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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.

Efforts are being made to be recognized of Viral Hepatitis Journal by indexes. Online article acceptance through website of the journal and all published volumes can be reached as full text without fee through the web site http://viralhepatitisjournal.org/.

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Instructions for Authors

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Viral Hepatitis Journal

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

Viral Hepatitis Journal (Formerly Viral Hepatit Dergisi) is an independent, peer-reviewed international journal published quarterly in April, August, December. The official language of the journal is English.

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.

Viral Hepatitis Journal does not charge any article submission, processing or publication charges. Any processes and submissions about the journal can be made from the website: http://viralhepatitisjournal.org/. Archive of the journal is also available at this website. Manuscripts should be submitted online from https://mc04.manuscriptcentral.com/viralhepatj.

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In the international index and database, the name of the journal has been registered as Viral Hepatitis Journal and abbreviated as Viral Hepat J.

SCIENTIFIC POLICIES

Scientific and Ethics Responsibility

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/).

The authors should acknowledge and provide information on grants, contracts or other financial support of the study provided by any foundations and institutions or firms.

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.

In case of retraction of the text by author(s) for any reason again needs a written and signed application explaining the reasons.

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The corresponding author must give the full corresponding address (including telephone, fax number and e-mail address). Contact information for corresponding author is published in the journal.

The authors should keep a copy of the submitted manuscripts and other documents.

If the whole or a part of the submitted manuscript needs to be published somewhere else, Editorial Office must be informed accordingly.

Review Process: Upon submission, all manuscripts are reviewed to check for requirements requested by the Journal. Manuscripts that do not comply with these requirements will be sent back to authors without further evaluations. All the papers are first evaluated by the editor; later the papers are sent to advisory board members. If needed, some questions can be asked to the authors to answer; or some defaults may have to be corrected by the authors.

The result can be acceptance, minor revision, major revision, rejection in the current form, or rejection. Accepted manuscripts are forwarded for publication; in this stage, all information and data are checked and controlled properly; the proof of the article to be published by the journal are forwarded to the writers for proof reading and corrections.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

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/),

STROBE statement—checklist of items that should be included in reports of observational studies (http://www.strobe-statement.org/),

MOOSE guidelines for meta-analysis and systemic reviews of observational studies (Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting Meta-analysis of observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283: 2008-12).

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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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Viral Hepatitis Journal

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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.

Keywords:

• 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).

• Turkish keywords should be appropriate to "Turkey Science Terms" (www.bilimterimleri.com).

Original researches should have the following sections;

Introduction: Should consist of a brief explanation of the topic and indicate the objective of the study, supported by information from the literature.

Materials and Methods: The study plan should be clearly described, indicating whether the study is randomized or not, whether it is retrospective or prospective, the number of trials, the characteristics, and the statistical methods used.

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.

References: Authors are responsible for the accuracy of the references. See General Guidelines for details about the usage and formatting required.

Case Reports

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).

Review Articles

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).

Letters to the Editor

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).

Format for journal articles; initials of author's names and surnames, titles of article, journal name, date, volume, number, and inclusive pages, must be indicated.

Example: Tabak F, Ozdemir F, Tabak O, Erer B, Tahan V, Ozaras R. Autoimmune hepatitis induced by the prolonged hepatitis A virus infection. Ann Hepatol. 2008;7:177-179.

Format for books; initials of author's names and surnames, chapter title, editor's name, book title, edition, city, publisher, date and pages.

Example: Vissers RJ, Abu-Laban RB. Acute and Chronic Pancreatitis. In: Tintinalli JE, Kelen GD, Stapczynski JS (eds.), Emergency Medicine: A comprehensive Study Guide. 6 st ed. New York: McGraw-Hill Co; 2005; p. 573-577.

Format for on-line-only publications; DOI is the only acceptable on-line reference.

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Explanations about figures, pictures, tables and graphics must be placed at the end of the article.

• Figures, pictures/photographs must be added to the system as separate .jpg or .gif files.

• The manuscripts containing color figures/pictures/tables would be published, if accepted by the Journal. In case of publishing colorful artwork, the authors will be asked to pay extra printing costs.

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Conflict of interest: If any of the writers have a relationship based on self-interest, this should be explained.

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

All manuscripts submitted to the Viral Hepatitis Journal are screened for plagiarism using the Crossref Similarity Check powered by "iThenticate" software. Results indicating plagiarism may result in manuscripts being returned or rejected.

Checklist for Submitted Articles:

Articles must be complete. They must include the following:

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• Title Page

• Article sections

• 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"

• All figures (with legends) and tables (with titles) cited.

• "Copyright Form" signed by all authors.

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CONTENTS

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Changing Trends in the Epidemiology of Delta Virus Infection

Delta Virüsü Enfeksiyonunun Epidemiyolojisinde Değişen Eğilimler

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ABSTRACT

Hepatitis delta virus (HDV) infection is an important health and economic problem worldwide. There are approximately 15 million patients with HDV worldwide and effects of 5-10% of all hepatitis B virus (HBV) infections globally. Chronic HDV infection results in 3 times more hepatocellular carcinoma (HCC) and 2 times more hepatic decompensation in cirrhosis patients compared with chronic HBV infection. HDV is associated with a higher economic burden than both HBV and hepatitis C virus (HCV) infection alone. Unlike HBV, HDV infection progresses to liver cirrhosis in 5 years, to HCC in 10 years. Risk factors for HDV infection are hepatitis B surface antigen (HBsAg) positivity, intravenous drug use, multi-partner sexual behaviors, anti-human immunodeficiency virus positivity, anti-HCV positivity, men who have sex with men, healthcare workers, immigrant people moving from high HBV infection endemic areas, prisoners, hemophiliacs, poor hygienic conditions, and low economic income. From West to East, HDV prevalence increased in both patients with chronic active hepatitis (CAH) and cirrhosis. However, the prevalence of HDV infection decreased both CAH and cirrhosis after 1995 in Turkey. Amazon basin, Indian population living in Venezuela, and the Santa Marta region of Colombia are areas of the highest HDV prevalence. Due to immigration from high HBV infection endemic areas to industrialized countries, Delta infection continues stably 5-10 % in HBsAg carriers. Each HBsAg-positive patient should be checked for anti-delta antibody to prevent rapid progress of parenchymal liver diseases.

Keywords: HDV, anti-HDV, cirrhosis, hepatitis, liver

ÖZ

Hepatit delta virüs (HDV) enfeksiyonu tüm dünyada önemli bir sağlık ve ekonomik sorundur. Dünya çapında yaklaşık 15 milyon HDV hastası vardır ve küresel olarak tüm hepatit B virüs (HBV) enfeksiyonlarının %5-10'unu etkilemektedir. Kronik HDV enfeksiyonu, kronik HBV enfeksiyonuna kıyasla siroz hastalarında 3 kat daha fazla hepatosellüler kanser (HCC) ve 2 kat daha fazla karaciğer yetmezliğine neden olur. HDV hem HBV hem de HCV enfeksiyonundan daha fazla ekonomik yüke sahiptir. HDV enfeksiyonu HBV'nin aksine 5 yılda karaciğer sirozu, 10 yılda karaciğer kanserine ilerleyicidir. HDV enfeksiyonu için risk faktörleri; hepatit B yüzey antijeni (HBsAg) pozitifliği, damar içi ilaç kullanımı, çok eşli cinsel davranışlar, anti-insan bağışıklık eksikliği virüsü (anti-HIV) pozitifliği, anti-HCV pozitifliği, erkeklerle cinsel ilişkiye giren erkekler, sağlık çalışanları, yüksek HBV enfeksiyonu endemik bölgelerden taşınan göçmenler, mahkumlar, hemofili hastaları, kötü hijyen koşulları ve düşük ekonomik gelir düzeyidir. Batı'dan Doğu'ya, HDV prevalansı hem kronik aktif hepatit (KAH), hem de siroz hastalarında artmıştır. Ancak Türkiye'de 1995 yılından sonra HDV enfeksiyonu prevalansı hem KAH hem de siroz için düşüş göstermiştir. Amazon havzası, Venezuela'da yaşayan yerli yaşam alanları ve Kolombiya'nın Santa Marta bölgesi HDV prevalansının en yüksek olduğu bölgelerdir. Yüksek HBV enfeksiyonu endemik bölgelerinden sanayileşmiş ülkelere göç nedeniyle, HBsAg taşıyıcılarında delta enfeksiyonu %5-10 oranında stabil olarak devam etmektedir. Parankimal karaciğer hastalıklarının hızlı ilerlemesini önlemek için her HBsAg pozitif hasta anti-delta antikoru açısından kontrol edilmelidir.

Anahtar Kelimeler: HDV, anti-HDV, siroz, hepatit, karaciğer

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Phone: +90 532 273 58 98 **E-mail:** normeci@yahoo.com **ORCID ID:** orcid.org/0000-0002-8909-2102 **Received:** 06.03.2023 **Accepted:** 05.06.2023

Introduction

Hepatitis delta virus (HDV) infection is an important health and economic problem all over the world, particularly in endemic areas such as the Mediterranean, Southern and Eastern Europe, the Middle East regions and Turkey. It was reported in the United States of America (USA) that the annual cost of HDV infection was 23,605$, which was 1.32 times higher and significantly more expensive than the annual cost of hepatitis B virus (HBV) infection (1).

HDV: HDV is a small, 36 nm in diameter, defective, negative single-stranded RNA virus requiring hepatitis B surface antigen (HBsAg), which allows HDV to enter hepatocytes. The virus was discovered by Rizzetto (2) in 1977. HDV is wrapped in HBsAg. HBV outer surface antigens such as large (Pre S1), medium (Pre S2), and small antigens are peripherally located surface proteins. Small and large delta antigens and single-stranded HDV-RNA take part in the central portion. Small HD Ag is essential for initiating viral replication, while large HD Ag is necessary for the assembly of new viral particles. Unlike the other RNA viruses, HDV uses host HDV polymerases for viral replication.

Epidemiology of HDV

HDV genotypes: Up to now, eight genotypes of HDV have been reported. Genotype 1 is common in Turkey as well as in North America, Europe, North Africa, Mediterranean countries and the Middle East. Sequence analysis has shown 82-95% similarity in patients with genotype 1. However, high genetic diversity was observed among the isolates, with a mean full-length dissimilarity score of 13.05% (3,4,5). Genotype 3 causes fulminant hepatitis and epidemics in East and South American countries (6).

HDV infection: There are approximately 15 million patients with HDV worldwide. It consists of 5-10.6 % of all HBV infections globally (7,8). People of the Amazon basin and Indian population living in Venezuela and the Santa Marta region of Colombia have long been known to have the highest HDV prevalence in the world (9). Reservoirs and transmission patterns of HDV infection are by nature in accordance with HBV infection. Delta prevalence was initially less than 5% in adults under 30 years of age and when the patients were over 40, the prevalence was around 20-33% in 1993 (9). Değertekin et al. (10) reported in a meta-analysis that HDV prevalence was found to be 84.9% in inactive HBsAg carriers, 20% in patients with chronic active hepatitis (CAH) due to HBV, 32.5% in patients with liver cirrhosis (LC). However, these prevalence rates have decreased from 20% to 11% in CAH, from 32% to 24% in LC patients in the last two decades (10).

Course of HDV infection: Chronic HDV infection is seen mostly during the 5th decade. It is associated with acute simultaneous co-infection of HBV and HDV, which results in mostly resolution of HBV infection but rarely causes severe or fulminant hepatitis; or superinfection, which is accelerated progressive replication of HDV and finally causes CAH, LC, hepatocellular carcinoma (HCC), and death (9). High HDV-RNA levels are commonly associated with high fibrosis scores, high necro-inflammations, high aspartate transaminase (AST) and alanine transaminase (ALT) levels, and lower albumin levels (11). When patients with chronic HBV are infected with HDV, approximately 76% of those patients may have chronic HDV infection within three years. Chronic HDV infection results in three-fold more HCC. In addition, it results in LC in a shorter period, which was observed 10-15% of patients within two years, in 30% of patients within 3 years. Moreover, hepatic decompensation was observed 2 times more compared with chronic HBV infection (1,7,12,13). Overall, HDV infection progresses to LC in 5 years, to HCC in 10 years (14).

Overall HDV prevalence: HDV prevalence of patients with acute, chronic, or fulminant hepatitis are 3-10 times more common compared with HBV seroprevalence (9). In a meta-analysis assessing 182 studies in 61 countries; the overall HDV prevalence was found to be 0.98% in HBsAg positives, where the pooled prevalence was found to be 14.6%. It was 37.6% in patients using intravenous drugs and 17% in patients with high-risk sexual behaviors (15). In a recent and large meta-analysis containing 120,293 patients in 282 studies, HDV prevalence was found to be 0.16 in the general population, 4.5% in HBsAg positive patients, 16.4% in patients who were followed by the outpatient liver clinics, 18% in patients with LC, 20% in patients with HCC (16).

Acute HBV infection and HDV

During acute HBV infection, HDV positivity rates were found to be 8.1% out of 766 patients in Turkey; 4% in Turin, and 91% in Naples out of 687 patients in Italy, and 0% out of 342 patients in Japan (10,17,18). In a meta-analysis in Turkey, the overall HDV positivity rate was 8.8% in 833 patients with acute hepatitis B (10).

Seroprevalence studies

Seropositivity of HBsAg and anti-delta immunoglobulin G (IgG) was checked in 29,960 volunteer persons from east to west parts of Turkey. Seropositivity of HBsAg and anti-delta IgG was found to be 1,805 (6.02%) and 43 (2.39%) out of 1,805 HBsAg positives; respectively (19). Accordingly, seroprevalence of HBsAg, anti-hepatitis C virus (anti-HCV), and anti-HDV was searched in volunteers; 19,250 persons during the years 2004-2006 in Urfa; and in 2012 individuals between 2007 and 2009 in Bolu. HDV seroprevalence was found 2.5% in Urfa but 0% in Bolu (20).

Chronic HBV-related liver disease and HDV

1. Data from Turkey

Viral hepatitis is one of the significant public health concerns in Turkey (21). Chronic HDV infection is endemically seen in countries where HBsAg positivity is common. It was reported that the positivity of HBsAg is 4% in a pivotal study in Turkey (22). In several studies, HDV rates were found between 1.76-6.8% of patients with HBsAg positive status in İzmir and this rate decreased from 5.2% in 2018 to 3.4% in 2019 (10). Similarly, HDV rates varied between 1.8% and 4.1% in İstanbul during the years between 2012 and 2019 (22,23,24,25,26,27,28,29,30) (Table 1). In East and Southeast provinces of Turkey, which have lower economic status, HDV prevalence rates in HBsAg positives were found to be 4-18.7% between 2002 and 2017 (31,32,33,34,35,36,37,38,39,40) (Table 2). In the central part of Anatolia, the HDV prevalence rate was reported as 23.9 % in 1986 (41). However, this rate became stable between 1.9% and 4.2% during the years 2000 and 2013 in Ankara and Konya (42,43,44,45) (Table 3).

Table 1. Prevalence of HDV between 2000 and 2018 in the western part of Turkey

References	Area	Date	Patients' types and numbers	HDV prevalence
İnci et al. (25)	İstanbul	2002-2012	HBsAg carriers (n=1,339)	3.4%
Gül Yurtsever et al. (28)	İzmir	2008-2010	HBsAg carriers (n=913)	6.3%
Özgenç et al. (29)	İzmir	2010	HBsAg carriers (n=170)	1.76%
Uzun et al. (30)	İzmir	2010-2011	HBsAg carriers (n=88)	3.4%
Eren (48)	İzmir	2013-2018	HBsAg carriers (n=968)	6.8%
Tozun et al. (22)	İstanbul	2015	HBsAg carriers (n=5,460)	2.8%
Yolcu et al. (24)	İstanbul	2015-2017	HBsAg carriers (n=2,089)	4.1%
Kaya et al. (27)	İzmir	2018	HBsAg carriers (n=8,250)	5.2%
Serin and Vatansever (23)	İstanbul	2019	CAH (n=587)	1.8%
			LC (n=84)	20%

HDV: Hepatitis delta virus, HBsAg: Hepatitis B surface antigen, CAH: Chronic active hepatitis, LC: Liver cirrhosis

Table 2. Prevalence of HDV in HBsAg carriers and chronic active hepatitis in East and South-East regions of Anatolia between 2002-2017

Authors	Location	Years	Number of patients	Prevalence of HDV
Celen et al. (31)	Diyarbakır	2002-2004	HBsAg carriers (n=889)	6%
			CAH (n=120)	27.5%
Güdücüoğlu et al. (32)	Van	2003-2004	HBsAg carriers (n=184)	19.5%
Bahcecioglu et al. (33)	Elazığ	2006-2009	CAH (n=282)	45.5%
Parlak et al. (34)	Erzurum	2008-2013	HBsAg carriers (n=2,540)	4.05%
Doğan et al. (35)	Ağrı	2009-2012	HBsAg carriers (n=787)	7% anti-HDV (+); 2.4% HDVAg (+)
Dulger et al. (36)	Van	2012-2014	HBsAg carriers (n=3,352)	18.4% in urban area; 12.5% in rural area
Ayaz and Sarı (37)	Gaziantep	2012-2017	HBsAg carriers (n=5,471)	4.44%
Mese et al. (38)	Diyarbakır	2014	HBsAg carriers in blood donors (n=186/6200)	6.98%
Sahin et al. (39)	Elazığ	2016-2017	HBsAg carriers (n=554)	9.6%
Eser-Karlidag (40)	Elazığ	2017-2019	CAH (n=455)	8.8%

HDV: Hepatitis delta virus, HBsAg: Hepatitis B surface antigen, CAH: Chronic active hepatitis

Table 3. Prevalence of HDV in central part of the Anatolia

Authors	Location	Years	Number of patients	Prevalence of HDV
Balik et al. (41)	Ankara	1986-1988	Acute HBV (n=237)	13.1%
			CAH (n=165)	32.7%
			Hemodialysis (n=12)	41.7%
			Poly-transfusion (n=45)	46.7%
Korkmaz et al. (44)	Eskisehir	2012-2013	HBsAg carriers (n=547)	1%
Türk-Arıbaş and Tekin (43)	Konya	2000-2002	Overall (n=107)	1.9%
			HBsAg carriers (n=30)	3.3%
			CAH (n=45)	2.2%
			Acute HBV (n=32)	0%
Gürkan et al. (42)	Ankara	2010-2013	HBsAg carriers (n=2,119)	4.2%
Altınbaş et al. (45)	Ankara	2009-2011	HBsAg carriers (n=348)	2%

HDV: Hepatitis delta virus, HBV: Hepatitis B virus, CAH: Chronic active hepatitis, HBsAg: Hepatitis B surface antigen

In a meta-analysis, 6,734 patients with CAH and 1,503 patients with LC were investigated in terms of HDV prevalence. From Western to Eastern Turkey, HDV prevalence increased in patients with CAH (from 5% to 19.6%) and LC (from 32.1% to 46.3%). However, both CAH (to 12%) and LC decreased to 27% after 1995 in Turkey (46). The reasons for the decrease in delta prevalence are the augmented hygienic measures, such as the use of disposable syringes, the decrease in sexual activity with multi-partners, the increase in awareness of HDV infection, improving education and socio-economic levels, and the vaccination of HBV.

In another study, HDV prevalence was found to be 1.56% of 2,314 patients with HBsAg positive status in Samsun, the Northern part of Anatolia, between 2005 and 2010 (47). In İzmir, located at the western tip of the country, it was found to be 6.8% among HBsAg carriers (48).

In a meta-analysis, anti-HDV positivity rates varied widely between 0.5-16.2% (mean was 4.9%) in 6,613 inactive HBsAg carriers. It decreased from 5.4% to 2.9%, years from 1991 to 2005. In the same paper, it was reported that HDV positivity in 5,961 patients with CAH-B and in 1,421 patients with LC was 20% and 32%, respectively. These rates increased from west to east. However, these ratios decreased in the West, Central, and East Anatolia years between 1980 and 2005. Anti-HDV positivity in patients with HCC was found 23% of 748 patients, but it varied widely from east to the west of Anatolia (10).

In another meta-analysis comprising 30 original studies, 6,734 patients with chronic liver diseases (n=5231) and LC (n=1503) were analyzed in terms of HDV seropositivity. When it was compared to anti-HDV seropositivity between east and west parts of Turkey, it was found that the prevalence of HDV was the lowest (5% and 20%; $p<0.0001$) in the west and the highest (27% and 46%; $p<0.0001$) in the southeast part of Turkey for chronic liver diseases and LC. However, when it was compared to HDV prevalence; both west and east, before and after the year of 1995; for chronic liver diseases and LC, it was reported that HDV prevalence decreased in both diseases after the year 1995. In conclusion, chronic delta infection is the most common of Turkey and is responsible for 1/4th of patients with CAH and 1/2nd of patients with LC in that area (46).

In a study from Elazığ located in the eastern part of Turkey, including the 2006-2009 period, 282 patients with CAH-B were investigated in terms of anti-delta seropositivity and HDV-RNA, and liver biopsy was performed. Anti-delta was positive in 128 (45.5%) patients. HDV-RNA was detected in 56.9% of patients. There was a close relationship between liver fibrosis stage, ALT levels, and serum albumin levels. HDV-RNA levels were higher in patients with high fibrotic stage and elevated ALT levels but low albumin levels. In patients with chronic HBV, chronic HDV infection and LC were 23.4% and 29.4%, respectively (11).

2. Global Data

In a meta-analysis analyzing 182 articles from 61 countries, it was reported that the global prevalence of HDV was 0.98. HDV prevalence was 14.57% in patients with HBsAg positive status; 37.57% in patients with intravenous drug users; 17.01% in patients with high-risk sexual behavior (15). In another meta-analysis, which included 282 studies from 95 countries, it was reported that the estimated global HDV prevalence among HBsAg-positives was 4.5%. In the general population, it was 0.16%, and in patients with LC and HCC were 18% and 20%, respectively (16).

In a meta-analysis including 332,155 people from 83 countries, it was reported that pooled HDV prevalence was 0.80 in the general population. HDV prevalence in HBsAg carriers was 13% out of 27,1,629 people in 83 countries. It was 26.75% in acute fulminant hepatitis and 25.77% in LC. HDV infection, which is highly prevalent in Central Asia, East and South Europe, Central Latin America, and Central and West Sub-Saharan Africa, was the leading cause of 19.8% of HCC. First in Asia, primarily in China (44.41%) and India (56.55%), then in Africa (22.30%) particularly in Nigeria (38.37%), HDV prevalence were predominant (14).

HDV prevalence was found to be higher than 20% in patients with HBsAg positivity between 1980 and 1990, and it decreased to 5-10% after 1990, most particularly due to HBV vaccination (49).

Buti et al. (50) reported from Spain that HDV prevalence was 1% until 1995. However, it increased to 28% between 1996 and 2008. Recently, HDV prevalence seems stable in West European countries; 8.5% in England, 8.1% in Italy, 11% in Germany (50).

HDV infection rates vary according to endemic areas, such as countries with limited resources in Africa, South America, throughout the Western Pacific (27.7%), Kiribati and Nauru Islands (84%) as high endemic areas; Mediterranean Basin, Italy (25%), Taiwan (24.7%) as intermediate endemic areas; North America, Korea; and cold areas with a low prevalence of HCV, HBV infection (0.85%) (51,52,53,54,55,56,57,58,59,60,61,62) (Table 4). The reason for wide differences the prevalence of HDV infection among all countries is associated with local socio-economic differences, genotype and virulence differences of HDV, and genetic differences of ethnic groups (63).

Immigrants and HDV Infection

In a study reported from USA, the overall estimated prevalence of HBsAg was found to be 0.36% and 3.4% in non-Hispanic Asian population between 2011 and 2016. However, the prevalence of HDV was found 42% in HBsAg carriers. HDV prevalence was 45% in Asian HBsAg-positive adults, while it was found 39% in HBsAg-positive adults of all other races (64). This study indicated that HDV seroprevalence was significantly higher in the United States than previously acknowledged, and it was disproportionately higher among Asians and persons born outside the United States.

HDV prevalence increased from 4.1% to 6.2% ($p<0.06$) among 1,307 HBsAg carriers in Dusseldorf between 1989 and 2008. Similarly, HDV prevalence increased from 32.1% to 46.2% in the former Soviet Union and from 0 to 17.2% in Africa. Seemingly, the reason for this increase is immigrants from high endemic areas of HBsAg carriers (49).

HDV prevalence in Italy was found to be 6.4% in native Italian and 26.4% in non-native Italian population in 2019 (58). Manesis et al. (62) reported that HDV prevalence was found 4.7% among 4,673 persons in Greece. However, this ratio was 2.8% in Greek people compared to 7.5% non-Greek immigrants (62). Hence, immigration seems to be a great facilitator for HDV spread in the community.

Use of Blood and Blood Products and HDV

Delta prevalence in patients with hemophilia and poly-transfused carriers was found to be significantly higher than in non-poly-transfused HBsAg carriers. In a multicentric study, HDV prevalence was found 50% in Italy, 48% of 273 patients with hemophilia in Maryland (65). HDV prevalence was found 6.98% of 6200 blood donors in Diyarbakır (38). This rate was found 3.8% in America (7).

HIV and HDV Co-infection

There was a close relationship among HDV, human immunodeficiency virus (HIV), and intravenous drug users (66). HDV infection predisposes co-infections such as HDV/HBV/HCV or HBV/HDV/HIV or HBV/HDV/hepatitis E virus (HEV) infections compared to HBV infection alone (25,61,67). HDV/HIV co-infection varies from 5% to 10.6% in the world, from 6% to 14% in North America and Europe, and from 10% to 20% in Asia and Africa (7). Soriano et al. (68) reported that HBsAg was positive in

Table 4. HDV prevalence of different geographic areas in the world

Name of Author	Country	Year	Number of patients	Prevalence of HDV
Ordieres et al. (51)	Spain	1983-1997	Chronic hepatitis B (n=786)	9.4%
		1998-2012	Chronic hepatitis B (n=429)	6.1%
Wu et al. (52)	China	2010-2013	HBsAg carriers (n=225)	4.9%
Genné and Rossi (53)	Switzerland	2008	HBsAg carriers (n=1,699) (76% had >F_2 fibrosis)	5.9%
Heidrich et al. (54)	Germany	1992-2006	HBsAg (+) (n=2,349)	11%
Aberra et al. (55)	Ethiopia	2017	CAH, HIV negative (n=1,267)	1.5%
Lago et al. (56)	Brazil	2013-2015	HBsAg carriers (n=1,240)	3.2%
Rizzetto (57)	Italy	1983	Asymptomatic carriers	7.1%
			Parenchymal liver disease	24.6%
		1987	HBsAg positives	23%
			Cirrhosis	40%
		1992	HBsAg carriers	14%
		1997	HBsAg carriers	8.3%
			Cirrhosis	11.7%
		2008	HBsAg carriers	9.7%
Mitamura et al. (17)	Japan	1991	HBsAg carriers (n=1,668)	0.59%
		1979-1985	CAH (n=690)	0.43%
		1986-1992	Cirrhosis (n=338)	1.47%
		-	Acute hepatitis (n=342)	0%
Stroffolini et al. (85)	Italy	2019	HBsAg carriers (n=894)	9.9% overall
			Italian native	4%
			Non-native	26.4%
Besombes et al. (59)	France	2019	HBsAg carriers (n=1,621)	10.6%
Cross et al. (60)	United Kingdom	2000-2006	HBsAg carriers (n=962)	8.52%
Coghill et al. (61)	Australia	1997-2016	HBsAg carriers (n=4,497)	4.1%
Manesis et al. (62)	Greece	1997-2010	HBsAg carriers (n=4,673)	4.7%
Değertekin et al. (10)	Turkey	1980-2005	HBsAg carriers (n=6,613)	4.9%
			Acute viral hepatitis (n=1,416)	3%
			CAH (n=5,961)	20%
			Acute hepatitis B (n=766)	8.1%
			Cirrhosis (n=1,421)	32.5%
Smedile et al. (18)	Italy	1978-1981	HBsAg carriers (n=492)	4.7%
			CAH (n=822)	4-51%
			Acute hepatitis B (n=687)	4-91%

HDV: Hepatitis delta virus, HBsAg: Hepatitis B surface antigen, CAH: Chronic active hepatitis

1,319 (7.9%) out of 16,597 patients with HIV (EuroSIDA study) in European countries. HDV prevalence was found in 422 (14.5%) patients with CAH B and HIV carriers (68). The combination of HBV and HIV infection progresses fast to chronic liver diseases. HCV is also a major cause of chronic liver diseases in patients with HIV (69). The most common cause of HIV, HBV, and HDV co-infection is intravenous drug use due to the similar transmission of those hepatotropic infections (70). Four hundred and eighty-four patients with HIV were assessed for hepatotropic virus in Buenos Aires. The prevalence of hepatitis B core antibody (58.5%), anti-HCV (14.5%), and anti-HEV (6.6%); were found to be higher than the control cases (p=0.001). Delta prevalence was 1.9% in those populations (71).

Sexual Associations

In an U.S. study, the prevalence of anti-delta in patients with men having sex with men varied from city to city. It was 0% in Chicago, 9.4% in San Francisco, 1.3% in Pittsburg, and 15.1% in Los Angeles. In addition, HDV prevalence was found to be 14.3% in 40 homosexual men in France and 21.73% in 154 homosexual men in Italy (72,73).

Intravenous Drug Use and HDV Infection

It is assumed that the number of persons who are using intravenous drugs is 10.6 million worldwide in 2016. Half of this population has been living in China, Russia, and U.S (7). In a study from U.S, 1,368 female prostitutes were checked for HBV and HDV viral markers and intravenous drug use. Fifty-six percent of them were HBsAg positives, 74% were intravenous drug users, and 38% were non-intravenous drug users. The HDV prevalence of patients who had HBsAg positive and intravenous drug users was 21%, while it was 6% in patients with non-intravenous drug users (74). Hence, intravenous drug use, even by inhalation, increases the risk of HBV, HCV, HIV, and HDV infections (75). Moreover, in Worcester, Massachusetts 135 patients with acute hepatitis were diagnosed due to intravenous drug use between 1983 and 1985. Eleven patients out of 13 with fulminant acute hepatitis died, and acute delta co-infection was found to be 54% among parenteral drug users (76).

HDV prevalence was checked in 194 intravenous drug users in 1988-1989 period and in 258 patients between 2005 and 2006 in Baltimore. HDV prevalence decreased from 15% to 11% between these two periods (77). Ninety-nine intravenous drug users were checked for anti-delta serology during 1972-1975 period in Washington, D.C., Miami, and New Jersey. Anti-delta was found to be positive in 10.1% of 99 patients and in 42.1% of intravenous drug users (78).

Eighty-eight HBsAg positive patients with intravenous drug users were searched in terms of anti-HDV and anti-HIV in New York city from 1985 to 1986. Anti-delta and anti-HIV were found positive in 67% and 58%, respectively. The presence of anti-delta and intravenous drug use were significantly associated with older age, longer duration of drug abuse, and presence of liver disease. The presence of anti-HIV and intravenous drug use are associated with younger age and increased serum globulin levels (79). Consequently, intravenous drug use is a noteworthy factor to facilitate the transmission of HDV infection.

Prisoners

In Taiwan, 1,137 prisoners were checked for HBsAg, anti-HCV, and anti-delta. Eighty-nine and 2% of these patients were intravenous drug users, and none were anti-HIV positive. HDV prevalence was 3.4% and triple infection (HBV, HDV and HCV) rate was 2.8% (80). In addition, inmates at Boston Municipal House were assessed for HBV and HDV in 1985. HBV markers were detected in 173 (43%) out of 406 inmates, whereas HBV markers were found in 10 (8%) out of 129 staff. Fourteen inmates (8%) had anti-HDV positivity among 173 inmates who had positive HBV markers, but no one had anti-delta (0%) among the staff. Intravenous drug use was found to be the strongest risk factor for the detection of HBV and HDV markers (81).

Mental Disorders and HDV Infection

Four thousand six hundred and seventy-one patients with mental retardation were searched in terms of HBsAg and anti-HDV in Illinois, USA in 1984. HBsAg was found in 238 of 4,671 patients. Seventy-one (29.8%) out of 238 patients had anti HDV (82). Hence, mentally disabled populations may impose significant risks for HDV infection.

Conclusion

Delta infection still causes health and economic problems, particularly in endemic countries. HDV infection is associated with HBV epidemiology and is significantly more common with intravenous drug use, multi-partner sexual behaviors, anti-HIV positivity, anti-HCV positivity, men who have sex with men, healthcare workers, immigrant people moving from high endemic areas, prisoners, hemophiliacs, poor hygienic conditions, and in those living in low economic income countries (14,15,16,51,83,84,85). Hence, delta infection continues stably 5-10% in patients with HBsAg carriers. Every patient with HBsAg positivity should be checked for delta infection to protect against the rapid progression of parenchymal liver diseases.

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ö., H.E., Concept: N.Ö., H.E., Design: N.Ö., H.E., Data Collection or Processing: N.Ö., H.E., Analysis or Interpretation: N.Ö., H.E., Literature Search: N.Ö., H.E., Writing: N.Ö., H.E.

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Research Article

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Evaluation of Hepatitis B Serology and the Effectiveness of Vaccination Program in Individuals Under the Age of Twenty-Four

Yirmi Dört Yaş Altı Bireylerde Hepatit B Serolojisinin ve Aşı Programının Etkinliğinin Değerlendirilmesi

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ABSTRACT

Objectives: The hepatitis B vaccine have been included in the routine vaccination program in our country since 1998 as part of the fight against hepatitis B virus (HBV). This study aimed to determine the HBV serology and to determine the effectiveness of the hepatitis B vaccination program in individuals born after the start of the hepatitis B vaccination program.

Materials and Methods: Data from 302 patients born after the hepatitis B routine vaccination program and 172 persons born before the vaccination program were evaluated. Those with hepatitis B surface antibody (anti-HBs) <10 mIU/mL were defined as non-immune, those with anti-HBs ≥10 mIU/mL were defined as immune, and those with isolated anti-HBs positivity were defined as the vaccinated group.

Results: Of the patients included in the study, 49.4% were female and 50.6% were male, with a mean age of 29.7±15.6 years. Anti-HBs, hepatitis B surface antigen (HBsAg), and anti-hepatitis B core antigen (anti-HBc) total positivity in patients were 41.4%, 3.2%, and 12.2%, respectively. 53% of the patients were unvaccinated, 36.5% were vaccinated, 4.4% were naturally immune, 3.2% were chronic hepatitis B, and 3% were isolated anti-HBc total positivity. A statistically significant difference was found in terms of HBsAg seropositivity anti-HBs seropositivity and naturally immune in individuals born before and after the routine hepatitis B vaccination program ($p<0.05$).

Conclusion: With the data obtained at the end of our study, it was determined that there was a significant decrease in HBsAg seropositivity and innate immunity numbers following the implementation of the routine vaccination program. This highlights the importance of the vaccination program and the usefulness of vaccination in preventing HBV infections.

Keywords: Anti-HBs, Turkey, vaccination

ÖZ

Amaç: Hepatit B aşısı, hepatit B virüsü (HBV) ile mücadele kapsamında ülkemizde 1998 yılından itibaren rutin aşılama programına alınmıştır. Bu çalışmada hepatit B aşılama programına başladıktan sonra doğan bireylerde HBV serolojisinin belirlenmesi ve hepatit B aşılama programının etkinliğinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Hepatit B rutin aşılama programından sonra doğan 302 hasta ve aşılama programından önce doğan 172 kişiden alınan veriler değerlendirildi. Hepatit B yüzey antikoru (anti-HBs) <10 mIU/mL olanlar non-immün, anti-HBs ≥10 mIU/mL olanlar immün ve izole anti-HBs pozitifliği olanlar ise aşılanan grup olarak tanımlandı.

Bulgular: Çalışmaya alınan hastaların %49,4'ü kadın, %50,6'sı erkekti ve yaş ortalaması 29,7±15,6 idi. Hastalarda anti-HBs, hepatit B yüzey antijeni (HBsAg) ve anti-hepatit B çekirdek antijeni (anti-HBc) toplam pozitifliği sırasıyla; %41,4, %3,2 ve %12,2 idi. Hastaların %53'ü aşılanmamış, %36,5'i aşılanmış, %4,4'ü doğal bağışık, %3,2'si kronik hepatit B ve %3'ü izole anti-HBc total pozitifti. Rutin hepatit B aşılama programı öncesi ve sonrası doğan bireylerde HBsAg seropozitivitesi, anti-HBs seropozitivitesi ve doğal bağışıklığı açısından istatistiksel olarak anlamlı fark bulundu ($p<0,05$).

Sonuç: Çalışmamız sonunda elde edilen verilerle rutin aşılama programının uygulanmasını takiben HBsAg seropozitivitesinde ve doğuştan gelen bağışıklık sayılarında anlamlı azalma olduğu belirlendi. Bu, aşılama programının önemini ve aşılamanın HBV enfeksiyonlarını önlemedeki yararlılığını vurgulamaktadır.

Anahtar Kelimeler: Anti-HBs, Türkiye, aşılama

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Introduction

Hepatitis B virus (HBV) is a serious cause of mortality and morbidity worldwide. Nearly one-third of the global population has been exposed to HBV (1). HBV is an enveloped DNA virus belonging to the orthohepadnavirus subgenus of the Hepadnaviridae family. The main transmission of the virus, which primarily infects liver cells, is parenteral contact with infected blood or body secretions, sexual contact, and perinatal, vertical, and intrafamily close contact (horizontal) (2). In highly endemic areas, the transmission is mostly parenteral or horizontal during childhood (3). Turkey, where the HBV carrier rate is 4-10%, is considered to be a moderately endemic region in terms of HBV incidence and HBV transmission in our country is mostly horizontal in childhood and adulthood (4).

Acute HBV infection becomes chronic at highly variable rates depending on age and HBV transmission routes. The risk of developing a chronic infection after exposure to HBV is 1-5% in adults and reaches 90% in the neonatal period (5). More than 250 million people worldwide live with viral hepatitis and the virus causes approximately 900.000 deaths annually due to hepatocellular carcinoma (HCC) and cirrhosis.

In 2016, the World Health Organization set the goal of eliminating hepatitis B globally by 2030 (2). Within the scope of this goal, it was decided to include the hepatitis B vaccine in the routine vaccination schedule of all countries as of 1997 (3). The hepatitis B vaccine has been included in the routine vaccination program in Turkey since 1998. This program prevents HBV infection and its complications including cirrhosis and HCC.

This study aimed to determine HBV serology in individuals born after the start of the routine hepatitis B vaccination program and to compare them with individuals born before the start of routine hepatitis B vaccination.

Materials and Methods

Patient Population

In our study, 474 patients whose hepatitis B surface antibody (anti-HBs), anti-hepatitis B core antigen (anti-HBc) total, and hepatitis B surface antigen (HBsAg) tests were studied for various reasons in the infectious diseases clinic of our hospital between January and September 2022 were retrospectively evaluated. Demographic characteristics and examination results of the patients were obtained from the hospital information system records. The patients were divided into two groups: those born before and after 1998 when the hepatitis B vaccination program started in our country. According to hepatitis B serology, patients with anti-HBs <10 mIU/mL were defined as non-immune, those with anti-HBs ≥10 mIU/mL were defined as immune, and those with isolated anti-HBs positivity were defined as vaccinated.

Statistical Analysis

The SPSS 21 program was used for the statistical analysis of the data. The chi-square test was used for comparison between groups born before and after 1998. $P<0.05$ was accepted as a statistical significance level.

Ethical Permission

Before starting the study, the approval of the Scientific Research Ethics Committee of the Ağrı İbrahim Çeçen University Faculty of Medicine was obtained (approval number: 244, date: 08.11.2022).

Results

Of the patients included in the study, 49.4% were female and 50.6% were male, with a mean age of 29.7±15.6 years. Anti-HBs, HBsAg, and anti-HBc total positivity rates were 41.4%, 3.2%, and 12.2%, respectively. 52.7% of the patients were unvaccinated, 36.5% vaccinated, 4.4% naturally immune, 3.4% chronic hepatitis B, and 3% isolated anti-HBc total positivity. Hepatitis B serologies according to gender are shown in Table 1.

Of the 302 patients born after 1998, when the routine hepatitis B vaccination program started in Turkey, 39.1% were female, 60.9% were male, and the mean age was 20.4±1.65 years. Of the 172 patients born before 1998 who were taken as the control group, 67.4% were female, 32.6% were male, and the mean age was 46.1±15.86 years.

HBsAg positivity was detected in 7 (2.3%) of 302 patients in the study group who were born from the year the routine hepatitis B vaccine program started. Anti-HBs were positive in 128 (43.3%) and anti-HBs negative in 167 (56.6%) of 295 patients found to be HBsAg negative. Isolated anti-HBs positivity was found in 124 (96.6%) of 128 patients with anti-HBs positive, anti-HBc total positivity in 4 patients (3.1%), and a serological profile indicating a previous infection was detected.

HBsAg positivity was detected in 8 (4.7%) of 172 patients in the control group born before hepatitis B vaccination was started. Anti-HBs were positive in 68 (41.4%) and anti-HBs negative in 96 (58.5%) of 164 HBsAg-negative patients. Isolated anti-HBs

Table 1. Hepatitis B serology by gender

Parameter	Females (%)	Males (%)	Total (%)	p-value
HBsAg positivity	2.1	4.2	3.2	0.2
Anti-HBs positivity	41	41.7	41.4	0.8
Anti-HBc total positivity	12.4	12.1	12.2	0.9

HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc total: The hepatitis B core total antibody

positivity in 49 (72%) of 68 patients with anti-HBs positive and anti-HBc total positivity in 20 patients (29.4%) and a serological profile indicating a previous infection were detected.

Considering the isolated anti-HBs positivity rates showing that the hepatitis B vaccine was applied; 28.5% of those born before the routine hepatitis B vaccination program and the rate determined as 41.1% in those born after the vaccination program. A statistically significant difference was found in terms of HBsAg seopositivity, anti-HBs seopositivity, and naturally immune in individuals born before and after the routine hepatitis B vaccination program ($p<0.05$). Serological data of the patients in both groups are shown in Table 2, There was no statistical difference between males and females in terms of isolated anti-HBs positivity, anti-HBs negativity, and HBsAg positivity both in the pre-vaccination and post-vaccination period, while HBsAg positivity was approximately 2 times higher in males than females in both groups (Table 3).

Discussion

Our country is among the middle endemic regions in terms of HBV frequency, and it is estimated that approximately 3 million people are infected with HBV (4). In the 2010 Report of the European Center for Disease Prevention and Control, the prevalence of hepatitis B in the general population in Turkey was reported to be between 2% and 8%, although it varies according to region (5). In various studies conducted in our country, it has been reported that the prevalence of hepatitis B varies between 4 and 10%, increases from west to east, and the HBsAg positivity rate reaches 10% in Diyarbakır (6,7,8,9). This regional difference in HBV positivity reemphasizes the role of close contact and intrafamilial transmission in HBV seroprevalence in regions with large families and poor hygiene conditions.

The population-based investigation of the prevalence of hepatitis B in Turkey was carried out for the first time by the Turkish Liver Research Association. In the study in which 5,471 people were screened, HBsAg, anti-HBs, and anti-HBc total positivity were found to be 4.0%, 32.0%, and 30.6%, respectively (10). In the study in which the TURHEP study group investigated the seroprevalence of HBV and HCV infections in the general population of Turkey in 2015, HBsAg seropositivity was found to be 4% and anti-HBs positivity was 30.9% (11). In our study, similar to the literature, HBsAg positivity was found to be 3.4% and anti-HBs positivity was 41.4%.

When isolated anti-HB positivity was evaluated according to age groups, the highest rate was seen in the 17-24 age group with 41.1%, while the lowest rate was observed in the group over 70 years of age (18.8%). Anti-HB positivity was increasing gradually, starting from the group over 70 years of age and progressing toward younger ages. This high rate observed in the younger age group is associated with the effective implementation of the vaccination program. It was determined that innate immunity and HBsAg positivity rate was high in middle-aged groups with a low isolated anti-HBs positivity rate. This situation shows once again the importance of the hepatitis B vaccine in the prevention of HBV exposure.

In various seroprevalence studies conducted in our country, HBsAg positivity rates were found to be higher in men and women (12,13,14). In our study, there was no significant difference between males and females in terms of anti-HBs and anti-HBc total positivity, whereas HBsAg positivity was found to be 2 times higher in males (4.2%) than females (2.1%). However, the difference was not statistically significant. HBsAg positivity was found to be 3.4% in females and 8.9% in males in the pre-vaccination group, this rate was 1.7% in females and 2.7% in males in the post-vaccination period. This situation can be associated with risky procedures such as shaving, tattooing, and circumcision in men where aseptic precautions are not adequately applied.

Table 2. Hepatitis B serology of individuals born before and after the hepatitis B vaccination program

	Those born after the HBV vaccination program (n=302)		Those born before the HBV vaccination program (n=172)		p-value
	n	%	n	%	
Isolated anti-HB positivity	124	41.1	49	28.5	0.03
Anti-HBs negativity	178	60	90	52.3	-
Anti-HBs positivity, anti-HBc total positivity	1	0.3	20	11.6	<0.01
HBsAg positivity	7	2.3	13	7.5	0.03
Isolated anti-HBc total positivity	1	0.3	14	8.1	<0.01

HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc total: The hepatitis B core total antibody

Table 3. Hepatitis B serologies by gender in pre- and post-vaccination groups

	Those born after the HBV vaccination program (n=302)		Those born before the HBV vaccination program (n=172)		p-value
	Females (%)	Males (%)	Females (%)	Males (%)	
Isolated anti-HB positivity	42.4	40.2	29.3	26.8	0.7
Anti-HBs negativity	55.9	56.3	50.9	37.5	0.7
HBsAg positivity	1.7	2.3	3.4	8.9	0.6

HBV: Hepatitis B virus, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, Anti-HBc total: The hepatitis B core total antibody

The primary goal of the hepatitis B vaccination program is to vaccinate all newborns to prevent the occurrence of HBV infection in early childhood. Since 1998, HBV vaccination has been given free of charge to all newborns. In various studies conducted in various regions of our country and evaluating the serology of hepatitis in babies born after the vaccination program, the anti-HBs level varies between 66-85% in the post-routine vaccination period (15,16). In our study, the average anti-HBs positivity rate was found to be 41.1% in those born in 1998 and later, and a lower rate was found compared to other studies. In this case, it is thought that regional differences in vaccination may be effective.

In various studies conducted in our country, the rates of previous infection and immunization vary between 0.4% and 44.5% (17,18,19). In our study, the rate of innate immunity was found to be 4.4%. These differences in the rates of previous infection and immunization show that hepatitis B seroprevalence results, which may vary from region to region, are observed, as the HBV seroprevalence in our country increases gradually from west to east (20,21,22). In our study, the rate of natural immunity was found to be 11.6% in those born before the routine vaccination program and 0.3% in those born after vaccination. This clearly shows the effect of the vaccine against HBV infection.

Detection of HBsAg positivity in 7 patients who were born after the vaccination program shows that this situation of HBsAg-positive mothers is still unknown during pregnancy and their babies cannot be vaccinated + hepatitis B immunoglobulin at birth. It is thought that this may be caused by deficiencies in pregnancy screenings or deliveries outside the hospital.

Study Limitations

The most important limitation of our study is that it was conducted in a single province and with a limited number of patients. If this study were based on a population in more than one city from different regions, the results would more accurately reflect the population. Another limitation of our study is that because all patients with anti-HBs <10 were included in the unvaccinated group and vaccinated anti-HBs >10, but the titer decreased over time, we accepted unvaccinated patients and could not accurately estimate the immune population.

Conclusion

As a result, HBV infection is still among the infectious diseases that do not lose their currency and importance in the world and our country. The most effective way to reduce the frequency of this disease, as in all infectious diseases that can be prevented by vaccination, is to mass vaccination vaccination. The national vaccination program has changed the epidemiology of HBV in Turkey, resulting in a significant reduction in HBsAg positivity and innate immunity rates. However, the same is not the case in the pre-vaccination period, and adult HBV vaccination should be expanded, especially in risk groups and those with HBsAg-positive cases in their families.

Ethics

Ethics Committee Approval: Before starting the study, the approval of the Scientific Research Ethics Committee of the Ağrı İbrahim Çeçen University Faculty of Medicine was obtained (approval number: 244, date: 08.11.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.C., Concept: Y.C.K., F.T., Design: Y.C., K.F.T., Data Collection or Processing: K.F.T., Analysis or Interpretation: K.F.T., Literature Search: Y.C., Writing: Y.C.

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Research Article

15

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Retrospective Investigation of Hepatitis B and Hepatitis C Virus Infections in Patients Evaluated Preoperatively

Preoperatif Değerlendirilen Hastalarda Hepatit B ve Hepatit C Virüs Enfeksiyonlarının Retrospektif Olarak İncelenmesi

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ABSTRACT

Objectives: This study aimed to determine the seroprevalence of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and anti-hepatitis C virus (anti-HCV) in preoperative patients and to discuss whether preoperative tests for hepatitis B virus HBV and HCV should be performed in light of new treatments and changing current information.

Materials and Methods: Patients were divided into three groups according to age groups: 18-44 years old, 45-64 years old and over 65 years old. Pre- and post-seropositivity medical records of patients with seropositivity in HBsAg and anti-HCV serological test results were obtained from the data processing center and analyzed using anonymized data.

Results: The mean age of 26,855 patients was 40.7±17.4 (18-98 years). It was observed that 57.4% (15,426) of the patients were between the ages of 18 and 44, 29.8% (8,008) were 45 and 64, and 12.7% (3,421) were over the age of 65. HBsAg seropositivity was highest in the 18-44 age group (49.5%). HBsAg reactivity in 569 (2.1%) patients; anti-HCV reactivity was determined in 50 (0.2%) patients. The highest reactivity rate for HBsAg (3.9%) was in the 45-64 age group; for anti-HCV, the highest reactivity rate (0.6%) was found in the group over 65 years old.

Conclusion: Secondary prevention of patients is now possible with early detection of HBV and HCV infections. It is thought that HBV and HCV screenings to be performed during the pre-operative preparation phase will contribute to this issue.

Keywords: Hepatitis, anesthesia, pre-operative evaluation

ÖZ

Amaç: Bu çalışmanın amacı preoperatif hastalarda hepatit B yüzey antijeni (HBsAg), hepatit B yüzey antikoru (anti-HBs) ve anti-hepatit C virüs (anti-HCV) seroprevalansını belirlemek ve yeni tedaviler ve değişen güncel bilgiler ışığında hepatit B virüs (HBV) ve HCV için preoperatif testlerin yapılıp yapılmaması gerektiğini tartışmaktır.

Gereç ve Yöntemler: Hastalar yaş gruplarına göre üç gruba ayrıldı: 18-44 yaş, 45-64 yaş ve 65 yaş üstüdür. HBsAg ve anti-HCV serolojik test sonuçları seropozitif olan hastaların seropozitiflik öncesi ve seropozitiflik sonrası tıbbi kayıtları bilgi işlem merkezinden elde edilmiş ve anonimleştirilmiş veriler kullanılarak analiz edilmiştir.

Bulgular: Yirmi altı bin sekiz yüz elli beş hastanın yaş ortalaması 40,7±17,4 (18-98 yıl) idi. Hastaların %57,4'ünün (15,426) 18-44 yaş arasında, %29,8'inin (8,008) 45-64 yaş arasında ve %12,7'sinin (3,421) 65 yaş üzerinde olduğu görülmüştür. HBsAg seropozitifliği en yüksek 18-44 yaş grubundaydı (%49,5). HBsAg reaktivitesi 569 (%2,1) hastada; anti-HCV reaktivitesi ise 50 (%0,2) hastada tespit edilmiştir. HBsAg için en yüksek reaktivite oranı (%3,9) 45-64 yaş grubunda; anti-HCV için ise en yüksek reaktivite oranı (%0,6) 65 yaş üstü grupta bulunmuştur.

Sonuç: HBV ve HCV enfeksiyonlarının erken teşhisi ile hastaların sekonder korunması artık mümkündür. Ameliyat öncesi hazırlık aşamasında yapılacak HBV ve HCV taramalarının bu konuda katkı sağlayacağı düşünülmektedir.

Anahtar Kelimeler: Hepatit, anestezi, preoperatif değerlendirme

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Introduction

One of the most important occupational risks that healthcare professionals are exposed to in their working environment is infections. During healthcare delivery, many infectious agents can be transmitted by percutaneous or mucosal contact of healthcare professionals with the blood or body fluids of infected patients (1). Hepatitis B virus (HBV) and hepatitis C virus (HCV) are among the factors transmitted through blood and other body fluids and cause serious consequences such as long-term illness, disability, and death (1,2,3,4).

Worldwide, HBV and HCV infections are important health problems. The World Health Organization (WHO) estimates that 296 million people were living with chronic HBV infection in 2019. In 2019, an estimated 820,000 deaths were caused by HBV, mostly from cirrhosis and hepatocellular carcinoma. By 2019, 30.4 million people (10.5% of all people estimated to be living with hepatitis B were aware of their infection, while 6.6 million (22%) of those diagnosed were receiving treatment (2). Turkey is among the middle endemic countries with a rate of 2-7% in terms of HBV infection (2,4,5,6). It is estimated that approximately 71 million people worldwide are infected with chronic HCV infection. It is predicted that some of them will develop cirrhosis or liver cancer. Approximately 399,000 people died due to HCV in 2016 (4). The prevalence of HCV in our country is approximately 1% (3,7).

In the diagnosis of HBV infections, it is essential to demonstrate HBV-specific serological markers and HBV-DNA, which is a replication, using molecular diagnostic methods. Hepatitis B surface antigen (HBsAg) is the first antigen detected at diagnosis (5). Detection of hepatitis C surface antibodies (anti-HBs) (anti-HCV) are the most common method used in the serological diagnosis of HCV infections. It is important that the HCV-RNA test follows a positive HCV antibody test to identify people with current (chronic) HCV infection, as a positive HCV antibody test cannot distinguish between someone who has been previously infected and someone who has a current infection (5). Because HCV infections are often subclinical, there may be delays in the diagnostic process. The diagnosis is made incidentally during blood donation, pregnancy, premarital, or pre-operative screening. Although preoperative anti-HCV screening is still a controversial issue in terms of cost and patient rights, these screenings are performed in most hospitals today (8). The Centers for Disease Control and Prevention (CDC) recommends that HCV screening tests be performed for people living in areas with high HCV prevalence or who are in the HCV risk group. It aims to increase the number of HCV tests performed to increase the chance of diagnosis and treatment and recommends expanding the screening to include individuals born between 1945 and 1965 (9). In our clinic, preoperative serological tests for HBV and HCV screenings are performed in every adult patient for whom elective surgery is indicated under general anesthesia.

This study aims to determine the seroprevalence of HBsAg, anti-HBs, and anti-HCV in preoperative patients and to discuss whether preoperative tests for HBV and HCV should be performed considering new treatments and changing current information.

Materials and Methods

Study Design and Patients Included in the Study

After the approval of the Balıkesir University Faculty of Medicine Local Ethics Committee (approval number: 2020/235, date: 09.12.2020, anti-HBs, HBsAg, and anti-HCV serological test results of the patients who were referred from different outpatient clinics for preoperative preparation to our hospital anesthesia polyclinics between 2017 and 2019 were retrospectively evaluated. Our study was conducted in accordance with the principles of the Helsinki Declaration. The first result determined for each patient was included in the study, and other recurrent results of the same patient were excluded from the study. Patients were divided into three groups according to age groups: 18-44 years old, 45-64 years old, and over 65 years. Patients were divided into three main groups as young, middle-aged, and elderly patients. No further grouping was made to avoid confusion.

Pre- and post-seropositivity HBV and HCV records of patients with seropositivity in HBsAg and anti-HCV serological test results were analyzed using patient files and anonymized data obtained from the hospital information system.

Serological Studies

Anti-HBs, HBsAg, and anti-HCV tests were performed with the i2000SR device (Abbott Diagnostics Division, Germany) used in routine diagnosis in the laboratory according to the manufacturer's instructions. Threshold values of 10 mIU/mL, 1.0 mIU/mL, and 1.0 mIU/mL were used for anti-HBs, HBsAg, and anti-HCV reactivity, respectively.

Molecular Studies

HBV-DNA and HCV-RNA tests were performed with the real-time polymerase chain reaction method (Bosphore HBV Panel Kit; Bosphore HCV Panel Kit, Anatolia Geneworks, Turkey) used in routine diagnosis in the laboratory.

Statistical Analysis

The data obtained in the study were recorded in the SPSS 22.0 (SPSS INC, Chicago, IL, USA) program and statistical analyzes were performed. Numerical data were given as percentage and mean ± standard deviation. Categorical data are given as percentages. The chi-square test was used to compare the distribution of categorical variables such as serological test results and demographic characteristics by age groups. Cases where the p-value was below 0.05 were considered as statistically significant results.

Results

The mean age of 26,855 patients included in the study was determined to be 40.7±17.4 (18-98 years). It was observed that 57.4% (15,426) of the patients were between the ages of 18 and 44, 29.8% (8,008) were between the ages of 45 and 64, and 12.7% (3,421) were over the age of 65. Nineteen thousand four hundred forty-nine (72.4%) of the patients were female and 7,406 (27.6%) were male. The patients included in the study mostly applied to obstetrics and gynecology outpatient clinic (n=11,983, 44.6%). Other polyclinic distributions are shown in Table 1.

While 59.33% (15,883) of 26,773 patients whose anti-HBs test was studied were found to be negative, 40.67% (10,890) were found to be positive. It was determined that the highest rate of reactivity (49.5%) was observed in the 18-44 age group. HBsAg reactivity was observed in 569 (2.1%) patients; anti-HCV reactivity was determined in 50 (0.2%) patients. The highest reactivity rate for HBsAg (3.9%) was in the 45-64 age group; for anti-HCV, the highest reactivity rate (0.6%) was found in the group over 65 years old. It was observed that the female/male ratio, anti-HBs, HBsAg, and anti-HCV reactivity ratios showed statistically significant differences according to age groups (p<0.001) (Table 2).

One hundred thirty three (23.4%) of the HBsAg seropositive patients were under control and treated in the past. HBsAg seropositivity was detected for the first time in 436 (76.6%) patients. Molecular methods have also shown that 119 (27.3%) of 436 patients whose first seropositivity was detected, aged between 20 and 77 years (mean age: 48.59±13.42 years) were under regular control for HBsAg carriage. The HBV-DNA results of the patients under control ranged from 10^1 to10^7 IU/mL (Table 3).

Fourteen (28.0%) of the anti-HCV seropositive patients were control and treated patients. It was observed that 36 (72.0%) were seropositive for the first time. It has also been shown by molecular methods that 5 (13.9%) of 36 patients with reactivity detected for the first time, aged between 26 and 73 years (mean age: 59.4±16.95 years) were under regular control after this date. The HCV-RNA values of these patients ranged from 10^5 to 10^6 IU/mL (Table 3).

Discussion

The global prevalence of HBV infections, which is an important public health problem, varies. Turkey is a medium-endemic country for HBV infection (2,7). It has been shown in different multicenter meta-analysis studies in our country that HBsAg seropositivity rates vary between 4.0 and 6.0% and anti-HBs seropositivity rates vary between 31.9 and 43.2% (7,10,11). In different studies conducted in our country, it was reported that preoperative HBsAg seropositivity rates ranged between 0.2 and 7.7% (Table 4). With the effective Hepatitis B Control Program implemented over the years, this rate has decreased over the years (12,13,14,15).

Similar to these rates in our study, the HBsAg seropositivity rate was 2.1% and the anti-HBs seropositivity rate was 40.6%. In our study, the age group with the highest HBsAg seropositivity rate (3.9%) was 45-64 years; it was determined that the age group with the highest anti-HBs seropositivity rate (49.5%) was 18-44 years (p<0.001). It is thought that this situation is related to the fact that the HBV vaccine is included in the childhood compulsory vaccination scheme in our country and that adults born before the vaccination scheme are at higher risk for HBV infections. In different studies, it has been shown that while anti-HBs seropositivity rates decrease with age, HBsAg seropositivity rates increase (16,17).

The chronic HCV infection is the leading cause of liver cirrhosis. Liver failure and hepatocellular carcinoma observed in these patients cause serious increases in the risk of early death (3,4,18). In studies conducted in different regions of our country, preoperative anti-HCV seropositivity rates were found to vary

Table 1. The number of patients by clinic

	n (%)
Patient	**26,855**
Male	7,406 (27.6%)
Female	19,449 (72.4%)
Clinic	
Gynecology and obstetrics	11,983 (44.6)
Cardiovascular surgery	4,020 (15.0)
Thoracic surgery	1,903 (7.1)
Otolaryngology	1,892 (7.0)
Plastic surgery	1,674 (6.2)
Urology	1,545 (5.8)
General surgery	1,263 (4.7)
Ophthalmology	1,173 (4.4)
Neurochirurgie	795 (3.0)
Orthopaedics and traumatology	607 (2.3)

Table 2. Female/male ratio, anti-HBs, HBsAg, and anti-HCV reactivity ratios by age groups

	18-44 years (n=15426)	45-65 years (n=8008)	65-year ≤ (n=3421)	p-value
Female/male ratio	4.5	1.9	0.8	<0.001
Anti-HB reactivity rate	49.5%	27.2%	32.3%	<0.001
HBsAg reactivity rate	1.1%	3.9%	2.7%	<0.001
Anti-HCV reactivity rate	0.04%	0.3%	0.6%	<0.001

Anti-HBs: Hepatitis B surface antibody, HBsAg: Hepatitis B surface antigen, anti-HCV: Hepatitis C surface antibody

Table 3. Demographic data of newly diagnosed patients				
	HCV		**HBV**	
Newly diagnosed patient (n)	36		436	
HCV-RNA (IU/mL)	10^5-10^6		-	
HBV-DNA (IU/mL)	-		10^1-10^7	
Age (mean ± SD)	61.2±13.9		50.1±14.1	
Age group distribution				
18-44 (n)	3		120	
45-65 (n)	15		246	
65≤ (n)	18		70	
Gender				
Male (n)	20		189	
Female (n)	16		247	
Patient under follow-up (n)	5		119	
Age (mean ± SD)	59.4±16.9		48.5±13.4	
Age group distribution				
18-44 (n)	1		32	
45-65 (n)	1		72	
65≤ (n)	3		15	
Gender				
Male (n)	1		46	
Female (n)	4		73	
	HBV		**HCV**	
Clinic	**New diagnosis**	**Patient under follow-up**	**New diagnosis**	**Patient under follow-up**
Obstetrics and gynecology	86	27	2	1
Ear, nose and throat disorders	30	9		
Neurochirurgie	13	6	1	
General surgery	122	27	10	1
Thoracic surgery	16	7	3	
Eye disease	20	4	4	1
Cardiovascular surgery	63	20	4	
Orthopedics and traumatology	44	8	8	1
Plastic and reconstructive surgery	16	3	1	
Urology	26	8	3	1

HBV: Hepatitis B virus, HCV: Hepatitis C virus, SD: Standard deviation

Table 4. Preoperative HBsAg and anti-HCV reactivity ratios				
Reference	**Year**	**Patient**	**HBsAg**	**Anti-HCV**
Karaayak Uzun et al. (15)	2013	4,367	7.7%	2.3%
Sayhan (14)	2015	994	1.5%	0.1%
Onerci Celebi et al. (13)	2018	3,731	3.6%	0.3%
Akpınar et al. (12)	2018	2,440	0.2%	0.1%
Erbay et al. (8)	2019	25,424	-	0.6%

HBsAg: Hepatitis B surface antigen, Anti-HCV: Hepatitis C virus

between 0.1-2.3% (Table 4) (9,13,14,15,16). Similar to these rates in our study, the rate of anti-HCV reactivity was found to be 0.2%. In our study, it was determined that the age group with the highest rate of anti-HCV seropositivity (0.6%) was patients over the age of 65 ($p<0.001$). Similarly, in different studies conducted in our country, it has been shown that the rate of anti-HCV seropositivity increases with age (16,17).

The CDC emphasized that HBV infections can be easily diagnosed even before symptoms appear with inexpensive, reliable, and easy-to-apply tests, and thus patients can be saved for many years with early initiation of treatment. Considering the expected benefits in the diagnosis of HBV infections, which is a serious health problem, the costs of screening tests have been reported to be reasonable (19). In our study, it was determined that 23.4% of patients with HBsAg reactivity were registered patients from the past, and 76.6% were patients with reactivity detected for the first time. It was shown in our study that 27.3% of patients (mean age: 48.5±13.4 years; minimum-maximum: 20-77 years) in whom reactivity was detected for the first time were followed up regularly for HBsAg carriers after this date.

Since individuals infected with HCV are usually asymptomatic until a late stage, it is thought that nearly half of infected individuals are unaware of their condition. Diagnosis in the early stages of the disease and rapid initiation of strong direct-acting antiviral treatments are critical in preventing late complications associated with HCV (3,4,20,21). Antiviral drugs can cure more than 95% of people with HCV infection and reduce the risk of death from cirrhosis and liver cancer. However, low diagnostic rates for HCV infections unfortunately reduce the rates of access to treatment (22). Since there is currently no effective vaccine against HCV, early diagnosis of HCV infections and thus the initiation of treatment as soon as possible is very important. In our study, it was determined that 28.0% of the patients with anti-HCV reactivity were registered patients from the past, and 72.0% were patients with reactivity detected for the first time. It was found that 13.9% (mean age: 59.4±16.9 years; minimum-maximum: 26-73) of the patients who were found to have reactivity for the first time were under regular follow-up and control after this date. In a study conducted in Germany by Winkelmann et al. (23), anti-HCV seropositivity was found in 21 (1.5%) of 1,373 patients screened before surgery, but it was reported that 7 (33%) of 21 patients were not aware of HCV infection before. Erbay et al. (8) found 21 (26.9%) people who did not know that they were anti-HCV positive before surgery. The current approach to the prevention and control of HCV infections is focused on testing people with risk factors. Recent studies have shown that screening of the general population is cost-effective compared with risk-based screening. In the new treatment environment with highly effective and well-tolerated direct-acting antiviral therapies, many countries are reconsidering their testing strategies (24,25). There is also a need to establish a universal HCV screening program to reach WHO's goals for HCV eradication by 2030 (24,26). In a study conducted in Europe examining the prevalence and cost-effectiveness of HBV and HCV, it was stated that HBV and HCV infections were generally asymptomatic and 40-80% of people with chronic hepatitis were not aware of their infection. Therefore, it has been emphasized that screening programs for chronic HBV and HCV infection can contribute significantly to the primary and secondary prevention of these infections (27).

The risk of percutaneous injury in healthcare workers in Turkey is higher than in developed countries. The risk of exposure in healthcare workers involved in surgical procedures is even higher than in other healthcare workers (28). Screening for HCV and HBV warns the surgeon about high-risk patients, provides a reconsideration of the surgical procedure, and provides an opportunity for the surgical team to take more intensive measures in the operating room to reduce the risk of infection (29). Universal screening for HCV is recommended for patients undergoing orthopedic surgery, especially since HCV-positive patients have a high risk of transmission in orthopedic surgeries, and these screening programs are applied in many surgical disciplines in high-risk areas (30). In fact, in countries with low seroprevalence rates, preoperative testing is uncommon because it is considered not cost-effective. However, preoperative screening is a very cost-effective strategy for patients living in areas with high HCV and HBV seroprevalence, and preoperative testing is recommended (31). With the widespread use of direct-acting antiviral agents in recent years, it has been emphasized that screening programs should not only be limited to high-risk populations but also be applied to the general population. Because the cost-effectiveness of these screenings was stated to be quite good compared to the costs of delayed viral hepatitis treatment (24,26).

Negative serological tests do not mean that the patient is not infected. The patient may be in the window period. Universal precautions must be taken. All the health staff must take preventive measures and consider as if the patients are potentially infected. Hepatitis B core antigen (anti-HBc) immunoglobulin M (IgM) can be checked to identify patients in the window period. However, it does not need to be examined unless there is a clinical suspicion.

Retrospective planning, anti-HBc IgG not checked, and questioning of the patients included in the study only through the system are limitations of our study. However, the fact that 27.3% of patients with HBsAg reactivity and 13.9% of patients with anti-HCV positivity are under regular follow-up and control after the pre-operative screening suggests that preoperative HBV and HCV screening should be performed in our country.

Study Limitations

Our study has some limitations. First, it is a single-center, retrospective study and includes a specific follow-up period. Secondly, since it includes a certain follow-up period, it contains limited information about the processes of the patients after the diagnosis.

Conclusion

The diagnosis of HBV and HCV infections should be established before cirrhosis and cirrhosis-related complications develop in asymptomatic infected individuals. Thus, early treatment will improve clinical results, reduce the risk of transmission, and provide significant savings in health costs. Now that secondary prevention of HBV and HCV infections is possible, there is a need to develop a strategy to identify chronic carriers who may benefit from treatment. It is thought that HBV and HCV screenings during

preoperative preparation will contribute to this issue. At the same time, it is predicted that this practice will increase awareness and attention and reduce the risk of transmission for healthcare workers who are at a high risk of transmission.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Balıkesir University Faculty of Medicine (approval number: 2020/235, date: 09.12.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Research Article

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Follow-up, Treatment and Non-invasive Scoring Systems in Chronic Hepatitis B: A Retrospective Observational Study

Kronik Hepatit B'de Takip, Tedavi ve Non-invaziv Skorlama Sistemleri: Retrospektif Gözlemsel Bir Çalışma

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ABSTRACT

Objectives: Chronic hepatitis B (CHB) may present with many clinical signs. This study evaluates the CHB cases followed in our center in terms of ELISA, treatment, and non-invasive scoring systems.

Materials and Methods: Four hundred CHB cases were retrospectively analyzed. ELISA and treatment status were recorded at the time of diagnosis and at the last admission. Fibrosis-4 (FIB-4) and aspartate aminotransferase - platelet ratio index (APRI) scores were calculated for the cases who underwent biopsy and received treatment (n=40) and for treatment-naive cases without biopsy (n=135). The cut-off values of FIB-4 and APRI were calculated in the groups. The obtained results were compared with the significance of fibrosis markers. The number of patients was determined as a percentage according to the cut-off value calculated for fibrosis ≥2 in FIB-4 and APRI scores in patients who did not undergo biopsy.

Results: Of the 400 patients, 52.5% were male. The mean age of the cases was 19.0-84.0 (49±12.7). Hepatitis B surface antigen negativity (p=0.012) developed in nine cases (2.25%) and hepatitis B virus-DNA negativity increased from 7.8% to 63.2% (p=0.001). Of the treatment-naive cases, 36.9% based on the FIB-4 score and 16.3% based on the APRI score were F ≥2. When biopsy was compared with FIB-4 and APRI, the positive predictive value of FIB-4 and APRI scores (87% and 95%, respectively) were found to predict low fibrosis (F ≤1), and negative predictive value NPV (94.7% and 95.8%, respectively) was found to predict advanced fibrosis (F ≥4).

Conclusion: The FIB-4 and APRI scores can guide some treatment-naive cases in terms of performing a biopsy and initiating treatment if necessary.

Keywords: APRI, chronic hepatitis B, FIB-4, treatment

ÖZ

Amaç: Kronik hepatit B (KHB) birçok klinik bulgu ile ortaya çıkabilir. Bu çalışmada merkezimizde takip edilen KHB olgularının ELISA, tedavi ve non-invaziv skorlama sistemleri açısından değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Dört yüz KHB olgusu retrospektif olarak incelendi. Tanı anında ve son başvuruda ELİSA ve tedavi durumu kaydedildi. Biyopsi yapılan ve tedavi alan olgular (n=40) ve biyopsi yapılmayan tedavisiz olgular (n=135) için fibrozis-4 FIB-4 ve aspartat aminotransferaz - trombosit oranı indeksi (APRİ) skorları hesaplandı. Gruplarda FIB-4 ve APRİ cut-off değerleri hesaplandı. Elde edilen sonuçlar fibrozis belirteçlerinin anlamlılığı ile karşılaştırılmıştır. Biyopsi yapılmayan hastalarda FIB-4 ve APRİ skorlarında fibrozis ≥2 için hesaplanan cut-off değerine göre hasta sayısı, yüzde olarak belirlendi.

Bulgular: Dört yüz hastanın %52,5'i erkekti. Olguların yaş ortalaması 19,0-84,0 (49±12,7) idi. Dokuz olguda (%2,25) hepatit B yüzey antijeni negatifliği (p=0,012) gelişti ve HBV-DNA negatifliği %7,8'den %63,2'ye (p=0,001) yükseldi. Tedavi almayan olguların FIB-4 skoruna göre %36,9'u ve APRİ skoruna göre %16,3'ü F ≥2 idi. Biyopsi FIB-4 ve APRİ ile karşılaştırıldığında, FIB-4 ve APRİ skorlarının pozitif öngörme değerinin (sırasıyla; %87 ve %95) düşük fibrozu (F ≤1), negatif öngörme değerinin (sırasıyla; %94,7 ve %95,8) ise ileri fibrozu (F ≥4) öngördüğü tespit edildi.

Sonuç: FIB-4 ve APRİ skorları, tedaviye yanıtsız olguların bir kısmına biyopsi yapılması ve gerekirse tedaviye başlanması açısından rehberlik edebilir.

Anahtar Kelimeler: APRİ, kronik hepatit B, FIB-4, tedavi

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Introduction

The World Health Organization reported in 2019, there were approximately 300 million cases of chronic hepatitis B (CHB) and 1.5 million new cases per year were added to this number. The most important causes of mortality in CHB cases are cirrhosis and hepatocellular cancer (HCC). In 2019, mortality was reported as approximately 820,000 (1). Treatment can be evaluated according to clinical and laboratory findings, family history, the presence of cirrhosis, and HCC. Antiviral treatments that prevent fibrosis in the liver and suppress hepatitis B virus (HBV)-DNA should be used for hepatitis B surface antigen (HBsAg) to become negative and hepatitis B surface antibody (anti-HBs) positivity to develop (2). Recently, low-level virema (LLV) has been reported as a persistent or intermittent elevation of detectable HBV-DNA (<2000 IU/mL, borderline 10 IU/mL) despite 12 months of HBV treatment. Oral antivirals such as entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alaninamide fumarate (TAF) have been reported to play an active role for treating CHB. Cases of LLV have been reported despite long-term effective oral antiviral treatments (3). Because biopsy is painful, invasive, costly and error prone, scoring systems and some biomarkers have been developed, which can be an alternative to biopsy in cases with advanced fibrosis. The fibrosis-4 (FIB-4) index, one of these scoring systems, is a reliable index with a high positive predictive value (PPV) in cases with advanced fibrosis. In cases with a high FIB-4 score, the FIB-4 score may be predictive of liver-related morbidity and mortality (4). Non-invasive scoring systems such as FIB-4 and aspartate aminotransferase (AST) - platelet ratio index (APRI) increase their importance day by day in estimating cases with a high risk of fibrosis and morbidity (5). The American Association for the Study of Liver Diseases recommends the FIB-4 index as an alternative to biopsy for hepatitis B to determine the severity of the disease, to detect cases that need antiviral therapy, and to determine the duration of treatment (6). The development of HBsAg negativity is a rare condition in CHB. The development of HB Ag negativity is less common in childhood CHBs than in adults. Although the development of HBsAg negativity also reduces the progression to HCC, there are cases that develop cirrhosis and HCC despite HBsAg negativity (7,8).

Materials and Methods

Study Design And Patients

Patients who applied to the ınfectious diseases outpatient clinic of our center due to chronic HBV infection between November 1, 2021 and September 19, 2022 were retrospectively included in the study. The data were obtained by scanning our hospital's automation system "Fonet Web HBYS". Demographic data, treatment status, laboratory values, radiological findings, accompanying factors, and histopathological findings were recorded. Fibrosis staging according to liver biopsy results was performed using the modified Ishak histological activity index (F 0-6). Biopsy patients (n=40) were analyzed in three different groups. The first group (F ≤1, F ≥2), the second group (F ≤2, F ≥3) and the third group (F ≤3, F ≥4) were divided into two groups: low and advanced fibrosis. In addition, in treatment-nave patients (n=135) who did not undergo biopsy, cases with F ≥2 were evaluated using non-invasive score markers.

Non-invasive Fibrosis Scoring Calculation

The FIB-4 score was calculated using the following formula. A score of <1.45 predicts the absence of fibrosis, and a score >3.25 predicts a significant fibrosis (9,10). The APRI was calculated according to the formula below. A score of 0.5 predicts the absence of fibrosis, >1.5 predicts significant fibrosis (F 3-4) and ≥2 (F 5-6) predicts advanced fibrosis (11,12). The FIB-4 and APRI scores of the untreated cases and the cases with a known biopsy date were calculated and recorded. For FIB-4 score calculation, age [(years) x AST (U/L(]/[PLT (10^9/L)] x [alanine aminotransferase (ALT) (U/L) ($^{(1/2)}$)] formulation and APRI score calculation, APRI= 100* [(AST/AST Upper Limit of Normal)/(platelet/1,000)] were used.

Ethics Committee Approval

Ethical approval was sought from the Ordu University Ethics Committee Unit (Black Sea Region/Ordu/Turkey) and permission was obtained with the decision of the ethics committee (approval number: 2022/220, date: 14/10/2022).

Statistical Analysis

For statistical analysis, we entered the data obtained in our study into the SPSS 25.0 (IBM New York, USA) software using descriptive statistical methods in data analysis. The Kolmogorov-Smirnov Z-test determined whether the data showed a normal distribution. Median (minimum-maximum) was calculated for nonnormally distributed variables, and the mean and standard deviation (SD) were calculated for normally distributed variables. Student's t-test was used to compare two numerical categories with normal distribution and the Mann-Whitney U test without normal distribution. Pearson's chi-square test and Fisher's exact test were used for qualitative categorical data comparisons. The McNemar test was used to compare the bilateral nonparametric values before and after treatment. The Pearson correlation test was used for correlating normally distributed data and the Spearman correlation test was used for correlating nonnormally distributed data. The cut-off values of non-invasive fibrosis markers in the determined fibrosis groups were calculated using receiver operating characteristic (ROC) curve analysis. The cut-off values for each parameter were determined according to the Youden index. Sensitivity, specificity, PPV, and negative predictive value (NPV) were determined according to these cut-off values. The obtained results were compared with the significance of fibrosis markers. The number of patients who did not undergo biopsy was determined as a percentage according to the cut-off value calculated for FIB-4 and APRI scores F ≥2. The significance level for all results was evaluated with $p<0.05$.

Results

Demography

A total of 400 patients, 210 (52.5%) males and 190 (47.5%) females, were included in the study. The mean age of the cases was 19-84 (49±12.7). Eleven (2.8%) of them were newly diagnosed. Eight (2%) of the cases followed up under treatment were LLV, two (0.5%) cases voluntarily, and two (0.5%) cases discontinued the treatment due to pregnancy. Biopsy did not meet the treatment criteria in two (0.5%) cases and biopsy could not be performed in seven (1.8%) cases due to contraindications. Hepatomegaly and steatosis were detected in 52 (13%) cases and coarsening and granulation in the parenchyma were detected in 29 (7.25%) cases in liver ultrasonography performed during the initial diagnosis.

ELISA

When the ELISA studied at the time of diagnosis and at the last control were compared, HBsAg negativity (p=0.012) developed in nine cases (2.3%) and anti-HBs positivity (p=0.064) developed in eight cases (2%). While data were missing for hepatitis B e antigen (HBeAg) and hepatitis B e antibody (anti-HBe), HBV-DNA negativity increased from 7.8% to 63.2% (p=0.001) (Table 1).

Treatment

Regarding the treatment status of the cases, approximately one-third of them did not need treatment, and the initial treatment of one-third was revised later, usually due to side effects. Of the cases, 135 (33.8%) were followed without treatment, 24 (6%) received prophylaxis, and the other 241 (60.2%) were treated. The date of biopsy could be determined in only 40 (10%) cases. While TDF was the most preferred treatment in the initial treatment, maintenance treatment was most frequently revised to TAF (Table 2).

The patients who received and did not receive treatment were compared in two groups by calculating the mean ± SD values in terms of sex, age and ELISA. While there was a significant difference between the two groups in terms of HBeAg (p=0.001) and anti-HBe (p=0.001), no difference was observed in terms of sex (p=0.506) and anti-HBs (p=1.000). The mean age was higher in the treated group (p=0.001). In addition, non-invasive scoring in the group that did not receive treatment, i.e., no/low expected fibrosis, was lower than that in the group that had received treatment. FIB-4 (p=0.001) and APRI (p=0.001) (Table 3).

Cases that were biopsied and reported according to the ISHAK scoring system were divided into two groups as low fibrosis (F ≤2) and advanced fibrosis (F ≥3) compared with age, laboratory, and ELISA direction. The AST value was found to be significantly higher in the advanced fibrosis group (p=0.034). There was no significant difference between other parameters (p>0.05). Other parameters data are given in Table 4.

Correlations were investigated between age (p=0.219), serum AST (p=0.015), ALT (p=0.199), platelet (p=0.589), APRI (p=0.047), and FIB-4 (p=0.171) scores and fibrosis levels in the patients. A positive and significant correlation was found between fibrosis and AST values and APRI score.

Relationship between scoring and fibrosis

The histological activity index and non-invasive scoring systems were compared according to the ISHAK scoring of the biopsy cases. The area under the curve was determined by performing ROC analysis for FIB-4 and APRI (Figure 1).

Because of ROC curve analysis, the best cut-off point was determined for detecting advanced fibrosis. Sensitivity, specificity, PPV and NPV were calculated. Table 5 shows the performance of non-invasive fibrosis scores according to cut-off values. Because of ROC curve analysis, the best cut-off value in detecting advanced fibrosis (F ≥3) of the FIB-4 score was taken as ≥1.340, sensitivity was 61.1%, specificity was 63.2%, PPV was 61.1%, and NPV was 63.2%. The best cut-off value for detecting advanced fibrosis (F ≥3) for the APRI score was ≥0.398, sensitivity was 72.2%, specificity was 73.7%, PPV was 72.2%, and NPV

Table 1. ELISA status of cases first and last study

ELISA		At the first diagnosis (n=400), (%)	At the last check (n=400), (%)	p-value
HBsAg	Pozitive	387 (96.8)	378 (94.5)	**0.012**
	Negative	13 (3.2)	22 (5.5)	
Anti-HBs	Pozitive	12 (3)	20 (5)	0.064
	Negative	388 (97)	380 (95)	
HBeAg	Pozitive	55 (13.8)	29 (7.2)	**0.001**
	Negative	304 (76)	304 (75.3)	
	No data	41 (10.2)	77 (17.5)	
Anti-HBe	Pozitive	294 (73.5)	282 (70.5)	0.078
	Negative	64 (16)	49 (12.3)	
	No data	42 (10.5)	69 (17.2)	
HBV-DNA	Pozitive	327 (81.8)	115 (28.7)	**0.001**
	Negative	31(7.8)	253 (63.2)	
	No data	42 (10.4)	32 (8.1)	

HBsAg: Hepatitis B surface antigen, anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen Anti-HBe: Hepatitis B e antibody, HBV: Hepatitis B virus

Table 2. Treatment status

Treatment status		**(n=400)**	**(%)**
Initial treatment	Untreated	135	33.8
	TDF	169	42.3
	TAF	10	2.5
	ETV	64	16
	Lamivudine	13	3.3
	Telbivudine	4	1
	ETV + TDF	1	0.3
	TDF + lamivudine	4	1
Treatment change	Yes	99	24.8
	No	166	75.3
Reason for treatment change	Side effect	78	19
	No response	20	4
	Pregnancy	1	0.3
Maintenance treatments after the change	TDF	12	3
	TAF	59	14.8
	ETV	26	6.5
	ETV + TDF	1	0.3
	TAF + lamivudine	1	0.3
Prophylaxis	Yes	24	6
	No	376	94

TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, ETV: Entecavir

Table 3. Comparison of ELISA and fibrosis scores by treatment status

Parameters		**Untreated (n=135), (%)**	**Receiving treatment (n=241), (%)**	**p**
Gender	Male	68 (50.4)	130 (54)	0.506
	Female	67 (49.6)	111 (46)	
Age	Mean ± SD	45.26±12.3	51.18±12.63	**0.001**
HBsAg	Pozitive	135 (100)	241 (100)	-
	Negative	0 (0)	0 (0)	
Anti-HBs	Pozitive	1 (0.7)	2 (0.8)	1.000
	Negative	134 (99.3)	239 (99.2)	
HBeAg	Pozitive	5 (3.7)	50 (20.7)	0.001
	Negative	101 (74.8)	182 (75.5)	
Anti-HBe	Pozitive	3 (2.2)	56 (23.3)	0.001
	Negative	102 (75.5)	175 (72.6)	
FIB-4	Mean ± SD	1.02±0.76	2.28±1.98	**0.001**
APRI	Mean ± SD	0.28±0.33	1.10±1.20	**0.001**

HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen, Anti-HBe: Hepatitis B e antibody, FIB-4: Fibrosis-4, APRI: Aspartate aminotransferase - platelet ratio index, SD: Standard deviation

was 73.7%. FIB-4 and APRI scores had a high PPV (87%, 95%) in the prediction of low fibrosis (F 1) and a high NPV (94.7%, 95.8%) in the prediction of advanced fibrosis (F ≥4).

In cases without biopsy and followed up without treatment (n=135), F ≥2 cases were estimated using non-invasive score markers. The cut-off was 1.03 for FIB-4 and 0.358 for APRI. F ≥2 was found in 36.9% of the patients according to the FIB-4 score and 16.3% according to the APRI score.

Discussion

FIB-4 and APRI are widely used models to detect fibrosis among NASH patients. A meta-analysis of 13 studies investigated the ability of FIB-4, NFS, and APRI scores to predict liver-related events in NASH patients. While FIB-4 and NFS were safer than APRI in predicting mortality, all three markers were found to be inconsistent in predicting the change in fibrosis stage (13). In another study that included 1,038 patients from four studies,

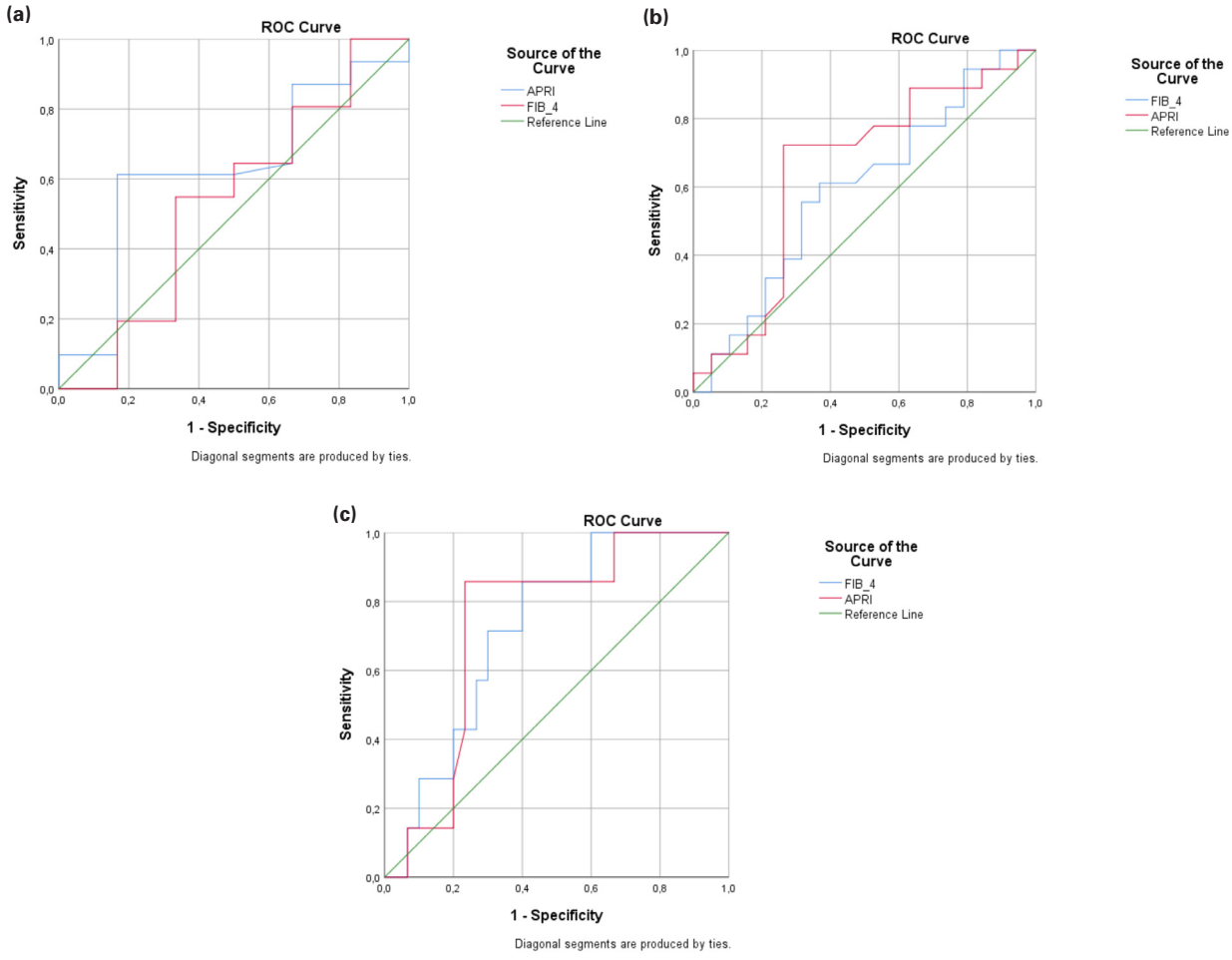

Figure 1. (a) ROC curves for non-invasive models in the diagnosis of fibrosis ≥2. (b) ROC curves for non-invasive models in the diagnosis of fibrosis ≥3. (c) ROC curves for non-invasive models in the diagnosis of fibrosis ≥4

ROC: Receiver operating characteristic

Table 4. Comparison of demographics, laboratory and histological characteristics of patients with low and advanced fibrosis

Parameters, (n)	**Low fibrosis (F ≤2)**	**Advanced fibrosis (F ≥3)**	**p**
Gender (female/male) (91/101)	49/52	42/49	0.744
Age*	49.13±13.60	50.64±12.16	0.421
AST†	23 (14-3030)	30 (11-813)	**0.034**
ALT†	29 (5-1525)	32 (8-1215)	0.410
AFP†	2.14 (0.1-37)	2.74 (0-20)	0.092
HBV-DNA†	$1.2x10^6$±(101-$5.1x10^9$)	$0.3x10^6$±(20-$12x10^9$)	0.180
PLT*	198.21±39.63	208.06±43.47	0.476
FIB-4†	1.14 (0.37-7.83)	1.58 (0.51-7.78)	0.598
APRI†	0.34 (0.15-3.83)	0.64 (0.18-5.32)	0.248
HBsAg (pozitive/negative), (192/0)	101/0	91/0	-
Anti-HBs (pozitive/negative), (89/103)	0/101	89/2	-
HBeAg (pozitive/negative), (38/147)	21/78	17/69	0.808
Anti-HBe (pozitive/negative), (142/43)	73/26	69/17	0.297

*Mean ± standard deviation, †Median (minimum-maximum), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AFP: Alpha fetoprotein, HBV: Hepatitis B virus, PLT: Platelet, FIB-4: Fibrosis-4, APRI: Aspartate aminotransferase - platelet ratio index, HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen, Anti-HBe: Hepatitis B e antibody

Table 5. The performance of non-invasive fibrosis scores by cut-off values								
Fibrosis	**Index**	**Cut-off**	**AUROC, (95%)**	**p**	**Sensitivity (%)**	**Specificity, (%)**	**PPV, (%)**	**NPV, (%)**
F≥2	FIB-4	1.03	0.532 (0.243-0.822)	0.805	64.5	50	87	21.4
	APRI	0.358	0.626 (0.382-0.871)	0.333	61.3	83.3	95	29.4
F≥3	FIB-4	1.340	0.592 (0.406-0.778)	0.338	61.1	63.2	61.1	63.2
	APRI	0.398	0.649 (0.464-0.835)	0.121	72.2	73.7	72.2	73.7
F≥4	FIB-4	1.340	0.724 (0.549-0.899)	0.068	85.7	60	33.3	94.7
	APRI	0.398	0.736 (0.556-0.916)	0.055	85.7	76.7	46.2	95.8

AUROC: Area under the ROC, PPV: Positive predictive value, NPV: Negative predictive value, FIB-4: Fibrosis-4, Aspartate aminotransferase - platelet ratio index

13% of the cases had fibrosis. The pooled sensitivity, specificity, and area under the ROC (AUROC) curve of the FIB-4 index with a 95% confidence interval (CI) were found to be 0.844 (0.772-0.901), 0.685 (0.654-0.716) and 0.8496±0.0680 when the cut-off value was 1.30. When the cut-off value was 3.25, the same parameters were calculated as 0.38 (0.30-0.47), 0.96 (0.95-0.98) and 0.8445±0.0981. When the cut-off was -1,455, the pooled sensitivity and specificity with 95% CI were 0.77 (0.69-0.84), 0.70 (0.67-0.73) and 0.8355±0.0667 when the cut-off was 0.676, 0.27 (0.19-0.35) and 0.98 (0.96-0.98), respectively, and the AUROC was 0.647±0.2208. The cut-off value of 1.30 for the FIB-4 index has a better prognostic diagnostic yield than 3.25 (14). In another study, the FIB-4 index was compared with 138 cases with liver biopsy and 372 cases with FibroTest. When the FIB-4 cut-off value was ≤1.45 and the liver biopsy size was ≥20 mm, NPV was 86%, sensitivity 71.1%, and specificity 73.1% in differentiating moderate fibrosis F 0-2 from severe fibrosis F 3-4. In the study, the FIB-4 index was more useful in determining fibrosis than the APRI score and showed an 89% correlation with the FibroTest (κ=0.27, p<0.001). The FIB-4 index is an easy, inexpensive and accurate method to exclude fibrosis in CHB patients (15). In another similar study, the distinction between mild/absent fibrosis (F 0-1) and severe fibrosis (F 2-4) was evaluated using APRI, FIB-4, and AST/ALT ratios. AUROCs were calculated as 0.81 (0.76-0.87) for APRI, 0.81 (0.75-0.86) for FIB-4, and 0.56 (0.49-0.64) for AST/ALT. APRI and FIB-4 are useful in differentiating severe fibrosis from mild/absent fibrosis and in the treatment follow-up of fibrosis (16). Our ROC curve analysis showed that when the FIB-4 score was taken as ≥1.340 for the detection of advanced fibrosis (F ≥3), the sensitivity was 61.1%, specificity 63.2%, PPV 61.1%, and NPV 63.2%. When the cut-off of APRI score was ≥0.398 in the detection of advanced fibrosis (F ≥3), sensitivity was 72.2%, specificity 73.7%, PPV 72.2%, and NPV 73.7%. The PPV (87%, 95%) of FIB-4 and APRI scores in predicting low fibrosis (F ≤1) and NPV (94.7%, 95.8%) in predicting advanced fibrosis (F ≥4) were found to be high. Our study yielded similar results to other studies. These scores have been confirmed to be useful, especially in detecting advanced fibrosis. When examining the correlation between age, serum AST, ALT, platelet count, APRI, and FIB-4 scores and fibrosis levels in patients, a positive correlation was found between fibrosis and AST values (p=0.015) and APRI score (p=0.047). Various studies have been conducted on many non-invasive scoring systems. However, there is not yet a scoring system that can be an alternative to liver biopsy alone (17,18,19,20,21). In our study, unlike other studies, we tried to estimate the level of fibrosis in cases that did not undergo liver biopsy and did not receive treatment. When the cut-off was 1.03 for FIB-4 and 0.358 for APRI, 36.9% of the cases according to the FIB-4 score and 16.3% according to the APRI score were found to be F ≥2.

A spontaneous loss of HBsAg occurs in approximately 0.5% of CHB patients per year and most of them develop anti-HBs. In cases of untreated CHB (>18 years of age), the incidence of cirrhosis within five years is 8% to 20%, and the risk of HCC is 2% to 5%. The main goal of treatment is to provide a permanent virological response (22). ETV, tenofovir, and tenofovir alaninamide are the preferred high-barrier oral antivirals (23). The American guidelines recommend TAF for initial treatment in adults. Tenofovir alaninamide has fewer side effects on the kidney and bone than TDF. It is easily recommended except for patients with very low creatinine clearance (24). In our study, HBsAg negativity (p=0.012) developed in 2.3% of the cases, and anti-HBs positivity (p=0.064) developed in 2% of the cases at the last control. In addition, HBV-DNA negativity increased to 63.2% (p=0.001). In the initial treatment of our cases, oral antiviral therapy with a high resistance barrier was initiated in more than 61%, in line with the literature recommendations. In 19% of the cases, treatment changes were made due to side effects. TAF, which has a low probability of side effects on bone and kidney, was preferred most frequently in the change of treatment. The mean age (p=0.001), FIB-4 (p=0.001), and APRI (p=0.001) scores were lower in the patients who did not receive treatment (n=135). Sex and efficacy of ELISA on treatment were not demonstrated. For people who have had hepatitis B virus infection in the past, the serum appears to clear HBsAg, while producing antibodies against the hepatitis B core antigen (HBcAb) detectable in their serum (25). In a study conducted in Turkey, patients with anti-HBc IgG positivity who were treated with biological agents were evaluated in terms of HBV reactivation. Reactivation was observed in only five (17.2%) of the 278 patients included in the evaluation (26). Our study found that 24 (6%) of the cases needed prophylaxis to prevent reactivation.

Study Limitations

Of course, the study has some limitations. Firstly, it is a single-center study. Therefore, it cannot be expected to reflect the country in a generalized way. Secondly, it is limited to 400 cases. The fact that the number of the biopsied group was 40 may have affected homogeneity in statistical evaluation. The

retrospective design of the study makes it difficult to access the initial presentation information of patients with long-term follow-up. Multicenter, prospective studies including large numbers of cases will reflect the population more objectively.

Conclusion

As a result, oral antivirals with high resistance barriers provided a high rate of HBV-DNA negativity. The need for treatment increased in the older age group. Particularly, due to the side effects of TDF on bone and kidneys, a treatment change is needed in one-third of cases. In line with the literature, our study found that FIB-4 and APRI scores alone are not an alternative to biopsy. However, reaching a few cases with a certain biopsy date is the weakness of the study. These scores have high NPV in differentiating advanced fibrosis. Unlike the literature, these scoring systems can be helpful in terms of biopsy in some treatment-naive cases. However, this needs to be supported by larger case series.

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Ethics

Ethics Committee Approval: Ethical approval was sought from the Ordu University Ethics Committee Unit (Black Sea Region/Ordu/Turkey) and permission was obtained with the decision of the ethics committee (approval number: 2022/220, date: 14/10/2022).

Informed Consent: Retrospective study.

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Authorship Contributions

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

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Research Article

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Impact of the COVID-19 Pandemic on the Management of Chronic Hepatitis C Infection: A Cross- Sectional Study

COVID-19 Pandemisinin Kronik Hepatit C Enfeksiyonunun Yönetimine Etkisi: Kesitsel Bir Çalışma

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ABSTRACT

Objectives: The coronavirus disease-2019 (COVID-19) pandemic have affected the chronic hepatitis elimination program globally. This study aimed to evaluate the effect of the COVID-19 pandemic on the rate of requesting hepatitis C virus (HCV) testing and the rate of initiating chronic HCV treatment, follow-up, and completion and compliance of treatment of chronic hepatitis C patients.

Materials and Methods: Between January 01, 2018 and December 12, 2021, the number of anti-HCV and HCV-RNA test requests and patients who started treatment were retrospectively evaluated. The rates of follow-up treatment compliance and treatment completion of the patients who were treated in the ınfectious diseases clinic were analyzed on a year basis.

Results: A positive anti-HCV test was found in 4,468 of 301,999 patients who underwent anti-HCV testing in 4 years. Significant reductions were observed in all three pandemic waves in both anti-HCV and HCV-RNA test requests. The data of 213 treated patients were analyzed. While the most common risk factor was intravenous drug usage, genotype 3 was determined to be the dominant genotype. While the rates of regular outpatient follow-up and completion of treatment were the lowest in 2020 (63.6% in both), no significant difference was found between years (p=0.118, p=0.087, respectively).

Conclusion: The pandemic affected the management of chronic hepatitis C. National microelimination programs should be rearranged to meet the elimination targets. In addition to the at-risk population, the whole population should be screened and training for awareness raising should be planned again for both society and physicians.

Keywords: Hepatitis C virus, chronic hepatitis C, COVID-19, management, elimination

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) salgını, küresel olarak kronik hepatit eliminasyon programını etkilemiştir. Bu çalışma ile, COVID-19 pandemisinin hepatit C virüsü (HCV) testi isteme oranına, kronik HCV tedavisine başlama, kronik hepatit C hastalarının takip ve tedavisini tamamlama ve tedaviye uyum oranlarına etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: 01 Ocak 2018-12 Aralık 2021 tarihleri arasında anti-HCV ve HCV-RNA testi istemi ve tedavi başlanan hastalar retrospektif olarak değerlendirildi. Enfeksiyon hastalıkları polikliniğinde tedavi gören hastaların takip-tedavi uyum oranları ve tedaviyi tamamlama oranları incelenerek yıl bazlı karşılaştırma yapıldı.

Bulgular: Dört yılda anti-HCV testi yaptıran 301.999 hastanın 4.468'inde anti-HCV testi pozitif bulundu. Hem anti-HCV hem de HCV-RNA test istemlerinde her üç pandemi dalgasında da önemli düşüşler tespit edildi. Tedavi edilen 213 hastaya ait veriler analiz edildi. En sık görülen risk faktörü intravenöz ilaç kullanımı iken, baskın genotip olarak genotip 3 saptandı. Poliklinikten düzenli takip ve tedaviyi tamamlama oranları 2020 yılında en düşük iken (her ikisinde de; %63,6) yıllar arasında anlamlı fark bulunmadı (sırasıyla; p=0,118, p=0,087).

Sonuç: Pandemi, kronik hepatit C yönetimini etkilemiştir. Ulusal mikro-eliminasyon programlarının eliminasyon hedeflerine ulaşacak şekilde yeniden düzenlenmesi gereklidir. Risk altındaki popülasyonun yanı sıra tüm popülasyon taranmalı ve hem toplum hem de hekimler için bilinçlendirme amaçlı eğitimler tekrar planlanmalıdır.

Anahtar Kelimeler: Hepatitis C virüs, kronik hepatit C, COVID-19, yönetim, eliminasyon

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Introduction

Chronic hepatitis C virus (HCV) infection is one of the leading causes of chronic liver disease. It is estimated that around 71 million individuals worldwide are chronically infected with HCV (1). The coronavirus disease-2019 (COVID-19) pandemic has seriously affected the global health system, and it has been determined that programs related to the prevention and control of infectious diseases have been seriously affected all over the world (2,3). One of the affected prevention programs is the chronic HCV infection elimination program. The World Health Organization (WHO) has published a global action plan for the prevention and control of viral hepatitis, aiming to prevent the transmission of hepatitis viruses, reduce complications and deaths related to viral hepatitis, improve patient care, and reduce the socio-economic negative effects of viral hepatitis in social areas (4). In May 2016, WHO established a 2016-2021 global health sector strategy on viral hepatitis. With the introduction of direct-acting antivirals (DAA), the global health sector strategy will reduce the risk of new HCV infections by 80%, HCV-related deaths by 65%, the diagnosis rate from 5 to 80%, and the rate of eligible patients to be treated from 1 to 80%.

The main elements of a successful strategy to combat viral hepatitis are prevention measures, appropriate screening, and surveillance practices that allow timely and accurate diagnosis. The American Centers for Disease Prevention and Control recommends that pregnant women be screened for hepatitis C at every pregnancy and at least once in a lifetime for all adults aged 18 years and older in areas with HCV-RNA positivity ≥0.1% (5). Since vaccine has not yet been developed for HCV, it is important to increase the diagnosis rate for elimination and evaluate patients in terms of treatment. This may lead to higher morbidity and mortality rates in individuals living with undiagnosed HCV during the pandemic, which may later be diagnosed at later stages of the disease and complications cannot be avoided (6). In addition, individuals with undiagnosed HCV continue to be a source of transmission, resulting in both patient burden and increased cost. To catch up with the pre-pandemic period, a systematic approach and more effort should be made by increasing the screening and treatment targets by 200% (7).

In this study, we aimed to evaluate the effect of the COVID-19 pandemic on the rate of requesting anti-HCV and HCV RNA tests and the rate of initiating chronic HCV treatment, follow-up, and completion of treatment.

Materials and Methods

Study Design and Patient Selection

Between January 01, 2018 and December 12, 2021, the patients whose anti-HCV test was studied in the laboratories of our hospital were evaluated. Our hospital is a tertiary training and research hospital with 1,550 beds, and chronic hepatitis C treatment is carried out in certain centers in our country, and one of these centers is our hospital. The number of anti-HCV test requests, the number of HCV-RNA tests requested from those with a positive anti-HCV test, and the number of treatments started from those with a positive HCV-RNA test were obtained by retrospective screening through the hospital automation system. The data were evaluated annually and monthly during the study period. Outcomes of adult patients aged 18 years and older who applied to the ınfectious diseases and clinical microbiology outpatient clinics in the same period and were treated with positive anti-HCV and HCV-RNA were evaluated. Compliance with the follow-up periods and treatments and the sustained virological responses (SVR) of the patients were investigated.

Definitions

The "SVR" was defined as an undetectable HCV-RNA level in serum at 12 weeks after the completion of treatment (8). Patients who did not apply to the monthly outpatient clinic control during the treatment and after completion of treatment (on months 3 and 6) were considered as "not follow-up".

Data Collection

Data regarding the patients' demographical, clinical, and laboratory characteristics, comorbid status, treatment regimens, and outcomes were obtained by retrospective review of electronic patient records.

Statistical Analysis

The data were analyzed using SPSS Statistics version 22.0 software (IBM Corp, Armonk, NY, USA). Continuous variables were evaluated for the normal distribution using the Shapiro-Wilk test. Categorical variables were expressed as frequency (n) and percentage (%), continuous variables that met the assumptions for parametric tests were presented as mean and standard deviation, and those that did not were presented as median, minimum, and maximum values. Chi-square and Fisher's exact significance tests were used in the analysis of categorical variables.

Results

The Effect of the COVID-19 Pandemic on Anti-HCV and HCV-RNA Tests

Anti-HCV testing was performed on a total of 301,999 patients, and 4,468 of them were found to be positive in 4 years. It was determined that 4,256 (95.3%) of the anti-HCV-positive patients were tested for HCV-RNA. It was found that 383 of those with 886 positive HCV RNA results had started treatment. When evaluated on a yearly basis, it was found that the rate of requesting anti-HCV and HCV-RNA and starting treatment, which increased in 2019, decreased in 2020 with the pandemic (Figure 1). Details of monthly requested anti-HCV and HCV-RNA test for 4 years are shown in Figure 2, 3. When the anti-HCV test request was evaluated, it was determined that the number of tests started to decrease in March 2020, when the first wave of the pandemic started in Turkey. The lowest rates were observed in April and May 2020. While a decrease was observed in November and December 2020 when the 2nd wave started, it was seen to have an increasing trend again in January 2021. Between May and July 2021, when the 3rd wave of the pandemic was experienced and the Delta variant dominated, there was a decreasing trend again (Figure 2). When HCV-RNA test request rates were evaluated, it was found that there was a sharper decrease than the decrease observed in anti-HCV during the same time frame (Figure 3).

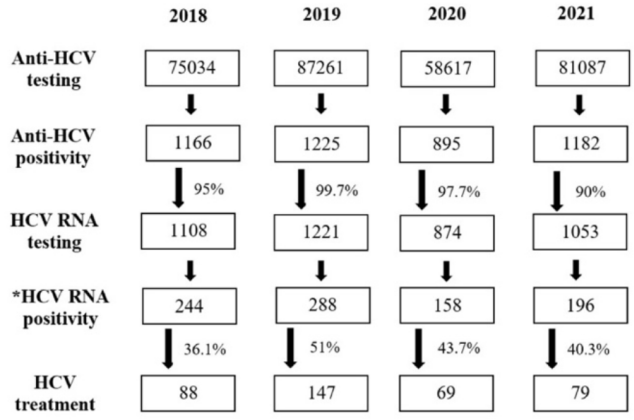

Figure 1. Evaluation of anti-hepatitis C virus (HCV), HCV-RNA test request, HCV-RNA test positivity, and chronic hepatitis C treatment initiation rates by years

*HCV-RNA was positive in 263 patients in 2018, 316 in 2019, 169 in 2020, and 212 in 2021. Patients who died before the test result and who could not start antiviral treatment because of taking immunosuppressive therapy were excluded

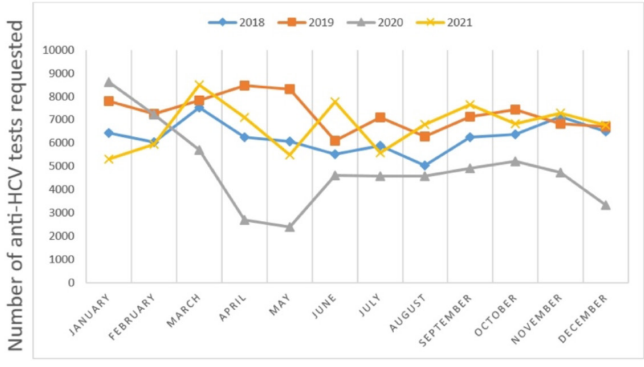

Figure 2. Monthly evaluation of anti-HCV test requests for 4 years

HCV: Hepatitis C virus

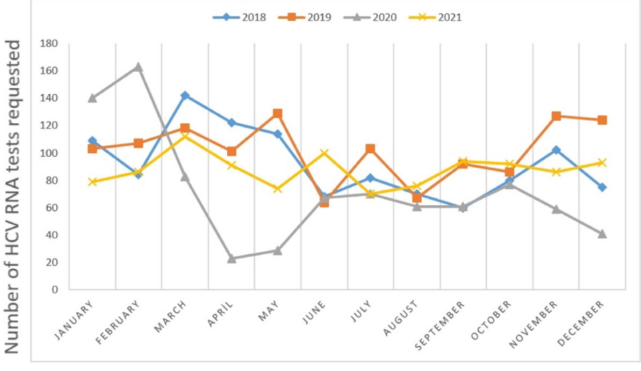

Figure 3. Monthly evaluation of HCV-RNA test requests for 4 years

HCV: Hepatitis C virus

Effect of the COVID-19 Pandemic on Treatment Management

The data of 213 patients who were treated in the infectious diseases and clinical microbiology clinic were analyzed. The median age of the patients was 30 (18-84) and 180 (4.5%) of them were male. The most common comorbid diseases were hypertension in 29 (13.6%) patients, chronic pulmonary disease in 16 (7.5%), and diabetes mellitus in 14 (6.6%). Intravenous drug usage was found to be the most common risk factor (n=151, 70.9%). The transmission route of 41 (19.2%) patients was unknown. Of the 213 patients, 151 (70.9%) were intravenous drug users (IVDUs) and 63 (29.6%) were prisoner individuals (Table 1). 40 (65.6%) patients in 2018, 69 (80.2) patients in 2019, 10 (90.9%) in 2020, and 32 (58.2) patients in 2021 were IVDU. When the genotype distributions were examined, it was determined that 93 (43.7%) patients were genotype 3, 47 (22.1) patients were genotype 1B, 29 (13.6%) were genotype 2, and 21 (9.9%) were genotype 1A. Infection with two different genotypes was detected in 22 patients. In one patient, there were 3 different genotypes as 1A, 2, and 3.

When the rates of compliance with the regular outpatient clinic controls of the patients whose treatment was initiated were analyzed yearly, it was found that it was at the lowest level in 2020 compared to other years (63.6%). However, no statistically significant difference was found between years in compliance rates (p=0.118). When the rate of completion of antiviral treatment was evaluated, there was no statistically significant difference between years (p=0.087), while the rate was lower in 2020 (63.6%) compared to other years (Table 2).

Discussion

Before the COVID-19 pandemic, the national elimination program in our country was created with the joint action of the Ministry of Health of the Republic of Turkey and associations, and in this context, practices such as awareness training for family physicians and screening of prisoners were initiated. In 2019, it was observed that the effects of these practices emerged, and increases in the rate of diagnosis and treatment were obtained (9). The hepatitis elimination program has been disrupted because of COVID-19 causing a major worldwide epidemic, and the vast majority of healthcare practices and opportunities are being used to combat this disease. With the COVID-19 pandemic, the delay in the diagnosis and treatment of hepatitis C is predicted to cause approximately 44,800 liver cancer and 72,300 HCV-related deaths by 2030 (6).

In our study, the year 2021 was evaluated and the pre-pandemic and early period of the pandemic. Our evaluation is not only based on tests but also on the rates of starting treatment, applying for regular follow-up, and completing treatment. In other words, the management of chronic hepatitis C was evaluated as a whole from a different perspective. Although it is a single center, it is seen that the number of cases included in our study is substantial.

With the introduction of national HCV microelimination programs in 2019, it is obvious that the rates of test requests and treatment initiation increased in our center compared to 2018. In 2020, with the effect of the pandemic, a decrease in test request rates was detected, and the negative effect of the pandemic

Table 1. Demographic and clinic characteristics of patients treated in infectious diseases clinic (n=213)	
The number of patients by year, n (%)	
2018	61 (28.6)
2019	86 (40.4)
2020	11 (5.2)
2021	55 (25.8)
Age, median (minimum-maximum)	30 (18-84)
2018	28 (18-77)
2019	31.5 (20-84)
2020	27 (22-59)
2021	33 (21-83)
Sex, n (%)	
Male	180 (84.5)
Female	33 (15.5)
Transmission route, n (%)	
Opioid/intravenous drug usage	151 (70.9)
Surgical procedure	6 (2.8)
Dental procedure	6 (2.8)
Blood/blood product transfusion	3 (1.4)
Hemodialysis	3 (1.4)
Occupational	3 (1.4)
Unknown route	41 (19.2)
HBV co-infection, n (%)	5 (2.3)
Comorbid diseases, n (%)	
Hypertension	29 (13.6)
Chronic pulmonary disease	16 (7.5)
Diabetes mellitus	14 (6.6)
Coronary artery disease	10 (4.7)
Cardiac failure	4 (1.9)
No comorbidity	167 (78.4)
Treatment, n (%)	
Naive	202 (94.8)
Non-naive	11 (5.2)
The treatment regimen, n (%)	
Glecaprevir + pibrentasvir	133 (62.4)
Sofosbuvir + ribavirin	31 (14.6)
Ombitasvir/paritaprevir/ritonavir + dasabuvir	27 (12.7)
Ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin	14 (6.6)
Sofosbuvir + ledipasvir + ribavirin	3 (1.4)
Sofosbuvir + ledipasvir	3 (1.4)
Ombitasvir/paritaprevir/ritonavir + ribavirin	2 (0.9)
The sustained virological response*, n (%)	
2018	56 (91.8)
2019	75 (84.3)
2020	7 (63.6)
2021	51 (92.7)
*The virological response of 4 patients each year could not be evaluated. HBV: Hepatitis B virus	

on the diagnosis, treatment, and management of chronic HCV infection has been shown in many studies (10,11,12,13). In the study of Mandel et al. (10), it was shown that there was a serious decrease in the number of anti-HCV and HCV-RNA tests in all three waves of the pandemic. Similar findings were obtained in our study. In particular, the decrease in the number of HCV-RNA tests in the first and second waves of the pandemic was remarkable. Especially in the first wave of the pandemic, the postponement of elective surgical interventions and the low rate of admission to outpatient clinics outside the emergency services are thought to directly affect the number of anti-HCV and HCV-RNA test requests. In another study, Schorr et al. (14) conducted a modeling study on the chronic hepatitis C microelimination program, and they predicted that in one scenario, there might be a 50% increase in HCV-related mortality in 2030, with the decrease in the number of patients to be treated with the effect of COVID-19 in the long term. In a survey conducted by the European Association for the Study of the Liver in Europe and non-European countries, it has been shown that there is a significant decrease in the number of HCV consultations, HCV RNA test requests, and HCV treatment initiation during the pandemic period (15). In a study from our country, it was found that the number of anti-HCV and HCV-RNA tests requested from different clinical disciplines decreased during the COVID-19 period (16).

The pandemic has affected not only the test request for HCV but also the number of patients in whom treatment was initiated and the compliance of patients with treatment (17,18,19). In our study, in which we obtained similar results, the number of patients who received treatment and adherence to treatment, regular outpatient visits, and completion of treatment was found to be lower in 2020, even if there was no statistically significant difference. When we examined the distribution of the ages of the treated patients by years, it was determined that the age range in 2020 consisted of younger patients. In the study of Barutçu et al. (16), HCV test requests were grouped according to age, and it was determined that the number of tests in patients aged 65 and over decreased significantly during the pandemic period (p=0.004). Restrictions and curfews for the 65-year-old and older group in our country for a long time and the elderly patients' unwillingness to apply to the hospital except for emergencies have reduced the number of applications to health institutions. When we evaluate 2021, although it is thought that the pandemic affected 2020, its effects continued in 2021 as well. With the resumption of elective surgeries that could not be performed in 2020, there has been an increase in anti-HCV test requests, but this increase was not reflected in HCV-RNA test requests in 2021. Since the surgical intervention of these patients was prioritized, there was a disruption in requesting HCV-RNA testing and directing the patients to the relevant branches. In the same year, although the HCV-RNA test request was low, the number of patients who started treatment, followed up, and obtained SVR increased, and compliance with treatment was found to be higher. Awareness training was planned to canalize patients with positive anti-HCV results to relevant clinics such as ınfectious diseases and gastroenterology.

Table 2. Evaluation of patients who started treatment in the ınfectious diseases clinic in terms of regular follow-up and completion of treatment

	The regular follow-up, n (%)	p-value	Completing the treatment, n (%)	p-value
2018, (n=61)	51 (83.6)	0.118	54 (88.5)	0.087
2019, (n=89)	69 (80.2)		71 (82.6)	
2020, (n=11)	7 (63.6)		7 (63.6)	
2021, (n=55)	50 (90.9)		50 (90.9)	

70.9% of the patients we treated consisted of IVDU patients. A study evaluating IVDUs found higher rates of syringe reuse, alcohol consumption, and greater reductions in syringe utility programs and buprenorphine use during the pandemic (20). Therefore, the reflection of the pandemic, especially in IVDUs, is expected to emerge more clearly in the future. The fact is that a significant portion of our patients are prisoners (29.6%) and that they were isolated in solitary cells for 15 days after the hospital examination, especially in the first and second waves of COVID-19. This situation caused these individuals not to want to go to the hospital, and this contributed to the decrease in the number of patients who applied for and received treatment in 2020. Unless the risky behavior was stopped, either the treatment of the patients can not be completed or reinfection were observed. These patients should first be provided with professional support for addiction therapy and cooperate with an experienced psychiatrist/psychiatrist and their family.

Although we were caught unprepared for the COVID-19 pandemic, there are also studies showing that chronic hepatitis C treatment and patient follow-up can be successfully carried out with telemedicine application in this process (21,22). In one of these studies, telemedicine application in the follow-up and treatment of 41 chronic hepatitis C patients during the lockdown period in Romania achieved 100% success in the rate of treatment compliance and SVR. When compared with the results in 2019, it is seen that there is a statistically significant difference in terms of adherence to treatment ($p<0.0001$) (22). Considering the disruptions experienced in the follow-up and treatment of these patients during the pandemic, similar action plans should be created for adverse situations that may occur in the health system.

Study Limitations

There are some limitations to this study. It was single-centered, retrospective and had a relatively small sample size.

Conclusion

The pandemic had a negative impact on the diagnosis, treatment, and management of chronic hepatitis C, and it was predicted that the planned elimination targets would not be realized until 2030. It is a clear fact that more effort is required to meet the elimination targets. For this, national microelimination programs should be reviewed and rearranged, awareness training should be emphasized again, and the effectiveness of DAA treatments should be emphasized. Both technical and financial support should be provided to the health system in this regard. Conducting surveillance on the whole population as well as on risky groups such as IVDUs and prisoners will achieve the elimination target.

Ethics

Ethics Committee Approval: Ethics committee approval was received from the Adana City Training and Research Hospital Ethics Committee (approval number: 10.05.2022/1931). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.A.G., T.T., E.O., H.K., N.Ü., Design: T.A.G., T.T., E.O., H.K., N.Ü., Data Collection and Processing: T.A.G., T.T., E.O., H.K., N.Ü., Analysis or Interpretation: T.A.G., T.T., E.O., H.K., N.Ü., Literature Search: T.A.G., T.T., E.O., H.K., N.Ü., Writing: T.A.G., T.T., E.O., H.K., N.Ü.

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Letter to the Editor

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Orthohepevirus C (Rocahpevirus Ratti): A New Human Threat

Ortohepevirüs C (Rocahpevirüs Ratti): Yeni Bir İnsan Tehdidi

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Dear Editor;

Orthohepevirus C, currently known as Rocahepevirus ratti, is an RNA virus belonging to the Hepeviridae family and can cause hepatitis E infection in mammals. Rocahepevirus ratti is commonly found in various animals, including humans, and is also referred to as "animal hepatitis E" (1).

Orthohepevirus includes 4 species according to ICTV: Orthohepevirus A [Paslahepevirus balayani-hepatitis E virus (HEV)], B (Avihepevirus-a-HEV), C (Rocahepevirus ratti), and D (Chirohepevirus-Ch-HEV). Orthohepevirus A, known as HEV. According to their genome sequences, HEVs are divided into 8 main genotypes. Genotypes 1 and 2 may be limited to humans through consumption of fecal contaminated water in Asian and African countries, while genotypes 3-8 are zoonotic agents with a worldwide distribution among humans and a large number of mammals through consumption of raw or undercooked meat (1).

The other 3 Hepeviridae genus appeared devoid of zoonotic threat and their circulation appeared restricted to their main hosts: Orthohepevirus B in birds, Orthohepevirus C in mustelids and rodents, and Orthohepevirus D in bats. However, in 2018, a case of rat HEV infection was reported in a liver transplant recipient in Hong Kong, after which 7 more cases of episodic human Rocahepevirus ratti infection were identified in a large scan in the same setting. Subsequently, the number of cases have increased above 20 in Asia and Europe (1,2).

Rocahepevirus ratti can be transmitted in different ways depending on the economic conditions, sanitation conditions, and hygiene practices of the countries. It is usually spread through the consumption of contaminated water or food. It can also be transmitted through contact. Rocahepevirus ratti infection is often mild or asymptomatic. However, in some cases, the infection can lead to liver damage and chronic hepatitis E. Chronic HEV infection can cause serious liver problems, particularly in people with compromised immune systems. There is no cure for Rocahepevirus ratti, but symptomatic treatments are available. Liver transplantation may be required in cases of chronic hepatitis E, particularly in people with compromised immune systems (3,4).

The genomic structure of Rocahepevirus ratti consists of an RNA molecule with a length of about 7.2-7.5 kilobases. This RNA molecule is divided into three regions called open reading frames: ORF1, ORF2, and ORF3. ORF1 encodes a protein called a polyprotein and contains the enzymes needed for the virus to replicate and multiply. ORF2 encodes a protein called the capsid protein and forms the outer surface of the virus. ORF3 encodes a protein that plays a role in virus replication (1,2,3).

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Rocahepevirus ratti showed signs of hepatitis in infected animals. These can include symptoms such as liver damage, jaundice, diarrhea, and inflammation of the liver. People can become infected with Rocahepevirus ratti and show symptoms similar to HEV infection (1,2,3,4).

There was no specific treatment against Rocahepevirus ratti. However, vaccines are being developed to prevent infection. To prevent Rocahepevirus ratti infection, access to clean water and hygienic living conditions are recommended (1,2,3,4).

Laboratory diagnosis of Rocahepevirus ratti infection is made through the analysis of clinical samples such as blood, serum, urine, stool, liver biopsy, bile samples, and other body fluids from a patient with symptoms of the disease caused by the virus.

The diagnosis of Rocahepevirus ratti is usually made by serological tests and molecular methods. Serological tests (ELISA and Western blot) determine the presence of the virus based on antibodies. However, these tests may be insufficient in the early stages of the disease, as antibodies are formed weeks and months after infection. Molecular methods, especially polymerase chain reaction-based tests, can detect Rocahepevirus ratti RNA very sensitively and give results even in the early stages of infection (1,2,3,4,5). However, the diagnosis of Rocahepevirus ratti infection should be made by a holistic assessment based on clinical signs and other laboratory tests.

Rocahepevirus ratti and HEV can sometimes be confused and cause similar symptoms. However, these two viruses belong to different virus families and have different genetic makeups (2,3,4).

The infection symptoms of both agents are similar: weakness, loss of appetite, abdominal pain, nausea, vomiting and jaundice. However, differences can be seen during the disease and their treatments are also different.

Rocahepevirus ratti infection is usually self-limiting and most people get over the disease without realizing it. However, in some cases, it can become chronic and cause liver damage. HEV infection is likewise transient on its own, but can have serious consequences in pregnancy and in people with chronic liver disease (1,2,3,4,5). Becasue the recent zoonotic potential of Rocahepevirus ratti, the associatted syndroms and risk population need to be clearified.

To summarize, Rocahepevirus ratti and HEV belong to the same virus family (hepeviridae), can cause similar symptoms and can be confused with each other. Therefore, the specific molecular diagnosis should be applied for HEV and Rocahepevirus ratti. There is no current cure for HEV and Rocahepevirus ratti. Therefore, the type of infection does not much change treatment or clinical management much.

Rocahepevirus ratti has currently only been identified in Hong Kong, Spain, and France (1). Risk factors for Rocahepevirus ratti include:

1. Animal contact: Rocahepevirus ratti can be found in animals (rodents and cattle,etc.), and contact with animals may increase the risk of infection.

2. Immunosuppressive people: Rocahepevirus ratti infection may be more serious in people with weakened immune systems. In particular, organ transplant patients, people with human immunodeficiency virus infection, and patients receiving chemotherapy or immunosuppressive drugs are at higher risk to developing a chronic Rocahepevirus ratti.

3. Blood or blood product transfusion: Patients who are transfused with blood or blood products might be at risk for Rocahepevirus ratti infection.

Given these risk factors, appropriate laboratory testing should be performed in persons with suspected Rocahepevirus ratti infection. People with symptoms, transfusions of blood or blood products, those with compromised immune systems, people with animal contact, or those who consume contaminated food are at risk and are advised to get tested in consultation with their doctor.

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