılmaz F, Özütemiz Ö, Karasu Z, İlter T. The place of ultrasonography in the diagnosis of early-stage cirrhosis. Turk J Gastroenterol. 1999 (Turkish).
27. Clevert DA, Beyer G, Nieß H, Schlenker B. Ultrasound—New Techniques Are Extending the Applications. Dtsch Arztebl Int. 2023;120:41-47.

Research Article

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Investigation of Hepatitis B Surface Antibody Levels in Adults with Routine Hepatitis B Vaccination in Childhood

Çocukluk Döneminde Rutin Hepatit B Aşılaması Yapılan Erişkinlerde Hepatit B Yüzey Antikoru Düzeylerinin Araştırılması

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ABSTRACT

Objectives: Recombinant hepatitis B vaccines provide effective and long-term protection. It is not well known whether it reaches protective levels of antibodies in adulthood. In this study, it was aimed to investigate hepatitis B surface antibody (anti-HBs) levels in adults who received routine hepatitis B vaccination in the newborn period and to reveal its change with age.

Materials and Methods: The hepatitis B surface antigen (HBsAg) and anti-HBs levels of those who applied to our hospital's health board between 01.01.2017 and 31.12.2021 and were at least 18 years old were evaluated by retrospectively scanned from the board records. Those with anti-HB titers above 10 mIU/mL were considered to have a protective antibody level.

Results: The mean age was 20.0±1.5 (18-24). Anti-HBs result was found to be above 10 IU in 1,691 (70.8%) of 2,395 people who were HBsAg negative. In the study, the rate of those who were found to be anti-HBs negative at the age of 18 and 19 was significantly higher than the older age groups, and those with more than 1000 mIU/mL in the 23 and 24 age groups compared to the younger age groups ($p<0.001$). A significant correlation was found between age and anti-HBs levels ($p<0.001$; $r=0.219$).

Conclusion: Our study is one of the rare studies measuring the level of hepatitis B vaccine protection for up to 24 years. Our findings demonstrated that the antibody level was found to be above 10 IU in 71% of adults included in the routine hepatitis B vaccination program after birth, and the antibody level did not decrease but rather increased with increasing age.

Keywords: HBV, hepatitis B vaccine, anti-HBs titer

ÖZ

Amaç: Rekombinant hepatit B aşıları etkili ve uzun süreli koruyuculuk sağlamaktadır. Erişkin çağda rutin olarak koruyucu düzeyde antikor seviyelerine ulaşıp ulaşmadığı iyi bilinmemektedir. Bu çalışmada, ülkemizde yenidoğan döneminde rutin hepatit B aşılaması yapılan yetişkinlerde hepatit B yüzey antikoru (anti-HBs) düzeylerinin ve bu düzeylerin yaşla ilişkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Hastanemiz sağlık kuruluna 01.01.2017-31.12.2021 tarihleri arasında başvuran ve en az 18 yaşında olanların hepatit B yüzey antijeni (HBsAg) ve anti-HBs düzeyleri kurul kayıtlarından geriye doğru taranarak değerlendirilmiştir. Anti-HBs titreleri 10 mIU/mL'nin üzerinde olanlar koruyucu antikor düzeyine sahip kabul edilmiştir.

Bulgular: Ortalama yaşı 20,0±1,5 (18-24) idi. HBsAg negatif olan 2.395 kişinin 1.691'inin (%70,8) anti-HBs sonucunun 10 IU'nin üzerinde bulundu. Çalışmada 18 ve 19 yaşında olanlarda anti-HBs negatif saptananların oranı daha büyük yaş gruplarına göre, 23 ve 24 yaş gruplarında >1000 mIU/mL olanların olanı daha küçük yaş gruplarına göre anlamlı yüksekti ($p<0,001$). Yaş ve anti-HBs düzeyleri arasında anlamlı korelasyon saptandı ($p<0,001$; $r=0,219$).

Sonuç: Çalışmamız 24 yıla varan hepatit B aşı koruyuculuğu düzeyini ölçen nadir çalışmalardandır. Bulgularımız doğumdan sonra rutin hepatit B aşılama programına dahil olan erişkinlerin %71'inde antikor seviyesinin 10 IU'nun üzerinde saptandığı, yaş artıkça antikor düzeyinin azalmadığı aksine artığını göstermiştir.

Anahtar Kelimeler: HBV, hepatit B aşısı, anti-HBs titre

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Introduction

Hepatitis B virus (HBV) is a DNA virus that can cause serious disease in the liver. If an individual is infected with HBV, he/she may carry the virus asymptomatically for a lifetime, develop chronic liver disease, liver cirrhosis, liver cancer, and even progress to liver failure, which may result in death. In the latter case, liver transplantation may be required (1,2,3).

Today, HBV infection is a vaccine-preventable infectious disease. Recombinant hepatitis B vaccines developed against HBV provide effective and long-term protection. In many countries around the world, three doses of hepatitis B vaccine were included in the routine vaccination program in infancy in the 1990s. By ensuring that the first dose is given immediately after birth, protection against hepatitis B infection that may be present in the mother is provided (4,5,6,7).

Serum anti-HB titers decrease over the years after vaccination. However, it is stated that protection against HBV infection continues as long as this decrease does not decrease below the level of 10 mIU/mL. In the case the titer falls below this level, a booster dose of vaccine is recommended. In some patients who are considered to be at risk for hepatitis B infection due to some underlying diseases, it has been stated that antibody titers should be kept above 10 mIU/mL (4,5).

In most studies, antibody levels decrease with age or with the time elapsed after vaccination (5,8,9,10). However, while it has been about 20 years since the introduction of vaccination programs worldwide, there are very few studies investigating antibody and protection levels in individuals with 20 years of time elapsed since their infancy vaccination (11,12,13,14,15). Therefore, it is not well known whether it reaches protective levels of antibodies in adulthood. In this study, it was aimed to investigate anti-HB levels in adults who received routine hepatitis B vaccination in the newborn period and to reveal its change with age.

Materials and Methods

Approval for the study was obtained from the Samsun University, Clinical Research Ethics Committee (approval number: 2023/4/4, date: 01.03.2023).

Participants and Tests

Hepatitis B surface antigen (HBsAg) and anti-HBs levels of patients who were at least 18 years old and applied to our hospital's health board between 01.01.2017 and 31.12.2021 were evaluated retrospectively. Anti-HB titers that were above 10 mIU/mL using the ELISA method had a protective antibody level and were considered immune to the vaccine. All data of the participants were retrospectively obtained from the board records.

Statistical Analysis

The sample size of the study was calculated by power analysis using G-Power (version 3.1.9.6, Franz Faul, Universität Kiel, Germany). Effect size 0.34; the type1 error was 0.05 and the test power was taken as 0.99 and the sample size was calculated as 554, however 2,396 participants whose data were available were included in the study.

Since ELISA results for anti-HBs values above 1000 mIU/mL were reported as more than 1000 in the study, mean values for age groups could not be calculated and compared. Instead, the median values were compared. While preparing the box plot graph, all values more than 1000 mIU/mL were accepted as 1000 mIU/mL.

All statistical analyzes in the study were performed using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as numbers and percentages. Comparisons between groups in terms of categorical variables were performed by Pearson's chi-square test. Differences between groups in terms of continuous variables were performed by Kruskal-Wallis test. The relationship between continuous variables was evaluated by Spearman correlation analysis. The results were evaluated within the 95% confidence interval and $p<0.05$ values were considered significant.

Results

The mean age of the participants in the study was 20.0±1.5 (18-24). In the study, seven (0.3%) of 3,402 people who were evaluated for HBsAg had a positive HBsAg test, 1,691 (70.8%) of 2,395 people who were HBsAg negative had a positive anti-HBs result (≥10 IU), and 704 (29.3%) was found to be negative (Table 1).

When anti-HB positivity according to age is examined, it has been shown that as age increases, antibody positivity increases and negativity decreases ($p<0.001$) (Table 2).

When the anti-HBs values were analyzed by grouping, significant differences were found in terms of the distribution of anti-HBs groups according to age groups, according to this, the rate of those with negative results in 18 and 19 years old was higher compared to the older age groups, and those with more than 1000 mIU/mL in the 23 and 24 age groups was significantly higher than the

Table 1. The distribution of HBsAg and anti-HBs results

HBsAg	Anti-HBs	n	%
Positive (n=7)	Negative	3	0.12
	Positive	4	0.18
Negative (n=2395)	Negative	704	29.3
	Positive	1691	70.4

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

Table 2. The distribution of anti-HBs results by age in HBsAg-negative patients

Age	Negative, n (%)	Positive, n (%)	p
18	223 (44.6)	277 (55.4)	<0.001
19	188 (36.2)	332 (63.8)	
20	131 (25.1)	390 (74.9)	
21	100 (22.1)	352 (77.9)	
22	42 (16.0)	220 (84.0)	
23	18 (15.1)	101 (84.9)	
24	2 (9.5)	19 (90.5)	
Total	704 (29.3)	1691 (70.7)	-

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

younger age groups (p<0.001). The rate of negativity and low-level positivity was higher at younger ages, whereas the rate of high-level positivity was higher at older ages. There were no participants in the 23 and 24 age groups with a score of 0. Only 3.8% of the 18-year-olds had more than 1000 mIU/mL levels (Table 3).

When the median anti-HBs levels were analyzed between age groups, it was found that there was an increase in anti-HBs levels with age, accordingly, the median values of 18, 19 and 20 year olds were significantly lower than all other age groups older than them (p<0.001) (Table 4) (Figure 1).

It was found that the mean age was significantly higher in the groups with antibody titers above 100 mIU/mL compared to the groups with antibody titers 10-100 mIU/mL and <10 mIU/mL (p<0.001) (Table 5).

In the correlation analysis, it was found that there was a positive but weak correlation between age and anti-HBs levels (p<0.001; r=0.219).

Discussion

In the 1990s, the hepatitis B vaccine began to be included in the routine vaccination program from birth in many countries around the world. It has been stated that anti-HB levels decrease rapidly in the first year after hepatitis B vaccination in children, but this decrease slows down in the following years. In addition, it has been reported that as long as the anti-HBs level remains above 10 mIU/mL, its protection continues for up to 23 years, and even below this level, protection might still be sustained (4,5,6). In our study, anti-HBs levels were examined in adults who were born after the addition of hepatitis B vaccine to the routine vaccination program in our country and who are up to 24 years old today, and it was observed that antibody levels did not decrease as expected in older patients.

In our study, seven (0.3%) of 3,402 people who were examined for HBsAg were found to be positive for HBsAg. This finding shows that it is important to examine the hepatitis B antigen of mothers during pregnancy because HBV can be transmitted from mother to baby during delivery.

Shakeri et al. (8) showed that 10 years after the hepatitis B vaccine, the protection rate was 96.5%, and Kazemeini and Owlia (16) showed that it was 90%. Floreani et al. (10) found 10-year antibody positivity rates between 81-88% after routine vaccination with two different vaccines. In the study of Qawasmi et al. (9) in which they examined people aged 0-19 years, they found that 37% of the 17-19 age group had a protective level of antibody positivity. The antibody positivity at a protective level 20 years after the first vaccination was reported to be 37% by Bagheri-Jamebozorgi et al. (12); 48% by Lin et al. (13); 49.3% by Fonzo et al. (15); 66.9% by Dini et al. (11); 71.8% by Lu et al. (14). In our study, it was found that anti-HBs was negative in 29.2% of adults who received a routine vaccination program during the neonatal period. This finding shows that despite the routine vaccination program, the protection rate against hepatitis B in the general population is at a very low

Table 3. The distribution of anti-HBs titer groups by age in HBsAg-negative patients

Age	Anti-HBs titres (titers/mL)						Total
	Negative, (0)	Negative, (0.1-9.9)	Positive, (10-19.9)	Positive, (20-99.9)	Positive, (100-1000)	Positive, (>1000)	
18	18 (3.6)	205 (41.0)	63 (12.6)	110 (22)	85 (17.0)	19 (3.8)	500 (100)
19	11 (2.1)	177 (34.0)	58 (11.2)	100 (19.2)	108 (20.8)	66 (12.7)	520 (100)
20	16 (3.1)	115 (22.1)	45 (8.6)	109 (20.9)	144 (27.6)	92 (17.7)	521 (100)
21	18 (4)	82 (18.1)	34 (7.5)	91 (20.1)	149 (33.0)	78 (17.3)	452 (100)
22	2 (0.8)	40 (15.3)	22 (8.4)	56 (21.4)	92 (35.1)	50 (19.1)	262 (100)
23	0 (0)	18 (15.1)	10 (8.4)	28 (23.5)	34 (28.6)	29 (24.4)	119 (100)
24	0 (0)	2 (9.5)	2 (9.5)	5 (23.8)	7 (33.3)	5 (23.8)	21 (100)
Total	65 (2.7)	639 (26.7)	234 (9.8)	499 (20.8)	619 (25.8)	339 (14.2)	2395 (100)

P<0.001. HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

Table 4. Mean and median anti-HBs titer values by age in HBsAg-negative patients

Age	n	Mean ± SD	Median	Minimum	Maximum
18	500	109.3±239.8	**12.750**	0	>1000
19	520	213±346	**25.700**	0	>1000
20	521	290.3±380.3	**67.900**	0	>1000
21	452	310±378.4	102.750	0	>1000
22	262	340.9±384.4	144.350	0	>1000
23	119	358.9±409.2	111.200	0.1	>1000
24	21	352±395.7	166.500	0.2	>1000
Overall	2395	248.9±359.2	46.600	0	>1000

P<0.001. SD: Standard deviation, HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

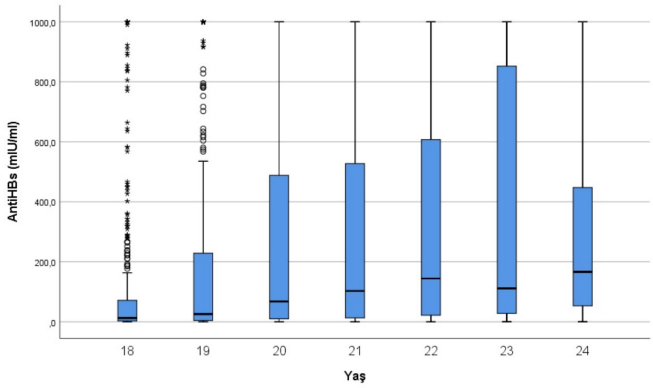

Figure 1. Mean and median anti-HBs titre values by age in HBsAg-negative patients

HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

Table 5. Comparison of mean ages between anti-HBs titer groups in HBsAg-negative patients

Anti-HBs, (mIU/mL)	Age, mean ± SD (year)
Negative (0-9.9)	19.4±1.4
Positive (10-100)	19.9±1.5
Positive (>100)	20.4±1.4
Overall	20±1.5

P<0.001. SD: Standard deviation, HBsAg: Hepatitis B surface antigen, HBs: Hepatitis B surface antibody

level of 70%. This finding also suggests that hepatitis vaccines should be tested for protection status after administration and booster doses should be given to those who do not develop antibodies and to those who become negative as antibody levels fall. Moreover, it appears in general that the administration of a booster dose can largely prevent anti-HB negativization in the general population and enhance collective immunity.

In European countries, recurrent hepatitis B vaccine has been recommended in risk groups, and it has been stated that antibody titers above 100 mIU/mL can also provide protection against HBV genotypes not included in the vaccine (17). In our study, the rate of those in the 18-24 age groups with antibodies above 100 mIU/mL was found to be 40%. This finding indicates that the proportion of adults with high levels of protection after vaccination in infancy is acceptable.

Dini et al. (11) found that 20 years after the first vaccination, those with antibody titers above 100 mIU/mL had a significantly higher mean age compared to the groups with a mean age of 10-100 mIU/mL and <10 mIU/mL. Mastrodomenico et al. (18) also found that the mean postvaccination period was significantly higher in individuals with anti-HBs titers >10 mIU/mL compared with those with antibody titer <10 mIU/mL (22.4 years vs. 21.8 years). Similarly, in our study, it was found that those with antibody titers above 100 mIU/mL were found to be significantly higher than the groups with a mean age of 10-100 mIU/mL and <10 mIU/mL. These findings suggest that antibody titers are higher in individuals with older age or with a longer time since hepatitis vaccination. When anti-HB positivity according to age is examined, it has been shown that as age increases, antibody positivity increases and negativity decreases. This finding shows that there is a more significant decrease in the protectiveness of those who are younger. In addition, in our study, when the anti-HBs values were analyzed by grouping, significant differences were found in terms of the distribution of anti-HBs groups according to age groups; accordingly, the proportion of negative results detected in those aged 18 and 19 was found to be significantly higher compared to older age groups, and those with more than 1000 mIU/mL in 23 and 24 age groups compared to younger age groups. While the ratio of negativity and low-level positivity was higher at younger ages, the ratio of high-level positivity was higher at older ages. In the 23 and 24 age groups, there were no participants with an antibody level of "0". Only 3.8% of 18-year-olds had antibody levels more than 1000 mIU/mL. All these findings suggest that antibody negativity is more frequent in younger individuals, whereas antibody positivity ratios are significantly higher in older individuals. Therefore, it is important to determine the level of protection against hepatitis B in younger patients.

Bagheri-Jamebozorgi et al. (12) found the mean anti-HBs titer as 55.4 mIU/mL 20 years after infancy vaccination. In our study, the mean antibody titer after approximately 20 years were found to be at a higher level of 248.9 mIU/mL. This difference may be attributed to various factors such as the population included in the study and the brand of vaccine administered in infancy.

Shakeri et al. (8) showed that anti-HBs levels were significantly lower in individuals with more than 16 years elapsed since last hepatitis B vaccination compared with those with a shorter period of time elapsed after last hepatitis B vaccination and reported that antibody levels decreased with age and older age was a negative predictive factor for antibody levels. Kazemeini and Owlia (16), however, found no relation between age and anti-HBs titer, but found a relation between the last vaccine dose and antibody titer Some other studies have also shown that there is a significant decrease in antibody titer during the time since the last vaccine (9,16,19,20,21). However, in our study, significant differences were found between age groups in terms of median anti-HBs levels, accordingly, the median values of those aged 18, 19 and 20 were found to be significantly lower than all other age groups who were older than them. This finding indicates that antibody levels are generally lower at younger ages and less protective in general terms. Furthermore, correlation analysis showed that there was a positive but weak relationship between age and anti-HB levels. This finding shows that as age increases, antibody levels are generally higher and the level of protection is better. It is rather unexpected that the antibody levels are higher in older patients, that is, higher anti-HBs levels are found despite a longer period of time since hepatitis B vaccination. This may be due to increased exposure to hepatitis B virus with age.

Qawasmi et al. (9) reported that the mean anti-HBs level in the 17-19 age groups was 5.3 mIU/mL. In our study, the mean anti-HB titer was found to be 109.3±239.8 mIU/mL in the 18-year-old group, and 213±346 mIU/mL in the 19-year-old group, and much higher antibody titers were observed in the older age groups. The fact that the mean values in our study were much higher than those in the aforementioned study may be attributed to the differences in regional and participant characteristics.

Study Limitations

There were limitations to our study. Since information on whether the subjects included in the study received the booster hepatitis B vaccine was not available, it could not be clarified whether the high anti-HBs levels were associated with the booster vaccine. The number of participants was kept very high to avoid statistical errors. In addition, individuals over the age of 24 could not be included in the study and changes in antibody levels could not be observed at older ages because the study was related to the introduction of a routine vaccination program.

Conclusion

To the best of our knowledge, our study is one of the rare studies measuring the level of hepatitis B vaccine protection for up to 24 years. Our findings showed that people who were included in the routine hepatitis B vaccination program after birth had 71% protection when they reached adulthood, and the antibody level did not decrease with increasing age, on the contrary, it increased**.** Further immunological studies are needed to explain the reason.

Ethics

Ethics Committee Approval: Approval for the study was obtained from the Samsun University, Clinical Research Ethics Committee (approval number: 2023/4/4, date: 01.03.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S., Concept: E.S., E.M.Y., Design: E.M.Y., Data Collection or Processing: E.S., M.A.O., Analysis or Interpretation: E.S., E.M.Y., M.A.O., Literature Search: E.S., E.M.Y., M.A.O., Writing: E.S., E.M.Y.

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References

1. Iannacone M, Guidotti LG. Immunobiology and pathogenesis of hepatitis B virus infection. Nat Rev Immunol. 2022;22:19-32.
2. Jeng WJ, Papatheodoridis GV, Lok ASF. Hepatitis B. Lancet. 2023;401:1039-1052.
3. Yuen MF, Chen DS, Dusheiko GM, Janssen HLA, Lau DTY, Locarnini SA, Peters MG, Lai CL. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:18035.
4. Nguyen MH, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. Clin Microbiol Rev. 2020;33:e00046-19.
5. Van Herck K, Van Damme P. Benefits of early hepatitis B immunization programs for newborns and infants. Pediatr Infect Dis J. 2008;27:861-869.
6. Pattyn J, Hendrickx G, Vorsters A, Van Damme P. Hepatitis B Vaccines. J Infect Dis. 2021;224(12 Suppl 2):S343-S351.
7. Parija PP, M MK. Hepatitis B vaccine birth dose in India: time to reconsider. Hum Vaccin Immunother. 2020;16:158-160.
8. Shakeri H, Rahmanian V, Shakeri M, Mansoorian E. Study Of Anti-Hbs Antibody Titer And Associated Factors Among Healthcare Staff Vaccinated Against Hepatitis B More Than Ten Years In Hospitals of Jahrom In 2016. Pharmacophore. 2018;9:156-161.
9. Qawasmi M, Samuh M, Glebe D, Gerlich WH, Azzeh M. Age-dependent decrease of anti-HBs titers and effect of booster doses using 2 different vaccines in Palestinian children vaccinated in early childhood. Hum Vaccin Immunother. 2015;11:1717-1724.
10. Floreani A, Baldo V, Cristofoletti M, Renzulli G, Valeri A, Zanetti C, Trivello R. Long-term persistence of anti-HBs after vaccination against HBV: an 18 year experience in health care workers. Vaccine. 2004;22:607-610.
11. Dini G, Toletone A, Barberis I, Debarbieri N, Massa E, Paganino C, Bersi F, Montecucco A, Alicino C, Durando P. Persistence of protective anti-HBs antibody levels and anamnestic response to HBV booster vaccination: A cross-sectional study among healthcare students 20 years following the universal immunization campaign in Italy. Hum Vaccin Immunother. 2017;13:440-444.
12. Bagheri-Jamebozorgi M, Keshavarz J, Nemati M, Mohammadi-Hossainabad S, Rezayati MT, Nejad-Ghaderi M, Jamalizadeh A, Shokri F, Jafarzadeh A. The persistence of anti-HBs antibody and anamnestic response 20 years after primary vaccination with recombinant hepatitis B vaccine at infancy. Hum Vaccin Immunother. 2014;10:3731-3736.
13. Lin YJ, Lan YC, Wan L, Lin TH, Chen DY, Tsai CH, Liu CS, Hsueh KC, Tsai FJ. Serological surveillance and IL-10 genetic variants on anti-HBs titers: hepatitis B vaccination 20 years after neonatal immunization in Taiwan. Clin Chim Acta. 2011;412:766-773.
14. Lu J, Yan B, Liu J, Wu W, Feng Y, Xu A, Zhang L. Comparison of anti-HBs persistence after hepatitis B vaccination on two-dose schedule and three-dose schedule among adults: results from a 12-year follow up study in China. Hum Vaccin Immunother. 2019;15:1171-1176.
15. Fonzo M, Bertoncello C, Trevisan A. Factors influencing long-term persistence of anti-HBs after hepatitis B vaccination. NPJ Vaccines. 2022;7:173.
16. Kazemeini S, Owlia F. Determination of HBS Antibody Titre in Vaccinated Health Care Workers of Shahid Sadoughi Burn Hospital in Yazd in 2011. Tolooe Behdasht. 2013;12:155-163.
17. Stramer SL, Wend U, Candotti D, Foster GA, Hollinger FB, Dodd RY, Allain JP, Gerlich W. Nucleic acid testing to detect HBV infection in blood donors. N Engl J Med. 2011;364:236-247.
18. Mastrodomenico M, Muselli M, Provvidenti L, Scatigna M, Bianchi S, Fabiani L. Long-term immune protection against HBV: associated factors and determinants. Hum Vaccin Immunother. 2021;17:2268-2272.
19. Talebi Taher M, Akbari M, Rezaee M, Ashaerii N, Omrani Z, Ghaderian H, Mohammadzadeh M. Determination of Anti-Hbs Titre Mean Induced By Hepatitis B Vaccine Among Health Care Workers in Firoozgar Hospital in Tehran. RJMS. 2004;11:789-795.
20. Whittle H, Jaffar S, Wansbrough M, Mendy M, Dumpis U, Collinson A, Hall A. Observational study of vaccine efficacy 14 years after trial of hepatitis B vaccination in Gambian children. BMJ. 2002;325:569.
21. Ayatollahi J, Sharifi R, Sabzi F, Zare A. Blood level Anti-HBs due to HB vaccine in health care personnel of Shahid Sadoughi Hospital-Yazd. Iran J Obstet Gynecol Infertility. 2004;7:48-51.

Research Article

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Relationships Between Liver Histopathology with Biochemical Parameters, and Hepatitis B Virus-DNA in Chronic Hepatitis B Infection

Kronik Hepatit B Enfeksiyonunda Karaciğer Histopatolojisi ile Biyokimyasal Parametreler ve Hepatit B Virüs DNA Arasındaki İlişkinin Araştırılması

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ABSTRACT

Objectives: We investigated the relationship between serum hepatitis B virus (HBV)-DNA levels and biochemical parameters and liver histopathology in patients with chronic hepatitis B (CHB).

Materials and Methods: In this single-center retrospective study, treatment-naive hepatitis B e antigen (HBeAg) negative CHB patients between 2015 and 2022 years were included.

Results: A total of 316 patients were included. There were significant correlations between the histological activity index (HAI) score and HBV-DNA (r=0.522, p<0.001), alanine aminotransferase (ALT) (r=0.349, p<0.001), aspartate aminotransferase (r=0.414, p<0.001), and fibrosis score (r=0.111, p=0.049). The fibrosis score did not have a significant correlation other than the HAI. Patients with normal ALT levels had higher minimal inflammation (19.6% vs. 4.7%, p<0.001) and mild fibrosis (88.7% vs. 80.4%, p=0.042) than patients with elevated ALT levels. High HBV-DNA (>2,000,000 IU/mL) (60.8% vs. 36.7%, p=0.003) and moderate inflammation (27.6% vs. 13.9%, p=0.042) were higher in patients with ALT >2x upper limit of normal (ULN) than in patients with ALT 1-2xULN. For predicting HAI ≥6, the area under the receiver operating characteristics (AUROC) values of HBV-DNA (cut-off: 33,427) and ALT (cut-off: 40.5) were 0.726 and 0.664, respectively. For predicting ≥F2 the AUROC values of HBV-DNA (cut-off: 721,062) and ALT (cut-off: 44.5) were 0.624 and 0.597, respectively.

Conclusion: This study revealed positive correlations between laboratory parameters and HAI score, but not with fibrosis score. In

ÖZ

Amaç: Çalışmamızda, kronik hepatit B (KHB) hastalarında serum hepatit B virüs (HBV)-DNA düzeyleri ve biyokimyasal parametreler ile karaciğer histopatolojisi arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Tek merkezli, retrospektif olarak yürütülen çalışmamıza, 2015-2022 yılları arasında tedavi naif hepatit B e antijeni (HBeAg) negatif KHB hastaları dahil edildi.

Bulgular: Toplam 316 hasta çalışmaya alındı. Histolojik aktivite indeksi (HAİ) skoru ile HBV-DNA (r=0,522, p<0,001), alanin aminotransferaz (ALT) (r=0,349, p<0,001), aspartat aminotransferaz (r=0,414, p<0,001) ve fibroz skoru (r=0,111, p=0,049) arasında anlamlı korelasyon mevcuttu. Fibroz skorunun ise HAİ dışında korelasyon gösterdiği bir parametre yoktu. ALT seviyeleri normal aralıkta olan hastalarda minimal enflamasyon (%19,6'ya karşı %4,7, p<0,001) ve hafif fibroz (%88,7'ye karşı %80,4, p=0,042), ALT seviyeleri yüksek olan hastalara göre daha fazla saptandı. ALT seviyeleri >2x normal üst sınır (NÜS) olan hastalarda ise yüksek viral yük (>2,000,000 IU/mL) (%60,8'e karşı %36,7, p=0,003) ve orta derecede enflamasyon (%27,6'ya karşı %13,9, p=0,042), ALT değeri 1-2xNÜS aralığında olan hastalara göre daha fazla saptandı. HAİ ≥6'yı öngörmede HBV-DNA (sınır değer: 33,427) ve ALT (cut-off: 40,5) için alıcı çalışma özelliklerinin altındaki alan (AUROC) analiz değerleri sırasıyla 0,726 ve 0,664 idi. ≥F2'yi öngörmek için HBV-DNA (sınır değer: 721,062) ve ALT'nin (sınır değer: 44,5) AUROC değerleri ise sırasıyla 0,624 ve 0,597 idi.

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addition, HBV-DNA and ALT showed poor diagnostic performance in predicting ≥F2. Therefore, while viral load and ALT are useful predictors of hepatic inflammation, the role of these markers in predicting fibrosis remains unclear.
Keywords: ALT, chronic hepatitis B, fibrosis score, HAI score, HBV-DNA

Sonuç: Çalışmamız, laboratuvar parametreleri ile HAİ skoru arasında pozitif korelasyon olduğunu, ancak fibrozis skoru ile olmadığını ortaya koymaktadır. Ek olarak, HBV-DNA ve ALT, ≥F2'yi öngörmede zayıf tanısal performans göstermiştir. Sonuç olarak; viral yük ve ALT, hepatik enflamasyonun belirteçleri olarak yararlı olabilir, fakat bu belirteçlerin fibrozu öngörmedeki rolü belirsizdir.
Anahtar Kelimeler: ALT, fibroz skoru, HAİ skoru, HBV-DNA, KHB

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Introduction

Hepatitis B virus (HBV) infection remains a serious public health problem as an important cause of cirrhosis and hepatocellular cancer, despite reduction in treatment management and vaccination policies (1). Worldwide, approximately 300 million people live with chronic HBV infection, and approximately one million deaths occur annually due to complications of this disease (2). Countries are divided into 3 classes according to the prevalence of hepatitis B surface antigen (HBsAg) as low (<2%), intermediate (2-7%), and high endemic (≥8%) (3). Turkey is in the intermediate endemic group with an HBsAg prevalence of 4.57%, comprising approximately 3.3 million people living with HBV (4).

Chronic HBV infection can be classified into five different clinical forms by evaluating serological markers, liver function tests, HBV-DNA levels, and liver biopsy results. The need for antiviral treatment in these patients was determined on the basis of alanine aminotransferase (ALT) and serum HBV-DNA levels. In patients whose treatment criteria are not fully met, it is recommended to evaluate inflammation and fibrosis scores by performing liver biopsy (5,6,7). In Turkey, health insurance covers antiviral treatment for patients with cirrhosis findings or any contraindications for liver biopsy, such as coagulopathy. Otherwise, to access HBV treatment covered by health insurance, histopathological examination with liver biopsy is mandatory for all patients who need to be treated with antivirals. Therefore, centers that follow patients living with HBV in Turkey have many liver histopathology results in chronic hepatitis B (CHB).

As the viral load increases, deterioration in hepatic histology is usually expected. However, there is no threshold for HBV-DNA levels to determine histological deterioration (8). In studies focused on this subject, heterogeneous populations (HBeAg positive and negative) were generally included. (8,9). In this study, we aimed to investigate the relationship between serum HBV-DNA levels and biochemical parameters and liver histopathology in treatment-naive hepatitis B e antigen (HBeAg) negative CHB patients.

Materials and Methods

In this retrospective study, patients aged 18 years who underwent liver biopsy with treatment-naive HBeAg-negative chronic HBV infection between 2015 and 2022 years were included. Patients co-infected with hepatitis C, delta virus, or human immunodeficiency virus and those non-compliant with treatment were excluded from the study. Demographic characteristics (age, gender), serological (HBsAg, HBeAg), and biochemical parameters including HBV-DNA, ALT, aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyl transferase, creatinine, albumin, platelet count, and liver biopsy results were retrospectively retrieved from patients' medical charts and electronic medical records.

The definition of "HBeAg-negative CHB" was provided by the European Association for the Study of the Liver (EASL) 2017 (5). Histopathological evaluation of liver biopsies was performed according to Ishak's scoring system for fibrosis and Knodell's histological activity index (HAI) for necroinflammation (10). The HAI score was classified as minimal inflammation (HAI: 1-3), mild inflammation (HAI: 4-8), moderate inflammation (HAI: 9-12), and severe inflammation (HAI: 13-18). The fibrosis score was classified as mild fibrosis (F0-F2) and moderate/severe fibrosis (F3-F6).

Patients were divided into three groups according to ALT levels [<upper limit of normal (ULN), 1-2xULN, >2xULN] and six groups according to HBV-DNA levels (IU/mL) (<$2x10^4$, $2x10^4$-$2x10^5$, $2x10^5$-$2x10^6$, $2x10^6$-$2x10^7$, $2x10^7$-$2x10^8$, >$2x10^8$). The primary outcome was detecting the correlations between the HAI score, fibrosis score, HBV-DNA, and ALT levels. Secondary outcomes were HAI ≥6 and fibrosis ≥2 in determining the diagnostic performance of ALT and HBV-DNA.

Statistical Analysis

Categorical variables are expressed as numbers and percentages. Continous variables are expressed as median (minimum-maximum) and mean ± standard deviation. To compare categorical variables, the chi-square test was performed. While the Student's t-test was used to compare normally distributed continuous variables, the Mann-Whitney U test was used to compare non-normally distributed continuous variables. Spearman correlation analysis was performed to explore possible relationships between HBV-DNA, ALT, and AST levels and HAI and fibrosis. Reciever operating characteristic (ROC) curve analyzes were performed for predicting HAI ≥6 and fibrosis ≥2. Results with a p-value <0.05 were accepted as statistically significant. Statistical analyzes were performed using the IBM SPSS-21 package program.

Ethical Approval

This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital

Clinical Research Ethics Committee (approval number: 2023-03-03, date: 06.02.2023). Written informed consent was waived because this study was conducted retrospectively.

Results

A total of 316 patients were included. Of these patients, 61% (n=193) were male, and the mean age was 47.3±11.3 years. In the liver biopsies of the patients, 12.7% (n=40) had minimal inflammation, 72.5% (n=229) had mild inflammation, 13.9% (n=44) had moderate inflammation, and 0.9% (n=3) had severe inflammation. In addition, 84.8% (n=268) had mild fibrosis and 15.2% (n=48) had moderate/severe fibrosis. The demographic characteristics, laboratory parameters, and liver biopsy results of the patients are presented in Table 1, 2.

Spearman's correlation analysis revealed significant correlations between HBV-DNA levels with ALT (r=0.449, p<0.001), AST (r=0.560, p<0.001) and HAI score (r=0.522, p<0.001), but not with fibrosis score (r=-0.011, p=0.849). There were significant correlations between HAI score with ALT (r=0.349, p<0.001), AST

Table 1. Demographic characteristics and laboratory parameters of patients with chronic hepatitis B

	Mean ± SD/n (%)	**Median (min.-max.)**
Age	47.3±11.3	47 (23-80)
Gender		
Male	193 (61.1)	
Female	123 (38.9)	
ALT (IU/L)	**77.4±161.3**	
<41 (ULN)	168 (53.2)	**38.5 (7-1,870)**
41-80 (1-2xULN)	79 (25.0)	
>80 (>2xULN)	69 (21.8)	
AST (IU/L)	50.6±93.3	29 (10-1190)
Albumin (g/dL)	4.35±0.59	4.40 (2.60-5.60)
ALP (U/L)	79.3±41.5	74 (7-449)
GGT (U/L)	34.0±38.3	23 (6-343)
Creatinine (mg/dL)	0.73±0.19	0.70 (0.30-2.70)
PLT (10^3/µL)	226±60	219.5 (71-455)
HBV-DNA (IU/mL)	**148,148,732±1,917,824,655**	**240,701 (2,045-33,915,235,786)**
2,000-20,000	80 (25.3)	
20,000-200,000	73 (23.1)	
200.000-2,000,000	72 (22.8)	
2,000,000-20,000,000	52 (16.5)	
20,000,000-200,000,000	28 (8.9)	
>200,000,000	11 (3.5)	
HAI score	6.2±2.1	6 (2-14)
Fibrosis score	2.0±0.8	2 (0-6)

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, HAI: Histologic activity index, PLT: Platelet count, SD: Standard deviation, ULN: Upper limit of normal, min.: Minimum, max.: Maximum

Table 2. Histopathological findings of patients with chronic hepatitis B

Fibrosis score	**Minimal inflammation (HAI 1-3) (n=40)**		**Mild inflammation (HAI 4-8) (n=229)**		**Moderate inflammation (HAI 9-12) (n=44)**		**Severe inflammation (HAI 13-18) (n=3)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
F0 (n=10)	0	0.0	9	3.9	1	2.3	0	0.0
F1 (n=43)	0	0.0	41	17.9	2	4.5	0	0.0
F2 (n=215)	38	95.0	154	67.2	22	50.0	1	33.3
F3 (n=40)	1	2.5	21	9.2	17	38.7	1	33.3
F4 (n=6)	1	2.5	2	0.9	2	4.5	1	33.3
F5 (n=0)	0	0.0	0	0	0	0.0	0	0.0
F6 (n=2)	0	0.0	2	0.9	0	0.0	0	0.0

HAI: Histological activity index, F: Fibrosis

(r=0.414, p<0.001) and fibrosis score (r=0.111, p=0.049). On the other hand, the fibrosis score did not have a significant correlation other than the HAI score (Figure 1).

Regarding viral load, 70.9% of patients with normal ALT levels and 22.9% of patients with elevated ALT levels had HBV-DNA <200,000 IU/mL (p<0.001). Patients with normal ALT levels had higher minimal inflammation (19.6% vs. 4.7%, p<0.001) and mild fibrosis (88.7% vs 80.4%, p=0.042) than patients with elevated ALT levels. Patients with elevated ALT levels were divided into two groups (1-2xULN vs. >2xULN). High HBV-DNA (>2,000,000 IU/mL) (60.8% vs. 36.7%, p=0.003) and moderate inflammation (27.6% vs. 13.9%, p=0.042) were higher in patients with ALT >2 ULN than in patients with ALT 1-2 ULN (Table 3). The distributions of HBV-DNA and ALT according to HAI grade and fibrosis stage are shown in Figure 2, 3.

According to the ROC curve, for predicting HAI≥ 6, the area under the ROC (AUROC) values of HBV-DNA (cut-off: 33,427 IU/mL) and ALT (cut-off: 40.5 IU/L) were 0.726 (sensitivity: 78.4%, specificity: 61.8%, p<0.001) and 0.664 (sensitivity: 53.7%, specificity: 70.8%, p<0.001), respectively (Figure 4A). For predicting ≥F2 the AUROC values of HBV-DNA (cut-off: 721,062 IU/mL) and ALT (cut-off: 44.5 IU/L) were 0.624 (sensitivity: 56.7%, specificity: 65.0%, p=0.004) and 0.597 (sensitivity: 56.6%, specificity: 61.2%, p=0.026), respectively (Figure 4B).

Discussion

In this study, we presented a detailed analysis of the liver biopsy results, biochemical features, and virological parameters of 316 patients with treatment-naïve HBeAg negative CHB. We demonstrated positive correlations between HBV-DNA, ALT,

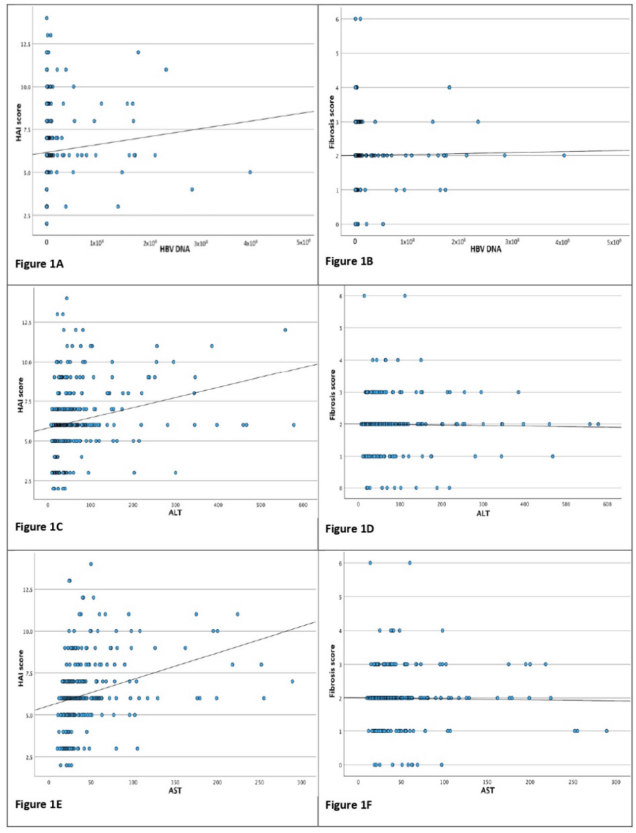

Figure 1. Correlations between HBV-DNA, ALT, and AST with HAI and fibrosis scores

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HAI: Histologic activity index,

Table 3. Comparison of virological and histopathological findings of patients according to ALT levels

	Normal ALT (n=168)		Elevated ALT (n=148)					
			1x2 ULN (n=79)		>2xULN (n=69)		p[1]	p[2]
	n	%	n	%	n	%		
HBV-DNA (IU/mL)								
2000-20,000	67	39.9	8	10.1	5	7.2	0.538	**<0.001**
20,000-200,000	52	31.0	10	12.7	11	15.9	0.568	**<0.001**
200,000-2,000,000	29	17.3	32	40.5	11	15.9	**0.001**	**0.013**
2,000,000-20,000,000	12	7.1	17	21.5	23	33.3	0.108	**<0.001**
20,000,000-200,000,000	6	3.6	8	10.1	14	20.3	0.082	**0.001**
>200,000,000	2	1.2	4	5.1	5	7.2	0.581	**0.033**
HAI score								
1-3	33	19.6	4	5.1	3	4.3	0.884	**<0.001**
4-8	119	70.9	63	79.7	47	68.1	0.108	0.484
9-12	14	8.3	11	13.9	19	27.6	**0.043**	**0.003**
13-18	2	1.2	1	1.3	0	0.0	0.551	0.642
≥6**	105	62.5	63	79.7	59	85.5	0.360	**<0.001**
Fibrosis score								
F0-2	149	88.7	65	82.3	54	78.3	0.539	**0.042**
F3-6	19	11.3	14	17.7	15	21.7		

ALT: Alanine aminotransferase, ULN: Upper limit of normal, HAI: Histological activity index. p[1]: Comparison of 1x2 ULN with >2 x ULN, p[2]: Comparison of normal ALT with elevated ALT

and AST with HAI score, but not with fibrosis score. However, patients with normal ALT levels had a lower fibrosis score (F0-2). In addition, HBV-DNA and ALT showed poor diagnostic performance in predicting ≥F2, while HBV-DNA had moderate diagnostic performance in predicting HAI ≥6.

International guidelines, including EASL, the Asian Pacific Association for the Study of the Liver (APASL), and the American Association for the Study of Liver Diseases (AASLD), have recommended that the decision to initiate antiviral treatment should be planned according to HBV-DNA and ALT levels (5,6,7). In all three guidelines, elevation of ALT levels more than 2 times the ULN are indicated as the initiation criterion for treatment. However, although 40 IU/L is accepted as the upper limit of ALT in the EASL and APASL guidelines (5,6), the limit value is 35 IU/L for men and 25 IU/L for women in the AASLD guidelines (7). In

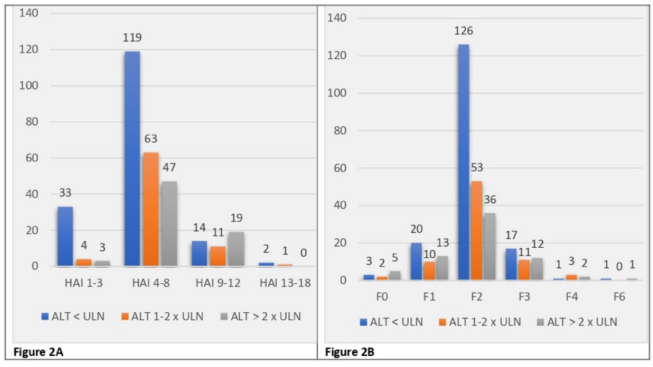

Figure 2. Comparison of ALT levels according to HAI grade and fibrosis stage

ALT: Alanine aminotransferase, HAI: Histologic activity index, ULN: Upper limit of normal

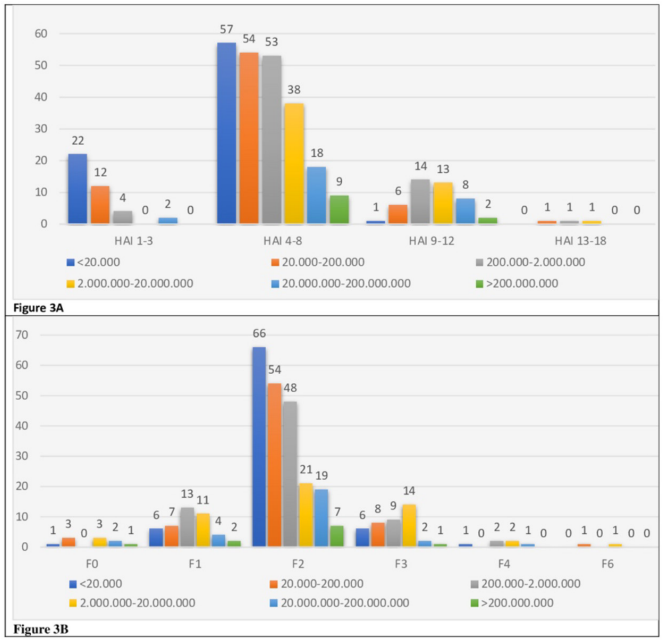

Figure 3. Comparison of HBV-DNA levels according to HAI grade and fibrosis stage

HBV: Hepatitis B virus, HAI: Histologic activity index

our study, approximately half of the patients receiving antiviral therapy had ALT levels in the normal range. In addition, moderate inflammation, which is accepted as the criterion for initiating antiviral treatment in international guidelines (5,6,7), was more common in patients with ALT >2xULN than in patients with ALT 1-2xULN. However, we found the ALT cut-off values to be 40.5 IU/L and 44.5 IU/L, respectively, in predicting HAI ≥6 and F ≥2, which are the indications for initiating antiviral treatment in our country. In the study by Alam et al. (11), 286 HBeAg-negative CHB patients were evaluated. Moderate to advanced inflammation (HAI ≥9) was 30.6% in the group with ALT 1-2xULN, whereas it was 51.0% in the group with ALT >2xULN (p=0.001). In the prediction of moderate inflammation, the sensitivity of ALT (cut-off 58.5 IU/L) value was 63% and the specificity was 65% (11). In the study by Seto et al. (12), ALT and fibrosis levels were compared. They reported that there was no significant difference between the group with ALT 1-2xULN and the group with ALT >2xULN in terms of significant fibrosis (≥F3) development. Similarly, in our study, there was no difference between the two groups (ALT 1-2xULN vs. ALT >2xULN) was detected in terms of significant fibrosis (≥F3) development.

In HBeAg-negative CHB patients, the HBV-DNA cut-off value, which is the treatment initiation criterion, is 20,000 IU/mL in the EASL guidelines (5), whereas it is 2,000 IU/mL in the APASL and AASLD guidelines (6,7). In our study, the HBV-DNA value of approximately a quarter of the patients who met the criteria (HAI ≥6 or ≥F2) for starting antiviral treatment with biopsy was between 2,000 IU/mL and 20,000 IU/mL. In addition, we found that the HBV-DNA cut-off values for predicting HAI ≥6 or ≥F2 were 33,427 IU/mL and 721,662 IU/mL, respectively. However, almost all patients (98.7%) with HBV-DNA between 2,000 and 20,000 IU/mL had minimal to mild inflammation (HAI ≤8). In the study of Yıldız Kaya et al. (13), although quantitative HBsAg levels were high (>1000 IU/mL) in patients with HBV-DNA values of 2,000-20,000 IU/mL, 78.9% of these patients had no fibrosis (<F2) and 57.9% had minimal inflammation (HAI <4). In another study, patients were divided into 2 groups according to their HBV-DNA values (<100,000 IU/mL vs. ≥100,000 IU/mL). Mild inflammation (81% vs. 19%, p<0.001) and mild fibrosis (81% vs. 21%, p<0.001) were found to be significantly lower in the group with HBV-DNA <100,000 IU/mL than in the group with HBV-DNA ≥100,000 IU/mL (14).

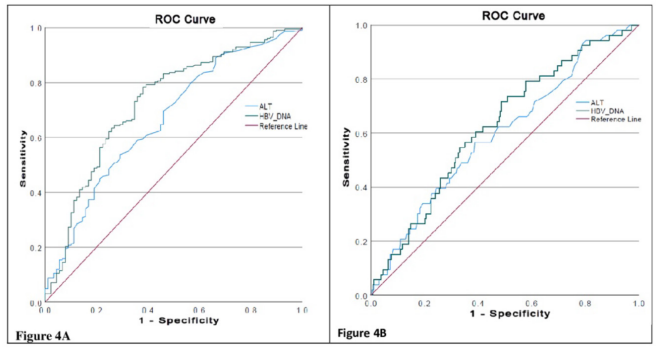

Figure 4. Receiver operating characteristic curves of the HBV-DNA and ALT in predicting ≥F2 and HAI ≥6

HBV: Hepatitis B virus, ALT: Alanine aminotransferase, HAI: Histologic activity index, ROC: Receiver operating characteristics

In our study, we showed that ALT, AST, HBV-DNA, and HAI scores were positively correlated with each other. No biochemical or virological parameters correlated with the fibrosis score. Shao et al. (9) reported that HBV-DNA levels were positively correlated with ALT (r=0.351, p=0.042), but not with AST, HAI score, and fibrosis score. In addition, no correlation was reported between ALT, AST with HAI and fibrosis scores (9). In the study of Diktas et al. (15), a positive correlation was found between HAI score and HBV-DNA (r=0.45, p<0.001), ALT (r=0.28, p=0.003) and AST (r=0.28, p=0.003), while only HBV-DNA was correlated with fibrosis score (r=0.21, p=0.024). In another study, a significant correlation was reported between AST, ALT, HBV-DNA, and HAI scores, similar to our study. However, the only parameter that correlated with the fibrosis score was AST levels (16).

Study Limitations

This study had several limitations. First, this was a single-center study enrolling patients admitted to an infectious diseases outpatient clinic and receiving antiviral therapy. Therefore, there may have been bias in the selection of inclusion. Second, the sampling error of liver biopsy, which is the gold standard reference method, was ignored. Third, instant virological and biochemical parameters were included. Therefore, ALT and HBV-DNA fluctuations in the natural history of HBeAg-negative CHB disease could not be detected and evaluated. However, our study had some strengths. First, we included only HBeAg -negative patients, and the number of patients was relatively high. Second, the diagnostic performance of virological and biochemical parameters was determined in the definition of histopathological findings, which is the indication for initiating antiviral treatment in our country.

Conclusion

In conclusion, although HBV-DNA and ALT are useful predictors of hepatic inflammation, the role of these markers in predicting fibrosis remains unclear. However, although the optimal ALT and HBV-DNA levels that predict hepatic damage remain uncertain, we emphasize that patients with both ALT levels in the normal range and HBV-DNA values <20,000 should be closely followed up for the need for antiviral treatment, considering our results.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2023-03-03, date: 06.02.2023).

Informed Consent: Written informed consent was waived because this study was conducted retrospectively.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.C.Ü., A.İ.S., Design: K.K.Y., Data Collection and Processing: E.S.D., A.S.D., Analysis or Interpretation: Y.E.Ö., O.F.B., Literature Search: D.B., Writing: Y.E.Ö., D.B.

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

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References

1. Yenilmez E, Cetinkaya RA. Are there optimal alanine aminotransferase and HBV DNA thresholds for discriminating HBeAg-positive chronic infection from chronic hepatitis? An evaluation of 215 young and male cases. Saudi Med J. 2019;40:131-139.
2. World Health Organization Fact Sheets/Hepatitis B. [Date of Access. 01.08.2023]. https://www.who.int/news-room/factsheets/detail/hepatitis-b
3. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-283.
4. Özkan H. Epidemiology of Chronic Hepatitis B in Turkey. Euroasian J Hepatogastroenterol 2018;8:73-74.
5. European Association for the Study of the Liver; EASL 2017 Clinical Practice Guidelines on the Management of hepatitis B virus Infection. J Hepatol. 2017;67:370-398.
6. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1-98.
7. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261-283.
8. Akdağ D, Yamazhan T, Pullukçu H, Işıkgöz Taşbakan M, Durusoy R. Relationship between Viral Load and Hepatic Histopathology in Patients with Chronic Hepatitis B. Viral Hepatitis Journal. 2020;26:1-4.
9. Shao J, Wei L, Wang H, Sun Y, Zhang LF, Li J, Dong JQ. Relationship between hepatitis B virus DNA levels and liver histology in patients with chronic hepatitis B. World J Gastroenterol. 2007;13:2104-2107.
10. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22:696-699.
11. Alam S, Ahmad N, Mustafa G, Shrestha A, Alam AK, Khan M. Evaluation of normal or minimally elevated alanine transaminase, age and DNA level in predicting liver histological changes in chronic hepatitis B. Liver Int. 2011;31:824-830.
12. Seto WK, Lai CL, Ip PP, Fung J, Wong DK, Yuen JC, Hung IF, Yuen MF. A large population histology study showing the lack of association between ALT elevation and significant fibrosis in chronic hepatitis B. PLoS One. 2012;7:e32622.
13. Yıldız Kaya S, Mete B, Kaya A, Balkan II, Saltoglu N, Tabak ÖF. The role of quantitative HBsAg in patients with HBV DNA between 2000-20,000 IU/ml. Wien Klin Wochenschr. 2021;133:647-653.
14. Bai H, Liu H, Chen X, Xu C, Dou X. Influence of age and HBeAg status on the correlation between HBV DNA and hepatic inflammation and fibrosis in chronic hepatitis B patients. Dig Dis Sci. 2013;58:1355-1362.
15. Diktas H, Karacaer Z, Özturk II, Cicek H. Comparison of relationship between histopathological, serological and biochemical parameters in patients with chronic hepatitis B infection. Postgrad Med J. 2016;92:693-696.
16. Esmaeelzadeh A, Saadatnia H, Memar B, Mokhtari Amirmajdi E, Ganji A, Goshayeshi L, Meshkat Z, Pasdar A, Vosoughinia H, Farzanehfar M, Tehranian S, Ghaffarzadehgan K, Rajabzadeh F, Ahadi M. Evaluation of serum HBV viral load, transaminases and histological features in chronic HBeAg-negative hepatitis B patients. Gastroenterol Hepatol Bed Bench. 2017;10:39-43.

Research Article

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Post-Treatment Course of Indices Predicting Liver Fibrosis in Adult Chronic Hepatitis C Patients Treated with Direct-Acting Antivirals

Doğrudan Etkili Antivirallerle Tedavi Edilen Yetişkin Kronik Hepatit C Hastalarında Karaciğer Fibrozunu Öngören Endekslerin Tedavi Sonrası Seyri

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ABSTRACT

Objectives: Hepatitis C virus (HCV) infection is a chronic infection that can lead to liver failure, cirrhosis, and hepatocellular carcinoma over time. In recent years, direct-acting antivirals (DAAs) have mostly eliminated the virus. Studies on their effect on the improvement of liver fibrosis are ongoing. Indices such as the aspartate transaminase platelet ratio index (APRI), fibrosis-4 index (FIB-4), aspartate transaminase to alanine transaminase ratio (AAR), fibrosis index, and gamma glutamyl transferase to platelet ratio (GPR) are suggested to predict liver fibrosis. The aim of this study was to evaluate the course of these indices before and after DAA treatment.

Materials and Methods: The data of patients aged 18 years and older who were treated with DAAs for HCV infection in certain outpatient clinics of infectious diseases and clinical microbiology of a reference center between February 19, 2019 and May 31, 2023 were collected from the electronic record system. Demographic information, comorbidities, information about HCV infection, hemogram, and biochemical tests required for calculating the indices were obtained.

Results: The study included 131 patients. The median age of the patients was 31 [interquartile range (IQR): 27] years. At the end of the treatment, the patients were followed up for a median of 183 days for hemogram (n=81) and 185 days for biochemical tests (n=82). Among the indices, APRI (p<0.001), FIB-4 (p<0.001), fibrosis index (p=0.004) and GPR (p<0.001) increased significantly after DAA compared with before, while AAR decreased.

Conclusion: In this study, it was determined that fibrosis predictive indices indicated a significant regression after treatment.

Keywords: APRI, FIB-4, direct-acting antivirals, fibrosis index, hepatitis C

ÖZ

Amaç: Hepatit C virüsü (HCV) enfeksiyonu, zamanla karaciğer yetmezliğine, siroza ve hepatoselüler karsinoma yol açabilen kronik bir enfeksiyondur. Son yıllarda doğrudan etkili antiviraller (DAA'lar) virüsü büyük ölçüde ortadan kaldırdı. Karaciğer fibrozisinin iyileştirilmesine etkileri üzerine çalışmalar devam etmektedir. Aspartat transaminaz trombosit oranı indeksi (APRI), fibrozis-4 indeksi (FIB-4), aspartat transaminaz/alanin transaminaz oranı (AAR), fibrozis indeksi ve gama glutamil transferaz/trombosit oranı (GPR) gibi indekslerin karaciğer fibrozisini öngördüğü ileri sürülmektedir. Bu çalışmanın amacı bu indekslerin DAA tedavisi öncesi ve sonrası seyrini değerlendirmektir.

Gereç ve Yöntemler: 19 Şubat 2019 ile 31 Mayıs 2023 tarihleri arasında bir referans merkezinin bazı enfeksiyon hastalıkları ve klinik mikrobiyoloji polikliniklerinde HCV enfeksiyonu nedeniyle DAA tedavisi gören 18 yaş ve üzeri hastaların verileri elektronik kayıt sisteminden toplandı. İndekslerin hesaplanması için gerekli olan demografik bilgiler, komorbiditeler, HCV enfeksiyonuna ilişkin bilgiler, hemogram ve biyokimyasal testler elde edildi.

Bulgular: Çalışmaya 131 hasta dahil edildi. Hastaların ortanca yaşı 31 [çeyrekler arası aralık (IQR): 27] yıldı. Tedavi sonunda hastalar ortalama 183 gün hemogram (n=81) ve 185 gün biyokimyasal tetkikler (n=82) için takip edildi. İndekslerden APRI (p<0,001), FIB-4 (p<0,001), fibrozis indeksi (p=0,004) ve GPR (p<0,001) DAA sonrası öncesine göre anlamlı derecede artarken, AAR azaldı.

Sonuç: Bu çalışmada fibrozis prediktif indekslerinin tedavi sonrasında anlamlı gerileme gösterdiği belirlendi.

Anahtar Kelimeler: APRI, FIB-4, doğrudan etkili antiviraller, fibrozis indeksi, hepatit C

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Introduction

Hepatitis C virus (HCV) is a hepatotropic virus that can lead to chronic infection, liver failure, cirrhosis, and hepatocellular carcinoma over time. Although therapeutic interventions were initiated before 1989 when the virus was identified, interferon, regulated interferon, and ribavirin were prescribed after the virus was identified. Because of long treatment durations and high probability of failure in sustained viral suppression, hepatitis C-directed therapies have been targeted. After the approval of the first direct-acting antivirals (DAAs) in 2011, many antivirals rapidly entered the market (1). In Türkiye, telaprevir and boceprevir were first introduced; however, they are not used in practice due to side effects and difficulty of use. In time, ombitasvir-paritapravir-ritonavir-dasabuvir (3D regimen) with/without ribavirin, sofosbuvir-ledipasvir, glecaprevir-pibrentasvir, sofosbuvir-velpatasvir, and voxilaprevir became available. DAAs are highly successful in achieving viral elimination and providing a sustained viral response (SVR) (2). However, studies on their effect on the improvement of liver fibrosis are ongoing.

Although liver biopsy is the gold standard in the evaluation of liver fibrosis, it is rarely performed today because it is an interventional procedure (3). There are indices such as the aspartate aminotransferase (AST) to platelet ratio index (APRI) (4), fibrosis-4 index (FIB-4) (5), aspartate aminotransferase to alanine aminotransferase (ALT) ratio (AAR)[6], fibrosis index (7), and gamma-glutamyl-transpeptidase (GGT) to platelet ratio (GPR) (8) recommended in the literature for the prediction of liver fibrosis.

This study aimed to evaluate the course of fibrosis predictive indices before and after treatment in adult patients treated with DAAs for chronic hepatitis C infection.

Materials and Methods

This cross-sectional study was conducted in the Department of Infectious Diseases and Clinical Microbiology at Ankara Bilkent City Hospital. The hospital where the study was conducted is a reference hospital with approximately 3,800 beds. This hospital was put into service in February 2019. The hospitals that make up this hospital have many years of experience in treating patients with viral hepatitis. However, to obtain more complete data, recruitment was conducted between February 19, 2019 and May 31, 2023.

Patients aged 18 years who were initiated on DAA therapy for chronic hepatitis C by certain outpatient clinics of the infectious diseases and clinical microbiology were included in the study. Patients were not excluded from any reason.

Data were obtained only through the hospital's electronic record system. No data were imputed for missing data. In the standardized data collection form prepared electronically for the study, demographic information, comorbid conditions, possible hepatitis C acquisition routes, HCV genotype, treatment experience, treatment regimen and dates, pre-treatment and post-treatment hemogram, biochemical tests, international normalized ratio and HCV-RNA results and dates, and liver biopsy findings, if any, were recorded. The patients' age at the time of treatment initiation was taken as the basis.

Within the scope of the study, the five indices predicting liver fibrosis for the pre- and post-treatment periods were calculated using the following formulas.

APRI (4) = AST(IU/L)/upper limit of normal (35 IU/L) (IU/L) x 100/platelet (109/L),

FIB-4 (5) = Age (years) x AST (IU/L)/platelet (10^9/L) √ ALT (IU/L),

AAR (6) = AST (IU/L)/ALT (IU/L),

Fibrozis index (7) = 8 - 0.01 x platelet (10^9/L) - serum albumin (g/dL),

GPR (8) = GGT (IU/l)/platelet (10^9/L).

SVR12 was accepted to be an undetectable HCV-RNA at 12 weeks post-treatment and SVR24 at 24 weeks post-treatment.

Ethical Considerations

The protocol of the study was ethically approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee on June 21, 2023 (approval number: E1-23-3715). The study was conducted according to the ethical principles of the Declaration of Helsinki. Identity information of the individuals was not collected. Because the data were collected retrospectively, informed consent was not obtained from the patients. The findings of the study will be presented as an oral presentation at the 16th National Viral Hepatitis Congress to be held in Antalya on October 12-15, 2023.

Statistical Analysis

Qualitative variables are presented as numbers and percentages, and quantitative variables are presented as medians [interquartile range = (IQR)]. The fit of quantitative variables to normal distribution was evaluated by normality tests (Shapiro-Wilk and Kolmogorov Smirnov) and visually (histogram, defended Q-Q plots). Because of non-normal distribution, pre- and post-treatment comparisons were made using the Wilcoxon signed-rank test. The correlation of the indices with each other was evaluated by Spearman's correlation for both pre- and post-treatment periods. Statistical significance was set as $p<0.05$ (two-sided). Analyses were performed using Statistical Packages for the Social Sciences (IBM Corp., Armonk, New York, U.S.A) version 23 software.

Results

The median age of the 131 patients included in the study was 31 [minimum (min)-maximum (max): 19-83, IQR=27] years. Of the patients 30.5% were female and 82.4% were treatment-naive. All patients were non-sirotic. All 45 patients who were followed up for 12 weeks or longer and 33 patients who were followed up for 24

weeks or longer were negative for HCV-RNA after treatment. The characteristics of the study group are presented in Table 1.

Table 1. Features of chronic hepatitis C patients treated with direct-acting antivirals

	n	%
Male gender	91	69.5
Co-morbidity*		
Substance abuse	52	39.7
Hypertension	18	13.7
Diabetes mellitus	11	8.4
Malignancy	10	7.6
Hepatitis B co-infection	5	3.8
Congestive heart failure	5	3.8
Coronary heart disease	4	3.1
Chronic renal disease	3	2.3
Chronic obstructive pulmonary disease	3	2.3
Human immunodeficiency virus co-infection	2	1.5
Asthma	2	1.5
Hypothyroidism	2	1.5
Hemophilia	2	1.5
Allergic rhinitis	2	1.5
Gastritis	2	1.5
Transmission route of hepatitis C		
Unknown	73	55.7
Intravenous drug use	56	42.7
Hemodialysis	1	0.8
Dental intervention	1	0.8
Genotype of the hepatitis C virus**		
1a	16	12.2
1b	52	39.7
2	15	11.5
3	29	22.1
4	12	9.2
Hepatitis C treatment		
3D regimen	13	9.9
3D regimen + ribavirin	6	4.6
Glecaprevir + pibrentasvir	80	61.1
Sofosbuvir + velpatasvir + voxilaprevir	32	24.4
Experience with hepatitis C treatment		
Treatment-naive	108	87.8
Treatment-experienced***	15	12.2

*There was one patient each with scoliosis, vasculitis, venous insufficiency, seizures, syphilis, and bone tuberculosis. A patient can have more than one disease. **Patients are infected with more than one genotype. ***Two patients had experience with interferon, five patients with pegylated interferon-ribavirin, three patients with 3D regimen, one patient each with sofosbuvir-ledipasvir, glecaprevir-pibrentasvir, and sofosbuvir-velpatasvir- voxilaprevir. The treatment regimens of the two treatment-experienced patients were unknown. Eight patients had missing data

Among the laboratory parameters used in the calculation of the indices, leucocytes, neutrophils, hemoglobin, and thrombocytes increased statistically significantly, whereas ALT, AST, and GGT decreased (Table 2).

Patients were followed up for a median of 183 (min-max: 1-1,396, IQR: 308) days for the hemogram (n=81) and 185 (min-max: 1-1,396, IQR: 329) days for the biochemical tests (n=82) after the end of treatment. The distribution of the indices and HCV-RNA values before and after DAAs is given in Table 3.

Among the indices examined in the pre- and post-treatment periods, AAR had a negative and statistically significant correlation only with FIB-4 in both periods and with GPR in the post-treatment period. There was a moderate positive correlation between the other indices (Table 4).

In the SVR12 confirmed subgroup, there was a statistically significant decrease in all indices except AAR and an increase in AAR before and after DAAs (Table 5).

Discussion

Hepatitis C infections, which are known to cause chronic liver disease, liver fibrosis, cirrhosis, and HCC in their natural course, are now successfully treated virologically (1). In hepatitis B infection, which was successfully suppressed by treatment earlier than hepatitis C, regression of fibrosis, which is believed to be irreversible over time, has been promising. As the number of patients treated with DAAs and the duration of follow-up increases, regression of liver fibrosis will be observed similar to that in hepatitis B (1). Currently, histopathologic examination of the liver, which is the gold standard for the evaluation of liver fibrosis, is not frequently preferred because it requires an interventional procedure. Indices calculated on the imaging and laboratory basis can be used in the evaluation of liver fibrosis (3). According to the results of this study, there was a significant regression in APRI, FIB-4, fibrosis index, and GPR values, indicating regression of liver fibrosis after treatment compared with pretreatment and an increase in AAR.

All patients who could be followed up for SVR were negative. In patients who reached SVR12, there was a significant regression in indices other than AAR, as in the whole group, and a significant increase in AAR. The fact that the results were similar to the overall group in the subgroup where the SVR status was known with certainty suggests that a high viral success was also achieved in the subgroup where the SVR status was not known with certainty.

In a study conducted by Bachofner et al. (9) in three centers and followed 549 patients between November 2013 and December 2015, a significant decrease in APRI and FIB-4 indices was reported in the post-treatment period. In a cohort study of 143 chronic hepatitis C patients receiving DAAs in Hannover, Germany, between 2014 and 2017, a rapid decrease in APRI and FIB-4 indices was observed in the first 24 weeks. It was reported to be more stable after the first 24 weeks, and there was no statistically significant difference. In the transient elastographic examination, a slower but significant decline was recorded between weeks 24 and 96. The group in this study had different characteristics from the group in the present study, as 48% of the participants were cirrhotic and the mean age was 58 years. In particular, the median

Table 2. Distribution of laboratory findings before and after the treatment

	Pretreatment		Posttreatment		
	n	**Median (IQR)**	**n**	**Median (IQR)**	**p-value**
Leucocyte (/µL)	119	7050 (2580)	107	7520 (3390)	**0.015**
Neutrophil (/µL)	119	3970 (2170)	107	4160 (2540)	**0.006**
Lymphocyte (/µL)	119	2150 (840)	107	2220 (1100)	0.22
Hemoglobin (g/dL)	119	14.6 (2.1)	107	14.8 (2.5)	**0.043**
Thrombocyte (x1000/µL)	119	233 (83)	107	235 (81)	**0.047**
Alanine aminotransferase (IU/L)	119	50.0 (72.0)	109	19.0 (11.0)	**<0.001**
Aspartate aminotransferase (IU/L)	118	37.5 (29.0)	109	17.0 (11.0)	**<0.001**
Alkaline phosphatase (IU/L)	98	82.5 (29.0)	90	78.0 (40.0)	0.39
Gamma-glutamyl-transpeptidase (IU/L)	95	30.0 (30.0)	84	19.0 (12.0)	**<0.001**
Total bilirubin (mg/dL)	101	0.60 (0.55)	89	0.60 (0.30)	0.67
Direct bilirubin (mg/dL)	102	0.20 (0.20)	88	0.20 (0.20)	0.44
Albumin (g/L)	104	46 (4)	83	46 (5)	**0.001**
INR	81	1.0 (0.1)	61	1.0 (0.1)	0.33

IQR: Interquartile range, INR: International normalized ratio

Table 3. Distribution of indices for predicting liver fibrosis before and after treatment

	Pre-treatment		**Post-treatment**		
	(n)	**Median (IQR)**	**(n)**	**Median (IQR)**	**p-value**
APRI	117	0.46 (0.55)	107	0.22 (0.17)	<0.001
FIB-4	116	0.78 (0.83)	107	0.67 (0.56)	<0.001
AAR	117	0.68 (0.40)	109	0.93 (0.58)	<0.001
Fibrosis index	103	1.06 (0.98)	82	1.02 (0.86)	0.004
GPR	94	0.15 (0.14)	83	0.08 (0.06)	<0.001
	Pre-treatment		**Post-treatment ≥ 12 weeks**		
	(n)	**Median (IQR)**	**(n)**	**Median (IQR)**	**p-value**
HCV-RNA	45	721443 (2446578)	45	0 (0)	<0.001
	Pre-treatment		**Post-treatment ≥ 24 weeks**		
	(n)	**Median (IQR)**	**(n)**	**Median (IQR)**	**p-value**
HCV-RNA	33	626519 (3400742)	33	0 (0)	<0.001

IQR: Interquartile range, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 index, AAR: Aspartate aminotransferase to alanine aminotransferase ratio, GPR: Gamma-glutamyl-transpeptidase to platelet ratio, HCV: Hepatitis C virus, RNA: Ribonucleic acid

Table 4. Correlations between the indices predicting liver fibrosis

Pretreatment	**APRI**	**FIB-4**	**AAR**	**Fibrosis index**	**GPR**
APRI	1.000	0.593*	-0.158	0.404*	0.509*
FIB-4		1.000	0.437*	0.526*	0.306*
AAR			1.000	0.066	-0.065
Fibrosis index				1.000	0.236*
GPR					1.000
Posttreatment	**APRI**	**FIB-4**	**AAR**	**Fibrosis index**	**GPR**
APRI	1.000	0.533*	0.179	0.382*	0.591*
FIB-4		1.000	0.541*	0.475*	0.254*
AAR			1.000	0.128	-0.285*
Fibrosis index				1.000	0.422*
GPR					1.000

*P<0.05 in Spearman's correlation, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 index, AAR: Aspartate aminotransferase to alanine aminotransferase ratio, GPR: Gamma-glutamyl-transpeptidase to platelet ratio

Table 5. Distribution of indices predicting liver fibrosis before and after treatment in patients with sustained viral suppression at week 12 (SVR12)

	Pre-treatment		Post-treatment		
	n	Median (IQR)	n	Median (IQR)	p-value
APRI	43	0.46 (0.34)	44	0.23 (0.15)	<0.001
FIB-4	43	0.87 (0.83)	44	0.75 (0.78)	<0.001
AAR	43	0.81 (0.38)	44	0.91 (0.61)	0.005
Fibrosis index	37	1.20 (0.86)	36	0.99 (0.76)	0.034
GPR	35	0.15 (0.14)	37	0.09 (0.06)	<0.001

IQR: Interquartile range, APRI: Aspartate aminotransferase to platelet ratio index, FIB-4: Fibrosis-4 index, AAR: Aspartate aminotransferase to alanine aminotransferase ratio, GPR: Gamma-glutamyl-transpeptidase to platelet ratio

of the first APRI (2.9) and FIB-4 (1.4) scores were higher compared with our younger group without cirrhotic patients (10).

In a prospective cohort study of 102 chronic hepatitis C patients in Beijing between 2017 and 2019, patients were evaluated at the end of DAA treatment and at 12, 24, and 48 weeks after completion. Significant regression was observed in the APRI and FIB-4 values at the end of treatment. Although there was a regression in subsequent follow-up periods, it was reported to be statistically insignificant. A more significant decrease was found in the metavir 3-4 subgroup (11). The more significant decrease in indices in the cohort in Hannover, which has a high proportion of elderly and cirrhotic patients, and in the subgroup with advanced fibrosis in the cohort in Beijing compared with our group is explained by the fact that the patients in our group were younger and had lower baseline index scores.

In a study involving 50 patients who received treatment between 2016 and 2017, which aimed to evaluate the efficacy of DAAs in chronic hepatitis C patients from Turkey, it was reported that there was a significant regression in APRI and FIB-4 scores until the 12th week compared with baseline, followed by a stable course to the 12th week at weeks 24 and 36 (12).

In a study conducted by Aydın and Köksal (2) in 95 patients who received DAA in a center and who were followed up for at least 12 weeks after treatment, it was found that the APRI and FIB-4 scores of the patients showed a significant decrease in the 4th week of treatment compared with pretreatment, and there was no difference at the end of treatment, i.e., the 12th week. Similar to our group, it was reported that AAR increased significantly at week 4 compared with pretreatment, and there was no significant difference afterwards (2).

APRI, FIB-4, GPR, and the fibrosis index were found to have significant, positive, and moderate correlations with each other before and after treatment. The fact that AAR does not significantly correlate with most of the other indices makes it more disadvantageous than other indices. However, its ease of calculation is an advantage.

Study Limitations

Because this study is a single-center study, the generalizability of the results is limited. In terms of the number of patients evaluated, it has a larger sample size than our country and many single-center studies. However, the retrospective collection of the data and the short follow-up period due to the young age of most patients and possibly reluctance and difficulty in accessing health care services are negatives. A limitation of this study is that the findings related to the indices studied cannot be correlated with liver histopathology as the gold standard.

Conclusion

In conclusion, it is recommended that APRI, FIB-4, GPR, and fibrosis indices, which are used in the prediction of liver fibrosis, should be calculated and followed up at the patient's admission and at the initiation of treatment.

Ethics

Ethics Committee Approval: The protocol of the study was ethically approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee on June 21, 2023 (approval number: E1-23-3715).

Informed Consent: Because the data were collected retrospectively, informed consent was not obtained from the patients.

Peer-review:

Authorship Contributions

Surgical and Medical Practices: İ.H., A.K.K., R.G., Concept: İ.H., A.K.K., R.G., Design: A.S., R.G., Data Collection and Processing: A.S., Analysis or Interpretation: A.S., İ.H., A.K.K., R.G., Literature Search: A.S., İ.H., A.K.K., R.G.,Writing: A.S., İ.H., A.K.K., R.G.

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References

1. Oancea CN, Butaru AE, Streba CT, Pirici D, Rogoveanu I, Diculescu MM, Gheonea DI. Global hepatitis C elimination: history, evolution, revolutionary changes and barriers to overcome. Rom J Morphol Embryol 2020;61:643-653.
2. Aydın NN, Köksal İ. An Evaluation of Chronic Hepatitis C Patients' Responses to Direct-Acting Antivirals According to Transient Elastography and Serum Biomarkers. Viral Hepatitis Journal 2022;28:18-24.

3. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. JHEP Rep 2020;2:100067.
4. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, Sánchez-Avila F, Vargas-Voráckova F. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. Ann Hepatol 2008;7:350-357.
5. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-1325.
6. Åberg F, Danford CJ, Thiele M, Talbäck M, Rasmussen DN, Jiang ZG, Hammar N, Nasr P, Ekstedt M, But A, Puukka P, Krag A, Sundvall J, Erlund I, Salomaa V, Stål P, Kechagias S, Hultcrantz R, Lai M, Afdhal N, Jula A, Männistö S, Lundqvist A, Perola M, Färkkilä M, Hagström H. A Dynamic Aspartate-to-Alanine Aminotransferase Ratio Provides Valid Predictions of Incident Severe Liver Disease. Hepatol Commun Jun 2021;5:1021-1035.
7. Bota S, Sirli R, Sporea I, Focsa M, Popescu A, Danila M, Strain M, Sendroiu M, Deleanu A, Dan I. A new scoring system for prediction of fibrosis in chronic hepatitis C. Hepat Mon 2011;11:548-555.
8. Li Q, Lu C, Li W, Huang Y, Chen L. The gamma-glutamyl transpeptidase to platelet ratio for non-invasive assessment of liver fibrosis in patients with chronic hepatitis B and non-alcoholic fatty liver disease. Oncotarget 2017;8:28641-28649.
9. Bachofner JA, Valli PV, Kröger A, Bergamin I, Künzler P, Baserga A, Braun D, Seifert B, Moncsek A, Fehr J, Semela D, Magenta L, Müllhaupt B, Terziroli Beretta-Piccoli B, Mertens JC. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017;37:369-376.
10. Pietsch V, Deterding K, Attia D, Ringe KI, Heidrich B, Cornberg M, Gebel M, Manns MP, Wedemeyer H, Potthoff A. Long-term changes in liver elasticity in hepatitis C virus-infected patients with sustained virologic response after treatment with direct-acting antivirals. United European Gastroenterol 2018;6:1188-1198.
11. Kang Q, Xu J, Luo H, Tan N, Chen H, Cheng R, Pan J, Han Y, Yang Y, Liu D, Xi H, Yu M, Xu X. Direct antiviral agent treatment leads to rapid and significant fibrosis regression after HCV eradication. J Viral Hepat 2021;28:1284-1292.
12. Öztürk-Çerik H, Esen Ş, Altıntaş-Öner B, Çelik M, Özdemir T, Tanyel E. Evaluation of the effectiveness of direct-acting antiviral agents in patients with hepatitis C. Klimik Journal 2020;33:297-306 (Turkish).

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A Case of Acute Hepatitis B Accompanied by COVID-19 Infection

COVID-19 Enfeksiyonunun Eşlik Ettiği Bir Akut Hepatit B Olgusu

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ABSTRACT

In coronavirus disease-2019 (COVID-19) infection, the liver is one of the most affected organs. Preliminary data suggest that patients with pre-existing liver disease have worse outcomes. Therefore, the prognosis of COVID-19 in patients with chronic liver disease has been examined in many studies. Most studies have been conducted in patients with chronic hepatitis B virus infection. However, there is no research on acute hepatitis B and COVID-19 to date. In the literature, only two cases have been reported. Both patients died of fulminant liver failure. Herein, we describe a case with acute hepatitis B that was later infected with severe acute respiratory syndrome-coronavirus-2. The patient's clinical course was stable, there was no worsening, and full recovery was achieved. This case showed that the prognosis is not always unfavorable in cases of acute hepatitis B accompanied by COVID-19.

Keywords: Acute hepatitis B, liver, COVID-19

ÖZ

Koronavirüs hastalığı-2019 (COVID-19) enfeksiyonunda karaciğer en çok etkilenen organlardan biridir. Konuyla ilgili ilk çalışmalar, altta yatan karaciğer hastalığı olanların daha kötü prognozlu olduğunu göstermiştir. Bu nedenle kronik karaciğer hastalığı olan hastalarda COVID-19 prognozu farklı çalışmalarda incelenmiştir. Bu çalışmaların çoğu kronik hepatit B virus enfeksiyonu olan hastalarda yapılmıştır. Şu ana kadar akut hepatit B ve COVID-19 ile ilgili herhangi bir araştırma bulunmamaktadır. Literatürde sadece iki olgu bildirilmiştir. Her iki hasta da fulminan karaciğer yetmezliğinden ölmüştür. Bu yazıda akut hepatit B nedeniyle takip edildiği sırada şiddetli akut solunum yolu yetmezliği sendromu ile enfekte olan bir olguyu sunduk. Hastanın kliniği stabil seyretti, kötüleşme olmadı ve tam iyileşme sağlandı. Bu olgu COVID-19'un eşlik ettiği akut hepatit B olgularında prognozun her zaman kötü olmayacağını göstermiştir.

Anahtar Kelimeler: Akut hepatit B, karaciğer, COVID-19

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic has had a significant impact on global health, leading to a range of clinical manifestations. Among these, liver injury has been observed in a substantial proportion of infected patients, both with and without pre-existing liver disease. Elevated aminotransferases have been reported in 14% to 58% of hospitalized COVID-19 patients (1). While typically mild, severe cases of acute hepatitis have also been mentioned (2). The pattern of elevation frequently involves aspartate aminotransferase (AST) being greater than alanine aminotransferase (ALT). To date, two patients with COVID-19 and acute hepatitis B have been reported as (3,4). Here we present a case of acute hepatitis B accompanied by COVID-19 infection.

Case Report

A 48-year-old woman was admitted to our hospital with complaints of fatigue and jaundice for 3 days. Upon initial examination, the sclera and skin were yellow and urine was dark. She had a medical history of villous adenomas and was negative for hepatitis B surface antigen (HBsAg) 4 months before

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undergoing surgical intervention. On admission, laboratory findings revealed leukocytes count of 10,500 cells/McL, AST of 1,050 IU/L (normal: 0-50), ALT of 1,192 IU/L (normal: 0-50), gamma-glutamyl transferase of 251 IU/L (normal: 0-38), alkaline phosphatase of 522 IU/L (normal: 30-120), total bilirubin: 13 mg/dL and international normalized ratio: 1 and C-reactive protein, sedimentation rate and procalcitonine were all normal. For further investigation regarding elevated liver enzymes, the patient was hospitalized in the infectious disease service. The patient reported no history of alcohol intake, herbal supplementation, or medication use. In blood analysis, HBsAg, hepatitis B e antigen (HBeAg), and anti-HBc IgM were positive. Other serology for Epstein-Barr virus, human immunodeficiency virus, hepatitis A, C, D, and E were all negative. No hepatosplenomegaly was noted on ultrasound. Five days later, she developed new onset cough and loss of smell and taste. Initial nasopharyngeal swab PCR testing for severe acute respiratory syndrome-coronavirus-2 was negative. However, two days later, the swab test was repeated and the result was positive. Her family members were infected with this virus, although they all received 2 doses of mRNA COVID-19 vaccine. Chest computed tomography was normal. No additional treatment was administered for COVID-19 infection, and no clinical worsening was observed. During hospitalization, liver enzyme levels gradually decreased and liver functions improved over 2 months, while serum hepatitis B virus (HBV)-DNA levels also decreased to 65 in the first month (Figure 1). Serum HBV-DNA levels decreased to 65 IU/L during the first month. She was discharged from the hospital after clinical and biochemical improvement. The patient cleared the infection and developed protective antibodies, namely negative HBsAg and positive hepatitis B surface antibody. On follow-up, no recurrence was observed for 6 months.

Discussion

Hepatitis B virus primarily affects the liver and leads to several diseases including hepatitis, cirrhosis, and hepatocellular carcinoma. HBV can interact with other viruses, affecting clinical outcomes. Hepatitis C virus and delta virus tend to suppress the replication of HBV. HIV and SARS-CoV-1 can exacerbate liver injury and cause poor clinical outcomes (5,6). Although SARS-CoV-2 can cause liver injury, its interaction with other viruses is not clearly understood.

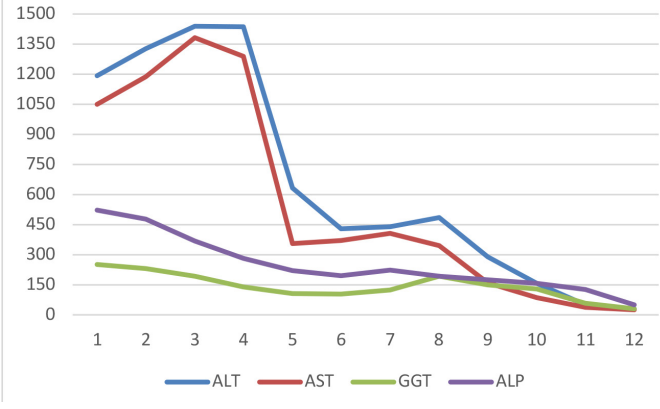

Figure 1. The fluctuation of hepatic enzyme levels

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase

In COVID-19 infection, many studies are limited to chronic HBV infection. Guan et al. (7) reported 32.1% of patients with hepatitis B infection had severe COVID-19 infection compared with 15.7% of patients who had no preexisting hepatitis B. Another relevant study showed that liver injury in patients with COVID-19 and chronic HBV co-infection was related to the severity and poor prognosis of disease (8). On the other hand, Lin et al. (9) found no significant differences in the discharge rate or duration of hospitalization, and inactive HBV carriers with SARS-CoV-2 co-infection are at a higher risk of abnormal liver function tests. However, it remains unclear whether SARS-CoV-2 co-infection may accelerate liver injury in patients with chronic HBV infection.

Literature reports on acute HBV and COVID-19 co-infection are scarce. There are two reports regarding acute HBV and COVID-19 co-infection (3,4). The first case presented with fulminant liver failure and was diagnosed with COVID-19 infection without lung involvement at the same time. The second was a 24-year-old man who had fulminant liver failure. The patients were not vaccinated and died in the hospital due to a severe and rapid course of illness. The authors suggested that COVID-19 may have caused the disease to progress to fulminant hepatitis. Contrary to these reports, our patient had a favorable outcome and the co-infection did not lead to worsening of the disease progress.

COVID-19 is a viral disease that may cause serious morbidity and mortality. To prevent the disease, various vaccines have been developed and administered to people worldwide. Although some side effects have been observed, they displayed a high level of efficacy and safety in all populations (10). In this case, although the patient received two doses of COVID-19 vaccination, she was infected with the virus and experienced a mild infection. In this case, the patient had received two doses of COVID-19 vaccination, which might have contributed to the favorable outcome.

In the pathogenesis of HBV infection, HBV-specific T-lymphocytes play an important role in liver inflammation and viral clearance. Although SARS-CoV-2 mainly acts on lymphocytes, especially T-lymphocytes, it is unclear how COVID-19 can affect HBV infection (11,12). In many studies, there is some evidence for a risk of HBV reactivation among co-infected patients who were given immunosuppression therapy during COVID-19 infection (13).

Acute hepatitis B may be more severe in patients co-infected with other viruses. Our findings reveal that COVID-19 may not worsen the progression of the disease. However, more studies are needed to clarify this issue.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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References

1. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol. 2020;5:428-430.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical

characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513.

3. Yigit Y, Haddad M, Elmoheen A, Shogaa MR, Tawel R, Mohamed YK, Salem W, Fawzy Eltawagny M. Can COVID-19 Cause Flare-Ups of Acute Hepatitis B? An Atypical Presentation of COVID-19 with Acute Hepatitis B. Case Rep Infect Dis. 2021;2021:8818678.
4. Ali E, Ziglam H, Kohla S, Ahmed M, Yassin M. A Case of Fulminant Liver Failure in a 24-Year-Old Man with Coinfection with Hepatitis B Virus and SARS-CoV-2. Am J Case Rep. 2020;21:e925932.
5. Ganesan M, Poluektova LY, Kharbanda KK, Osna NA. Human immunodeficiency virus and hepatotropic viruses co-morbidities as the inducers of liver injury progression. World J Gastroenterol. 2019;25:398-410.
6. YueHua H, ZhiLiang G. Study of relationship SARS and hepatitis virus B. Chin J Clin Hepatol. 2003;19:342-343.
7. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, Liu XQ, Chen RC, Tang CL, Wang T, Ou CQ, Li L, Chen PY, Sang L, Wang W, Li JF, Li CC, Ou LM, Cheng B, Xiong S, Ni ZY, Xiang J, Hu Y, Liu L, Shan H, Lei CL, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Cheng LL, Ye F, Li SY, Zheng JP, Zhang NF, Zhong NS, He JX; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55: 2000547.
8. Zou X, Fang M, Li S, Wu L, Gao B, Gao H, Ran X, Bian Y, Li R, ShanshanYu, Ling J, Li D, Tian D, Huang J. Characteristics of Liver Function in Patients With SARS-CoV-2 and Chronic HBV Coinfection. Clin Gastroenterol Hepatol. 2021;19:597-603.
9. Lin Y, Yuan J, Long Q, Hu J, Deng H, Zhao Z, Chen J, Lu M, Huang A. Patients with SARS-CoV-2 and HBV co-infection are at risk of greater liver injury. Genes Dis. 2021;8:484-492.
10. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020;383:2603-2615.
11. Qin C, Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis. 2020;71:762-768.
12. Lv X, Yang J, Deng K. Clinical Outcomes of COVID-19 Patients With Chronic Hepatitis B Virus Infection Still Need To Be Explored. Clin Gastroenterol Hepatol. 2020;18:3055-3056.
13. Rodríguez-Tajes S, Miralpeix A, Costa J, López-Suñé E, Laguno M, Pocurull A, Lens S, Mariño Z, Forns X. Low risk of hepatitis B reactivation in patients with severe COVID-19 who receive immunosuppressive therapy. J Viral Hepat. 2021;28:89-94.