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AIM AND SCOPE

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

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

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

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

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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.

The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org.

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.

The name of the institution where the authors work and the name of the institution or the department in which the study has been conducted should not be mentioned in the submitted manuscript.

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.

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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.

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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).

MANUSCRIPT PREPARATION

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

• Research articles and article collections should not exceed 15 pages including the text, figures, tables and references, while short announcements and case report presentations should not be longer than 5 pages.

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

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

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.

• All abbrevations used, must be listed in explanation which will be placed at the bottom of each figure, picture, table and graphic.

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• Pictures/photographs must be in color, clear and with appropriate contrast to separate details.

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.

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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.

• Manuscripts lacking any of the above elements will be rejected from the production process.

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VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

CONTENTS

RESEARCH ARTICLES

VIRAL HEPATITIS SOCIETY

Viral Hepatitis Journal

VİRAL HEPATİT DERGİSİ

CONTENTS

Research Article

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Viral Hepatitis Journal 2021;27(2):36-41

The Etiology and Clinical Follow-up of Patients with Acute Viral Hepatitis in an Adult Population: A Prospective Multi-center Study

Erişkin Popülasyonda Akut Viral Hepatitli Hastaların Etiyolojisi ve Klinik Takibi: Prospektif Çok Merkezli Bir Çalışma

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ABSTRACT

Objectives: To assess the causes, patient characteristics, clinical follow-up of acute viral hepatitis in adults.

Materials and Methods: This prospective study is conducted in acute viral hepatitis patients from different centers across Turkey.

Results: From 8 hospitals in 6 provinces, 75 patients (59 males/79%) between 20 and 69 years of age (mean age: 34.65±11.82 years) with proven viral hepatitis were included into the study. There were 54 (72%) patients with acute hepatitis B virus (HBV), 19 (25%) with acute hepatitis A virus (HAV), 1 (1.3%) with acute Epstein-Barr virus, and 1 (1.3%) with acute cytomegalovirus infection. Patients between 23-33 years of age represented that greater majority of the patient group (41.3%), followed by those between 34 and 43 years of age (20%). The mean age among acute HAV patients, i.e. 27±5.7 years (20-38 y) was significantly (p<0.001) lower than the mean age of 37.6±12.2 years (20-69 y) acute HBV group. Of 51 isolated acute HBV patients: 44 (86%) developed immunity during the follow up [anti-hepatitis B core antibody immunoglobulin G (anti-HBc IgG) and

ÖZ

Amaç: Erişkinlerde akut viral hepatitin nedenlerini, hasta özelliklerini ve klinik takibini değerlendirmektir.

Gereç ve Yöntemler: Bu prospektif çalışma, Türkiye genelinde farklı merkezlerden akut viral hepatitli hastalarda yapılmıştır.

Bulgular: Altı ildeki 8 hastaneden, 20-69 yaşları arasında (ortalama yaş: 34,65±11,82) viral hepatiti kanıtlanmış 75 hasta (59 erkek/%79) çalışmaya dahil edildi. Akut hepatit B virüslü (HBV) 54 (%72), akut hepatit A virüslü (HAV) 19 (%25), akut Epstein Barr virüslü (EBV) 1 (%1,3) ve akut sitomegalovirüs enfeksiyonlu 1 (%1,3) hasta vardı. Hasta grubunun büyük çoğunluğunu 23-33 yaş arası hastalar (%41,3) temsil etmekteydi ve bunu 34-43 yaş arasındakiler (%20) izlemekteydi. Akut HAV hastaları arasındaki ortalama yaş, yani 27±5,7 yıl (20-38 yıl), akut HBV grubunun ortalama yaşı 37,6±12,2 yıldan (20-69 yıl) önemli ölçüde (p<0,001) daha düşüktü. Takip sırasında 51 izole akut HBV hastasının 44'ünde (%86 bağışıklık gelişti anti-hepatit B çekirdek antikoru immünoglobulin G (anti-HBc IgG) ve anti-HBs pozitifliği). İzole anti-HBc IgG pozitifliği 4 hastada (%8) görüldü ve 3

Tosun S, Albayrak A, Durmuş G, Çetin Altaş İ, Özel AS, Tülek N, Kadanalı A, Erol S, Altunçekiç Yıldırım A, Ceran N, Dağlı Ö, Olut AI. Viral Hepat J. 2021;27:36-41.

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ABSTRACT

anti-HBs positivity], while isolated anti-HBc IgG positivity persisted in 4 patients (8%) and 3 patients (%6) were considered as chronic HBV infection due to persistence of hepatitis B surface antigen positivity beyond 6 months.

Conclusion: Acute HBV infection remains an important health problem in our country, and horizontal and sexual transmission became the predominant routes of transmission for HBV. Also, acute HAV infection is a prevalent condition in young adults.

Keywords: Acute viral hepatitis, hepatitis A virus, hepatitis B virus

ÖZ

hasta (%) hepatit B yüzey antijeni pozitifliğinin 6 aydan uzun sürmesi nedeniyle kronik HBV enfeksiyonu olarak kabul edildi.

Sonuç: Akut HBV enfeksiyonu ülkemizde önemli bir sağlık sorunu olmaya devam etmektedir ve yatay ve cinsel yolla bulaşma HBV'nin baskın bulaşma yolları haline gelmiştir. Ayrıca akut HAV enfeksiyonu genç erişkinlerde yaygın bir durumdur.

Anahtar Kelimeler: Akut viral hepatit, hepatit A virüsü, hepatit B virüsü

Introduction

According to the information provided by the World Health Organization (WHO), there are an estimated 325 million chronic hepatitis [hepatitis B virus (HBV) + hepatitis C virus (HCV)] cases globally in 2015. Again, as reported by the WHO, an estimated 7,134 fatalities due to hepatitis A occurred in 2016, comprising 0.5% of all deaths associated with viral hepatitis. Annual number deaths due to HBV-related complications is around 900,000 (1,2,3,4). In a review estimating the global morbidity and mortality of acute viral hepatitis, cirrhosis due to viral hepatitis, and hepatocellular carcinoma (HCC) prevalence using global disease burden data, it has been reported that the global number of deaths due to viral hepatitis increased from 0.89 million to 1.45 million between 1990 and 2013, and that while viral hepatitis was the 10th most common cause of death in 1990, it was the 7th most common cause of death in 2013. The authors explained this increase on the basis of an increased number of cases presenting with chronic complications such as hepatic failure, cirrhosis, or HCC, emphasizing the need for more widespread vaccination, effective preventive strategies, and increased access to therapy (5).

Viral hepatitis A and B are the most common type of viral hepatitis in our country. National hepatitis B vaccination program initiated in 1998 to target newborns and at-risk individuals followed by the routine vaccination against hepatitis A again in newborns and at-risk individuals (e.g. healthcare workers, medical trainees, chronic hepatitis patients) have contributed significantly to the reduced number of hepatitis due to these two viral agents. Other cases of primary viral hepatitis due to hepatitis C, hepatitis D, hepatitis E, Epstein-Barr, herpes simplex, varicella-zoster, enterovirus, adenovirus, and measles-mumps-rubella viruses are less frequent. Updated national epidemiological data is important for reducing the burden associated with viral hepatitis.

This multi-center, prospective study conducted across different sites in our country over a one-year period aimed at assessing the causes of acute viral hepatitis, patient characteristics, and prognosis in an adult cohort.

Materials and Methods

This multi-center study was conducted at 8 hospitals in 6 provinces between 1 May 2016 and 30 June 2017 after ethics committee approval by the Local Ethics Committee, University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (approval number: 1, date: 09.02.2016). Informed consent forms were obtained from all patients included in the study. Patients over 18 years of age presenting with clinical signs and symptoms of acute hepatitis were included. Sociodemographic data, complaints at presentation, clinical signs, laboratory results, potential routes of transmission, clinical course, treatments administered, complications, prognosis, and follow-up results after discharge were recorded. All patients were prospectively followed weekly during the 1st month, and then HBV patients were asked to attend follow-up visits at 3, 6, and 12 months post-discharge. The following routine tests were performed in patients with symptoms and signs suggestive of acute viral hepatitis: complete blood count, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (GGT), total and indirect bilirubin, international normalized ratio (INR), abdominal ultrasound, anti-HAV IgM and IgG, hepatitis B surface antigen (HBsAg), anti-HBc IgM [in those with HBsAg positivity, also anti-HBc IgG, hepatitis B e antigen (HBeAg), anti-HBe, HBV-DNA, delta antigen and antibody], toxoplasma IgM and G, cytomegalovirus (CMV) IgM and G, EBV virus capsid antigen (VCA) IgM and G, anti-hepatitis E virus (HEV) IgM and G were tested for diagnostic purposes.

Statistical Analysis

Statistical analyses were performed with JAMOVI (Version 1.1.5.0) software for Windows. Descriptive data were expressed as number and percentage (n and %) for categorical variables, and mean, standard deviation, minimum, and maximum for numerical variables. Comparison of categorical data for independent groups was done with chi-square test. The distribution of the numerical data was evaluated using Kolmogorov-Smirnov test. For independent groups, the numerical data were compared with Student's t-test and Repeated Measures Variance Analysis. Data without normal distribution were assessed with Mann-Whitney U test, Kruskal-Wallis test, non-parametric Friedman's test, and Wilcoxon test. The statistical alpha level of significance was set at a p value of <0.05.

Results

A total of 75 patients (69 males/92%) between 20 and 69 years of age (mean age: 34.65±11.8 years) with proven viral hepatitis were included. There were 19 patients (25%) with acute HAV, 54 (72%) with acute HBV, one (1.3%) with acute EBV, and one (1.3%) acute CMV infection. No cases of HCV, HEV or toxoplasma were identified.

Patients between 23-33 years of age represented that greater majority of the patient group (41.3%), followed by those between 34 and 43 years of age (20%), 44 and 53 years of age (18.7%), and 20 and 22 years of age (16%). However, there was a significant age difference when the specific types of hepatitis were taken into consideration. Thus, most of the patients with acute HAV infection were between 23 and 33 years of age (47.3%), mostly between 20 and 22 years of age (42%) and there were no patients in >44 age groups. Most cases of acute HBV infection were between 23 and 33 years of age (39%), followed by those between 44-53 years of age (26%), 34-43 years of age (22%), 20-22 years of age (7.4%), and those above 64 years of age (5.6%). The mean age among acute HAV patients, i.e. 27±5.7 years (20-38 y) was significantly (p<0.001) lower as compared to the mean age of 37.6±12.2 years (20-69 y) in acute HBV group (Table 1).

A socio-demographic data analysis was also made in this study.

There were 47 (62.7%) white-collar and 22 (29.3%) blue-collar employees in the study group, whereas 6 (8%) were unemployed. With regard to education, there were 5 (6.7%) illiterate individuals, 16 (21.3%) primary school graduates, 39 (52%) secondary school graduates, and 15 (20%) university graduates. Although no statistical association between educational status and the type of hepatitis could be detected, there was a trend toward higher educational level among acute HAV cases than acute HBV cases (proportion of just literate-illiterate, primary school, secondary school, and university degree among acute HAV cases: 5.2%, 15.7%, 52.6%, and 26.3%, respectively; the corresponding figures in HBV group were 7.4%, 24%, 51.8%, and 16.7%, respectively). No associations were observed between occupational category and the type of hepatitis (p=0.255), although there were more blue-collar workers in the acute HBV group.

Only three patients (two with acute HBV, and one with EBV) were treated as outpatients and 72 as (96%) inpatients. The median duration of hospital stay was 13.5±8 days (4-21 days). Most patients presented within 3 to 7 days of the onset of symptoms. Underlying/comorbid conditions included malignancy (lung cancer) in 1, diabetes mellitus in 3, Down's syndrome in 1, chronic renal failure in 1, epilepsy in 2, and gall bladder stones in 1. One male patient admitted with acute HBV + human immunodeficiency virus (HIV) infection, two male patients admitted with primary syphilis + acute HBV infection.

Possible routes of transmission could be detected in 10 of the 19 (52.6%) acute HAV patients (suspected beverage/food consumption in 9, domestic travel history in another). Among HBV patients, possible risk factors could be detected in 23 (42.9%), including presence of chronic HBV infection in household members in 3 and in close family members in 2, penetrating injury in 2 (blood sugar measurement with lancet in a patient with chronic hepatitis B infection), and contact with blood or body fluids in 15. No risk factors could be found in 31 (57.4%) of the acute HBV cases. In three acute HBV cases with suspicious history of sexual intercourse, two had 1st stage syphilis, and one had acute retroviral syndrome.

There were no significant seasonal differences in the distribution of acute HAV patients (spring 3, summer 6, autumn 4, winter 5), while there were more acute HBV cases during autumn and winter (spring 9, summer 13, autumn 18, winter 16).

The most common symptom at presentation was malaise (88%) followed by urine darkening (80%), apetite loss (78%) jaundice and nausea (77%). Symptoms were given at Table 2.

The most common clinical examination findings included the following: icteric course in 51 patients (68.1%; 12 HAV, 38 HBV, 1 CMV), anicteric course without scleral jaundice in 13 patients (17.3%; 4 HAV, 8 HBV, and 1 EBV), sub-icteric course in 11 patients (14.6%; 3 HAV, 8 HBV), fever in 13 patients (17.3%), hepatomegaly in 14 patients (18.7%; HAV 4), splenomegaly in 2 (2.7%, HBV), hepatosplenomegaly in 7 patients (9.3%, one HAV).

Laboratory findings were as follows at day 0; among acute HAV patients, mean ALT: 2,177 IU/mL, AST: 1,398, GGT: 242, total bilirubin: 8.84, INR: 1,24, white blood cell (WBC): 6,920, platelet count: 221,000. The corresponding values in acute HBV patients were as follows: ALT: 1,967 IU/mL, AST: 1,431, GGT: 216, total bilirubin: 8.24; INR: 1,2; WBC: 7,590, platelet count: 236,220 (Figure 1, 2).

Mean ALT values were significantly different between acute HAV and acute HBV hepatitis patients, with a more rapid regression in ALT in acute HAV patients (p=0.002, p<0.005-F=6.32). When the decline in mean AST during the first 7 day period was evaluated, a significantly more rapid decline was found in acute HAV patients as compared to acute HBV patients (p<0.001). However, the decline in AST from day 7 to day 14 did not differ significantly between HAV and HBV patients (for HAV p=0.05, for HBV p>0.05. On the other hand, the rate of decrease in AST levels after day 14 among acute HAV patients was significantly less marked than those with acute HBV (p<0.001). Again, the rate of decline in mean GGT from day 0 to 7 was also significantly different between acute HAV and acute HBV hepatitis patients. Among acute HAV patients, there was a significantly (p<0.05) more rapid decline of GGT in the first 7-day period as compared to HBV patients, while no significant differences between HAV and HBV patients were observed thereafter (p>0.05) (Figure 1, 2).

Table 1. Distribution of cases with acute HAV and HBV by age groups

Age groups	Acute HAV cases (n/%)	Acute HBV cases	Total*
20-22	8 (42%)	4 (7.5%)	12 (16%)
23-33	9 (%47%)	21 (39%)	30 (41%)
34-43	2 (%11%)	12 (22%)	14 (20%)
44-53	0	14 (26%)	14 (19%)
54-63	0	0	0
>64	0	3 (5.6%)	3 (4%)
	19	54	73

**One male patient born in 1990 with acute EBV and one male born in 1979 with acute CMV infection is not included in the table.
HAV: Hepatitis A virus, HBV: Hepatitis B virus, EBV: Epstein Barr virus, CMV: Cytomegalovirus

Table 2. Complaints of acute viral hepatitis patients at admission (in order of frequency)						
Complaints at admission	**HAV (n=19)**	**HBV (n=54)**	**EBV (n=1)**	**CMV (n=1)**	**Total (n=75)**	**%**
Weakness	18	46	1	1	66	88
Urine darkening-tea-like color	15	45			60	80
Loss of appetite	16	41	1	1	59	78.6
Jaundice	15	43			58	77.3
Nausea	16	41		1	58	77.3
Vomiting	14	24		1	39	52
Abdominal pain	10	16		1	27	36
Muscle pain	7	18		1	26	34.6
Acholic stool	11	14			25	33.3
Headache	10	11	1	1	23	30.6
Flu-like symptoms	8	12	1		21	28
Itching	5	14			19	25.3
Fever	11	6			17	22.6
Dizziness	5	11			16	21.3
Constipation	3	7			10	13.3
Diarrhea	1	4			5	6.6
Examination findings						
Sclera/skin normal	4 (21%)	8 (15%)	1			9 (12%)
Sclera/skin subicteric	3 (15.8%)	8 (15%)		1		12 (16%)
Sclera/skin icteric	12 (63%)	38 (70.5%)				40 (53%)
Hepatomegaly	1 (5.3%)	10 (18.5%)				11 (15%)
Splenomegaly	0	2 (3.7%)				2 (2.7%)
Hepato-splenomegaly	0	6 (11.1%)				6 (8%)

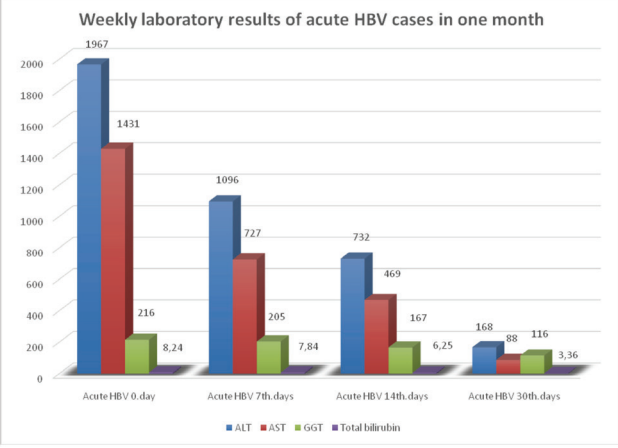

Figure 1. Weekly laboratory results of acute HBV cases in one month
HAV: Hepatitis B virus

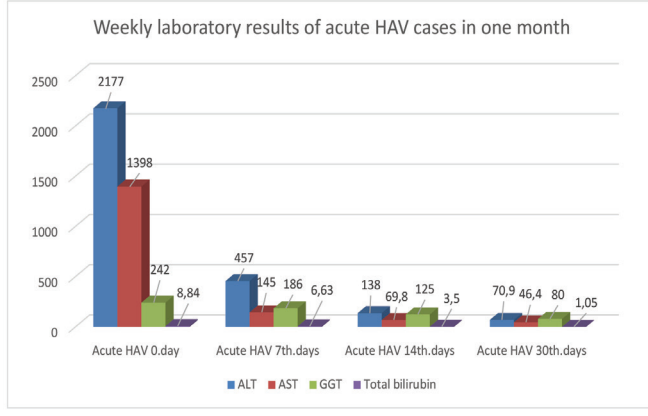

Figure 2. Weekly laboratory results of acute HAV cases in one month
HAV: Hepatitis B virus

With regard to prognostic indicators, 2 of the 19 acute HAV patients developed cholestasis, which resolved rapidly. All acute HAV patients improved during the follow-up period, with normalization of laboratory values with a maximum delay of 2 months.

Of 51 isolated acute HBV patients, 44 (86%) developed immunity during the follow up (anti-HBc IgG and anti-HBs positivity), while isolated anti-HBc IgG positivity persisted in 4 patients (8%), with no anti-HBs and 3 patients (6%) were considered as chronic HBV infection due to persistence of HBsAg positivity beyond 6 months. One patient with HBV + HIV co-infection was referred to a liver transplant center, but the patient died before transplantation.

Discussion

According to the 1994 National Viral Hepatitis Report from Turkey, there were 27,474 reports of adult acute viral hepatitis in

1,989, and 19,518 in 1,992, most of which were due to acute HBV, followed by acute HAV infection (6). In our study group of 75 adult patients with proven viral hepatitis, most of the cases were due to (72%) acute HBV infection followed by acute HAV infection (25%). In a comprehensive review of epidemiological analysis of viral hepatitis in Turkey, most cases of acute HAV occurred in children, and HBV in adults, during the period between 1985 and 2000 (7). Again, in a recent 2018 review on hepatitis B etiology in Turkey, it was emphasized that although there were acute HBV reports in infants between 1996-2000, no acute HBV was reported in that age group after year 2005, with very low rates in children aged 1 to 4 years with a subsequent increase among those aged 15-19 years, reaching a peak in 30-44 years, followed in frequency by those aged 20-29 years, 45-64 years, and >65 years (8). As explained in both reviews, the most common etiological factor for acute hepatitis among adults was HBV, followed by HAV, a special emphasis was made on the fact that there was a striking decrease in acute HBV incidence in children and adolescents in close association with the national HBV vaccination program (8). In another 2011 review looking at the causes of acute hepatic failure in children and adults in Turkey, a total of 308 patients were analyzed between the ages of 1 month and 75 years from 41 studies conducted between 1998 and 2010. In that review, HAV was the most common (20.9%) cause of acute hepatic failure in children, while it was HBV (34.7%) in adults. The mean age of the 98 adult patients with acute hepatic failure was 36 years (17-75 y), and 68% of the patients were female. A total of 39 etiological agents were identified, 34 of which were HBV, 4 were HAV, and one was CMV hepatitis (9).

Over the recent years, some studies examining the etiology of acute hepatitis in adult patients both HAV and HBV infections were more common among males (10,11,12,13,14,15,16,17). In line with these observations, males comprised the great majority of the cases in our study (n=59, 79%), with 48 acute HBV and 11 acute HAV infection.

While in some studies an association between the type of hepatitis and seasons was reported, with more common occurrence of these infections during autumn or winter, no such associations were observed in some others. In the current study, although there was no significant seasonality in acute HAV infections, there were more patients diagnosed with acute HBV infection during autumn and winter months. This might reflect the small number of acute HAV patients included. Despite no significant association between the type of hepatitis and socio-demographic data was observed, patients with acute HAV infection tended to have higher educational level, patients with acute HBV were more likely to be blue-collar workers in our study.

The presenting symptoms in our patient group were consistent with literature reports. The most common of these were malaise, dark urine, jaundice, loss of appetite, nausea, and vomiting, with other symptoms being less frequent. While 68.1% of the patients reported jaundice, anicteric disease course was detected in 17.3%, and sub-icteric in 14.6% during the physical examination.

In many previous studies possible routes of transmission for these conditions could be poorly defined, with only a minority of studies reporting clear-cut results. In the present study, possible risk factors could be identified in near half of the patients either with acute HAV or acute HBV infection. Since all previously published studies from our country are of retrospective nature, this is not an unsurprising finding. We believe that the prospective design of our study may at least partially explain the higher rates of detection for possible routes of transmission.

The reported prognosis and complications in patients with acute viral hepatitis show little variation between studies. Cholestasis has been relatively more frequently reported in previous studies of acute HAV patients in Turkey; again fulminant disease course and acute hepatic failure were relatively more frequent among acute HBV patients, who also had a higher mortality. Although 2 of the 19 cases with acute HAV infection in our study developed cholestasis, these resolved rapidly with complete recovery during the follow up in both cases.

In 44 (86%) of the acute HBV patients, immunity developed during the follow-up period (anti-HBc IgG and anti-HBs positivity), 3 patients (6%) were considered as chronic HBV infection due to persistence of HBsAg positivity beyond 6 months. Isolated anti-HBc IgG positivity persisted in 4 (8%) others with no emergence of anti-HBs positivity. At 2 years of follow-up, both patients remained positive for isolated anti-HBc IgG with no anti-HBs. Two cases of acute HBV infection also had 1st stage syphilitic disease, which was treated. One patient with acute HBV infection had concomitant acute retroviral syndrome, was referred to a hepatic transplantation center, but died due to fulminant hepatic failure before transplantation. When the medical records of this patient was retrospectively evaluated, he was found to have negative serology for HBV and HIV.

Obviously, vaccination is indispensable for diseases against which immunization can confer protection. Using the national surveillance data between 1990 and 2012, the most dramatic decline in reported rates of HBV in Turkey was observed in adolescents and children ≤15 years of age, as a result of the nationwide implementation of three doses of HBV vaccination and catch-up vaccination strategy (18). Finally, the "Turkish Viral Hepatitis Prevention and Control Program 2018-2023" initiated by the Ministry of Health in 2018 clearly underscores the importance of surveillance and vaccination, with a 5-year target of reduction in the number of cases with hepatitis (19).

Study Limitations

As collected in one-year period, number of acute viral hepatitis patients (i.e.: 75) may be low. But we believe that the data provided herein may shed some light on the current status of acute viral hepatitis in Turkey.

Conclusion

In contrast with many studies with a retrospective design, this up-to-date prospective study showed that acute HBV infection remains an important health problem in our country, and that horizontal and sexual transmission became the predominant routes of transmission for HBV, due to the fact that vaccination has conferred immunity to most children and adolescents in recent years. Also, acute HAV infection is a prevalent condition in young adults, and it appears that it will remain so, until children vaccinated in the context of the national vaccination program reach adulthood in a decade or so.

Ethics

Ethics Committee Approval: This multi-center study was conducted at 8 hospitals in 6 provinces between 1 May 2016 and 30 June 2017 after ethics committee approval by the Local Ethics Committee, University of Health Sciences Turkey, İzmir Bozyaka Training and Research Hospital (approval number: 1, date: 09.02.2016).

Informed Consent: Informed consent forms were obtained from all patients included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.T., A.A., G.D., İ.Ç.A., A.S.Ö., N.T., A.K., S.E., A.A.Y., N.C., Desing: S.T., A.A., G.D., İ.Ç.A., A.S.Ö., N.T., A.K., S.E., A.A.Y., N.C., Materials: S.T., A.A., G.D., İ.Ç.A., A.S.Ö., N.T., A.K., S.E., A.A.Y., N.C., Data Collection or Processing: Ö.D., A.I.O., Analysis or İnterpretation: Ö.D., A.I.O., Literature Search: Ö.D., A.I.O., Writing: Ö.D., A.I.O.

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Research Article

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Direct-acting Antiviral Agents in Patients with Chronic Hepatitis C: Real-life Data

Kronik Hepatit C Hastalarında Direkt Etkili Antiviral Ajanlar: Gerçek Yaşam Verileri

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ABSTRACT

Objectives: In the treatment of chronic hepatitis C (CHC), very high rates of sustained virological response (SVR) have been obtained with direct-acting antivirals. In this study, we aimed to evaluate the efficacy and safety of therapies containing ledipasvir + sofosbuvir (Led + Sof), Sof, paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD) and PrO.

Materials and Methods: Three hundred patients with CHC, who received Led + Sof, Sof, PrOD or PrO treatment were included in the study.

Results: One hundred two (34%) of the patients were treatment-naive patients and 198 (66%) had undergone treatment. Cirrhosis was present in 70 (23.3%) of the patients. Thirty-five (11.7%) of the patients were with genotype 1a, 261 (87%) were with genotype 1b, 1 (0.3%) was with genotype 2a, 2 (0.7%) were with 3a and 1 (0.3%) was with genotype 4a. While the rate of SVR was 98% in patients receiving Led +Sof ± ribavirin (R), it was 100% in patients receiving PrOD ± R. Cirrhosis was found to be the only factor affecting SVR. An adverse event was observed in 60 (40.5%) of patients using PrOD or PrOD + R, and in 68 (44.7%) of those using Led + Sof or Led + Sof + R.

Conclusion: In CHC patients, PrOD and Led + Sof treatments are effective and reliable treatments and shows promise.

Keywords: Chronic hepatitis C, direct-acting antiviral agents, real-life data

ÖZ

Amaç: Kronik hepatit C (KHC) tedavisinde direkt etkili antiviraller ile çok yüksek kalıcı virolojik yanıt (KVY) oranları elde edilmiştir. Bu çalışmada, hastalarda ledipasvir + sofosbuvir (Led + Sof), Sof, paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD) ve PrO içeren tedavilerin etkinliğinin ve güvenilirliğinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya KHC'li Led + Sof, Sof, PrOD veya PrO tedavisi alan 300 hasta alındı.

Bulgular: Hastaların 102'si (%34) naif hasta, 198'i (%66) tedavi deneyimliydi. Hastaların 70'inde (%23,3) siroz mevcuttu. Hastaların 35'i (%11,7) genotip 1a, 261'i (%87) genotip 1b, 1'i (%0,3) genotip 2a, 2'si (%0,7) 3a ve 1'i (%0,3) genotip 4a olarak saptandı. Led + Sof ± ribavirin (R) alan hastalarda KVY oranı %98 saptanırken, PrOD ± R alan hastalarda %100 saptandı. Siroz, KVY'yi etkileyen tek faktör olarak saptandı. PrOD veya PrOD+R kullanan hastaların 60'ında (%40,5), Led + Sof veya Led + Sof + R kullanan hastaların 68'inde (%44,7) herhangi bir advers olay görüldü.

Sonuç: KHC hastalarında, PrOD ve Led + Sof tedavileri, etkin ve güvenilir tedaviler olup, umut vadetmektedir.

Anahtar Kelimeler: Kronik hepatit C, direkt etkili antiviral ajanlar, gerçek yaşam verileri

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Introduction

The prevalence of hepatitis C virus (HCV) infection in the world is around 3%. This indicates that an estimated 170-180 million people are infected with HCV. Of all HCV cases, 42.2% are with genotype 1, 30.1% are with genotype 3, 9.1% are with genotype 2, 8.3% are with genotype 4, 5.4% are with genotype 6, and less than 1% are with genotype 5 (1). In terms of the HCV cases in Turkey, 66.7 to 100% of the patients are with genotype 1b , 3.45 to 33.7% are with genotype 1a and 3.7% are with genotype 4 (2).

HCV infection is a slowly progressive, insidious disease. The natural course of HCV infection differs among individuals. This difference is due to many factors that concern both virus and host (3). Clinical significance of liver disease associated with HCV involves the fact that 50-85% of the disease becomes chronic after acute infection and that cirrhosis develops in 2-20% of chronic cases after 20-30 years as well as presence of 1-4% risk for developing hepatocellular carcinoma (HCC) per year in cases with cirrhosis (4).

The primary goal of treatment in chronic hepatitis C (CHC) infection is to prevent liver necroinflammation, fibrosis, cirrhosis, HCC and extrahepatic findings by accomplishing eradication of HCV. Thus, the need for liver transplantation, morbidity and mortality is reduced (5,6). Permanent response was confirmed in more than 98% of patients with negative HCV-RNA in serum during long-term follow-up studies in the 24th week following the completion of the treatment (7). Even in patients with advanced fibrosis, significant reductions in liver-related deaths and hepatic decompensation can be observed after successful treatment (8,9,10). In patients responding to treatment, a decrease in the incidence of HCC has been detected (11). It has been shown that life expectancy is prolonged in patients with advanced fibrosis and liver cirrhosis if SVR is achieved (12).

In this study, we aimed to evaluate the efficacy and safety of therapies containing ledipasvir/sofosbuvir (Led + Sof), Sof, paritaprevir/ritonavir/ombitasvir + dasabuvir (PrOD) and PrO.

Materials and Methods

Patients

Three hundred patients who admitted to Gaziantep University Faculty of Medicine Hospital, Hepatology and Infection Outpatient Clinic between June 2016 and December 2017 with a diagnosis of CHC and received Led + Sof, Sof, PrOD or PrO treatment were retrospectively included in the study.

The study was carried out in accordance with principles of the Helsinki Declaration of 1975 as revised in 2008, and with the approval number 08/05/2017/187 of the Gaziantep University Faculty of Medicine Clinical Research Ethics Committee. All patients provided written consent and study entry with all clinical investigations conducted according to the principles expressed in the Declaration of Helsinki.

Methods

Age, gender, body mass index (BMI) of patients, previous treatment experiences, responses to previous treatment, presence of cirrhosis, Child-Pugh score, HCV genotype, concomitant disease status, fibrosis staging of liver biopsies, treatment regimen, duration of treatment regimen, pre-treatment HCV-RNA level, complete blood count, biochemical parameters, international normalized ratio (INR) level and alpha fetoprotein (AFP) level were examined. HCV-RNA, complete blood count, biochemical parameters, INR level, AFP level, and side effects that occurred during treatment were evaluated on the 4th and 8th weeks of treatment, end of treatment and 12th week after treatment. The efficacy and safety of treatments with direct-acting antiviral agents (DAA) were investigated. Patients were divided into two subgroups; those receiving PrOD or PrO and those receiving Led + Sof or Sof.

Laboratory Testing

Anti-HCV test is a two-step immunoassay and chemiluminescent microparticle immunoassay technique (Architect i1000, Abbott, USA) was studied. HCV-RNA measurement was performed using COBAS® AmpliPrep/COBAS® TaqMan® HCV Quantitative v2.0 (Roche Molecular Diagnostics, USA) commercial kits according to the manufacturer's instructions. HCV-RNA genotyping was performed with sequence primers in the PyroMark Q24 device.

Statistical Analysis

The compliance of the numerical data to the normal distribution was tested with the Shapiro-Wilk test. Student's t-test was used to compare variables that comply with normal distribution in 2 groups. The paired sample t-test was used to compare measurements of normally distributed dependent variables. The relationship between categorical variables was tested by chi-square test. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) package program was used in the analysis. A p-value ≤0.05 was considered statistically significant.

Results

Three hundred patients were included in this study. Ninety-seven (32.3%) of the patients were male and 203 (67.7%) were female. Thirty-five (11.7%) of the patients were with genotype 1a, 261 (87%) were with genotype 1b, 1 (0.3%) was with genotype 2a, 2 (0.7%) were with genotype 3a and 1 (0.3%) was with genotype 4a. The number of patients with cirrhosis was 70 (23.3%). In terms of previous treatment experiences; 102 (34%) of the patients were naive, 185 (61.7%) received peginterferon alpha (Peg-IFN α) + ribavirin and 13 (4.5%) received Peg-IFN α + ribavirin + first generation protease inhibitor (PI). Ninety-four of the patients (31.3%) had at least one additional disease. Fifty patients (16.7%) had diabetes, 16 (5.3%) had chronic renal failure (CRF), 35 (11.7%) had hypertension (HT) and 3 (1%) had hepatitis B virus (HBV) infection. The number of liver transplant patients was 10 (3.3%). In terms of the DAA regimens received by patients; 12 patients (4%) were given Led + Sof for 12 weeks, 112 (37.3%) patients received Led + Sof for 24 weeks, 27 (9%) patients received Led + Sof + R for 12 weeks, 1 (0.3%) patient received Sof for 12 weeks, 139 (46.3%) patients received PrOD for 12 weeks, 8 (2.7%) patients received PrOD + R for 12 weeks and 1 (0.3%) patient received PrO + R for 12 weeks. Ribavirin could not be administered to one patient with genotype 2a who received the Sof regimen because the hemoglobin (Hb) value of that patient was 8.6 g/dL. The demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients	
Patients	**n (%)**
Age	61.65±9.76
Diagnosis year	9.32±3.92
BMI, (kg/m^2)	27.72±4.22
Gender, female	203 (67.7)
Genotype	
1A	35 (11.7)
1B	261 (87)
2A	1 (0.3)
3A	2 (0.7)
4A	1 (0.3)
Cirrhosis	70 (23.3)
Child Pugh	
A	35 (50)
B	26 (37.1)
C	9 (12.9)
Treatment experience	
Naive	102 (34)
Peg-IFN + R	185 (61.7)
Peg-IFN + R + PI	13 (4.3)
Treatment response	
Relapse	158 (52.7)
Partial response	4 (1.3)
Unresponsive	31 (10.3)
Stop treatment due to side effects	6 (2)
Additional disease	
CRF	16 (5.3)
DM	50 (16.7)
HT	35 (11.7)
HBV	3 (1)
Liver transplantation	10 (3.3)
DAAs	
Led + Sof 12 week	12 (4)
Led + Sof 24 week	112 (37.3)
Led + Sof + R 12 week	27 (9)
Sof 12 week	1 (0.3)
PrOD 12 week	139 (46.3)
PrOD + R 12 week	8 (2.7)
PrO + R 12 week	1 (0.3)
Fibrosis	
F1-2	32 (23.8)
F3-4	67 (50)
F5-6	35 (26.2)

BMI: Body mass index, Peg-IFN + R: Peginterferon + ribavirin, Peg-IFN + R + PI: Peginterferon + ribavirin + protease inhibitor, CRF: Chronic renal failure, DM: Diabetes mellitus, HT: Hypertension, HBV: Hepatitis B virus, DAAs: Direct-acting antiviral agents, Led + Sof: Ledipasvir + sofosbuvir, PrOD: Paritaprevir/ritonavir/ombitasvir + dasabuvir

The mean baseline HCV-RNA levels of the patients were 1,854,026±2,577,916 IU/mL. The mean baseline AFP levels were 10±16.1 ng/mL. The mean baseline alanine transaminase (ALT) and aspartate transaminase (AST) levels were 53.5±35 U/L and 58±38.6 U/L, respectively. The mean baseline total bilirubin (TB) level was 1±0.9 mg/dL. The mean baseline albumin level was 3.9±0.5 g/dL, whereas the mean baseline INR level was 1.1±0.5. The mean baseline of creatinine was 1±0.7 mg/dL. The mean baseline complete blood count parameters were as follows; white blood cell (WBC): 6.80±2.79x10^3/µL, neutrophil: 3.74±1.70x10^3/µL, lymphocyte: 2.06±1.00x10^3/µL, Hb: 13.6±2 g/dL and platelet (PLT): 194.77±88.14x10^3/µL (Table 2).

Patients were divided into two groups in this study. Those who received Led + Sof for 12 weeks, Led + Sof for 24 weeks, Led + Sof + R for 12 weeks and Sof for 12 weeks were defined as Led + Sof ± R group, while those who received PrOD for 12 weeks, PrOD + R for 12 weeks and PrO + R for 12 weeks were defined as PrOD ± R group. Led + Sof ± R group consisted of 152 patients whereas PrOD ± R consisted of 148 patients. When the virological response between the groups were assessed, there was no significant difference in the evaluation of the 4th, 8th, end of treatment and 12th week of SVR. In the 4th week of treatment, HCV-RNA was negative in 135 (88.8%) of patients receiving Led + Sof ± R and in 133 (89.8%) of patients receiving PrOD ± R. In the 8th week of treatment, HCV-RNA was negative in 150 (98.7%) of patients receiving Led + Sof ± R and 146 (98.6%) of patients receiving PrOD ± R. At the end of treatment, HCV-RNA was negative in all patients in both groups. While relapse was detected in 3 of the patients who received Led + Sof ± R at 12th weeks, HCV-RNA negativity persisted in all patients who received PrOD ± R (Figure 1).

Two of the patients who had relapse received Led + Sof for 24 weeks and one received Led + Sof for 12 weeks. Two of the patients were male and one was female. Patient 1 was 54 years old, patient 2 was aged 61, and patient 3 was aged 41. When the genotype was examined, patient 1 was with 1b, patient 2 was with 1a and patient 3 was with 3a. Patient 1's HCV-RNA level was

Table 2. Initial laboratory characteristics of the patients	
HCV-RNA (IU/mL)	1854026±2577916
AFP (ng/mL)	10±16.1
ALT (U/L)	53.5±35
AST (U/L)	58±38.6
Total bilirubin (mg/dL)	1±0.9
Albumin (g/dL)	3.9±0.5
INR	1.1±0.5
Creatinine (mg/dL)	1±0.7
WBC (×10^3/µL)	6.80±2.79
Neutrophil (×10^3/µL)	3.74±1.70
Lymphocyte (×10^3/µL)	2.06±1.00
Hemoglobin (g/dL)	13.6±2
Thrombocyte (×10^3/µL)	194.77±88.14

HCV: Hepatitis C virus, AFP: Alpha fetoprotein, ALT: Alanine transaminase, AST: Aspartate transaminase, WBC: White blood cell, INR: International normalized ratio

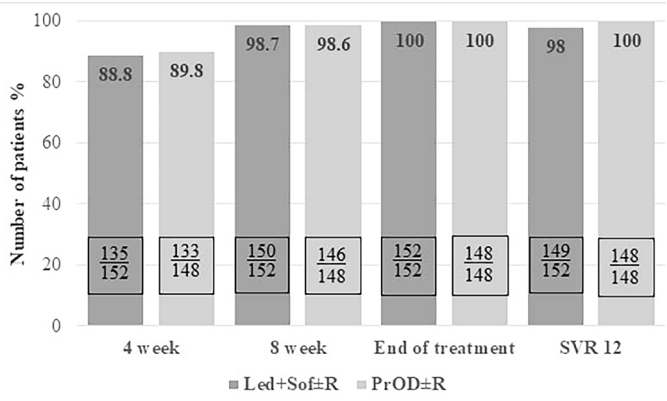

Figure 1. Response to treatment rates

Led + Sof: Ledipasvir + sofosbuvir, SVR: Sustained viral response, PrOD: Paritaprevir/ritonavir/ombitasvir + dasabuvir

163,000 IU/mL, patient 2's was 1,200,000 IU/mL, and patient 3's was 1,700,000 IU/mL. Two patients had cirrhosis, while one did not. According to the Child-Pugh classification, patient 1 was B and patient 2 was C. One patient had received Peg-IFN α + ribavirin before, while the other two were naive. While patient 1 had HT and CRF, patient 2 and patient 3 had no additional disease.

Factors affecting SVR are examined in Table 3. These factors included age, gender, BMI, HCV-RNA level, genotype, presence of cirrhosis, previous treatment experience, CRF, diabetes mellitus, HT, HBV, newly received treatment and use of ribavirin. Among these, the only factor affecting SVR was the presence of cirrhosis and a significant relationship was found (p=0.013).

In treatment groups, the change between baseline TB levels and levels in the 4th week, 8th week of treatment end-of-treatment, and SVR 12th week were examined. There was a significant increase in TB levels in the 8th week of treatment in the PrOD group. However, there was a significant decrease in TB levels in the 12th week of SVR in both groups.

In treatment groups, the change between the baseline Hb levels and the 4th week, 8th week of treatment, end-of-treatment and SVR 12th week was examined.

The relationship between mean ALT, AST, TB, albumin, INR, PLT and Hb levels and SVR 12th week levels in all patients were examined. Significant decreases were observed in AST, ALT and TB levels in the 12th week of SVR, while significant increases were observed in albumin levels and PLT counts. No significant change was observed in Hb and INR Levels.

In terms of the side effects occurring in patients, the most common side effect in both groups was pruritus, insomnia and weakness. Side effects that would require discontinuation of treatment were seen in 2 (1%) patients. Both patients were in the group receiving PrOD ± R and the treatment was terminated at the 8th week due to the grade 3 TB elevation. HCV-RNA was negative in both patients at the 12th week of SVR. There was no significant difference between the groups in terms of itching, insomnia and weakness. Nausea was seen in 14 (9.2%) of patients receiving Led + Sof ± R, in 5 (3.4%) of patients receiving PrOD ± R and difference was statistically significant (p=0.038). Grade 2 anemia (Hb: 8-10 g/dL) occurred in 2 (1.3%) of patients receiving Led + Sof ± R and in 3 (2%) of patients receiving PrOD ± R, while grade 3 anemia (Hb: <8 g/dL) was not seen in either group and no significant relationship was found between the groups. Grade 2 TB elevation (1.5-3 fold increase) was seen in 3 (2%) of patients receiving Led + Sof ± R, and in 2 (1.4%) of patients receiving PrOD ± R. Grade 3 TB height (>3 times) was not seen in Led + Sof ± R group, it was seen in 2 (1.4%) of patients receiving PrOD ± R. There was no significant relationship between groups with regard to TB elevation (p=0.333) (Table 4).

Table 3. Evaluation of the factors affecting the sustained virological response

Patient characteristics	SVR, n (%)	p
Age group		
Over 65	117 (100)	0.084
Under 65	180 (98.4)	
Gender		
Male	95 (98)	0.221
Female	202 (99.3)	
BMI, (kg/m²)		
<25	69 (98.5)	0.801
25-30	156 (99.4)	
>30	72 (98.6)	
HCV-RNA (IU/mL)		
>800,000	166 (98.8)	0.705
<800,000	131 (99.2)	
Genotype		
1A	34 (97.1)	0.071
1B	260 (99.6)	
2A	1 (100)	
3A	1 (50)	
4A	1 (100)	
Treatment experience		
Naive	100 (99)	0.478
Peg-IFN + R	184 (99.4)	
Peg-IFN + R + PI	13 (100)	
Additional disease		
Cirrhosis	42 (97.1)	**0.013***
CRF	15 (93.7)	0.129
DM	50 (100)	0.294
HT	34 (97.1)	0.320
HBV	3 (100)	0.806
The use of ribavirin	36 (100)	0.380
Treatment regimen		
Led + Sof ± R	149 (98)	0.055
PrOD ± R	148 (100)	

*: Statistically significant, SVR: Sustained viral response, BMI: Body mass index, Peg-IFN + R: Peginterferon + ribavirin, Peg-IFN + R + PI: Peginterferon + ribavirin + protease inhibitor, CRF: Chronic renal failure, DM: Diabetes mellitus, HT: Hypertension, HBV: Hepatitis B virus, Led + Sof: Ledipasvir + sofosbuvir, PrOD: Paritaprevir/ritonavir/ombitasvir + dasabuvir

Table 4. Adverse effects			
	Led + Sof ± R (n=152) (%)	**PrOD ± R (n=148) (%)**	**p**
Any adverse effects	68 (44.7)	60 (40.5)	0.463
Serious adverse effects	0 (0)	2 (1.4)	0.092
Itching	42 (27.6)	27 (18.2)	0.053
Insomnia	21 (13.8)	14 (9.5)	0.240
Weakness	19 (12.5)	21 (14.2)	0.667
Nausea	14 (9.2)	5 (3.4)	**0.038***
Headache	13 (8.6)	12 (8.1)	0.889
Anorexia	14 (9.2)	9 (6.1)	0.308
Anemia			
Grade 2	2 (1.3)	3 (2)	0.737
Grade 3	0 (0)	0 (0)	
Total bilirubin increase			
Grade 2	3 (2)	2 (1.4)	0.333
Grade 3	0 (0)	2 (1.4)	
*: Statistically significant, Led + Sof: Ledipasvir + sofosbuvir, PrOD: Paritaprevir/ritonavir/ombitasvir + dasabuvir			

Discussion

DAA are extremely important since they have very low rates of side effects as well as the SVR rates exceeding 95%.

While HCV-RNA was negative in all patients at the end of the treatment, the rates of 12th week of SVR were found to be 98% in the Led + Sof ± R group and 100% in the PrOD ± R group. The results of this study are consistent with studies previously performed in patients with CHC. In the study by Juanbeltz et al. (13), the 12th week rate of SVR was 97.3% in all patients. When we look at the factors that affect SVR in our study, it was found that only the presence of cirrhosis was effective. The high number of patients with cirrhosis in the Led + Sof ± R group may be the reason that the rate of SVR is not 100% in this group.

In a study by Colombo et al. (14) in patients with genotype 1b, the 12th week rate of SVR was 98.3% in the group who were with or without cirrhosis, naive or had previous treatment and received PrOD + R treatment. In the non-cirrhotic, naive or previously treated group receiving PrOD therapy, the 12th week rate of SVR was 99.3% (14).

In the LONESTAR study, the 12th week rate of SVR was 100% in the Led + Sof + R group and 95% in the Led + Sof group (15). In our study, it was 100% in the Led + Sof + R group and 97.6% in the Led + Sof group.

In a study by Calleja et al. (16) in patients with genotype 1b, the 12th week SVR rates were 91.7% in patients receiving Led + Sof for 8 weeks, 94.6% in patients receiving Led + Sof for 12 weeks, 98.0% in patients receiving PrOD for 12 weeks and 95.5% in patients receiving PrOD + R for 12 weeks (17). In our study, 12th week SVR rates were 98.2% for patients receiving Led + Sof for 24 weeks, and 91.7% for those using Led + Sof 12 weeks, while it was 100% in other regimes.

In the study by Calleja et al. (16), 12th week SVR rates were 95.8% in Led + Sof ± R group and 96.8% in PrOD ± R group. Another point highlighted by the study is that rapid virological response (RVR) rates are low in patients receiving Led + Sof ± R (17). In the study by Backus et al. (18), it was found that RVR rates were low in similar rates. In our study, the rate of RVR was 88.8% in Led + Sof ± R group and 89.8% in PrOD ± R group. Calleja et al. (17) stated that there is a significant relationship between cirrhosis status and RVR rate. They have shown that RVR rates are lower in the cirrhosis group. This was not noted in our study. Although the number of patients with cirrhosis was higher in Led + Sof ± R group, the rate of RVR was similar in both groups. However, it was assumed that cirrhosis might be effective in SVR rates.

Ioannou et al. (19), demonstrated that the SVR rates of Led + Sof and PrOD treatments without ribavirin were slightly higher, but this difference was not statistically significant. Regardless of the treatment regimens, the 12th week SVR rates were 92.8% in all patients with genotype 1. In our study, the 12th week SVR was 98.8% in treatments without ribavirin and 100% in regimens with ribavirin. The 12th week SVR rate in 296 patients with genotype 1 was 99.3%.

In a study with patients over 65, the 12th week SVR rate was 88.3% (20). Of these patients, 95% were with genotype 1 and combinations of different DAAs, Led + Sof ± R and PrOD ± R, were given as the treatment regimen. In our study, there were 117 patients over 65 years of age and the 12th week SVR rate was 100%. It was predicted that the treatment regimens used in our study, especially for patients with genotype 1, did not require different combinations as they provide HCV-RNA negativity in all elderly patients.

In our study, at least one side effect was observed in 128 (42.7%) of 300 patients. The most common side effect was itching followed by weakness, insomnia, headache, anorexia and nausea. Intergroup evaluation revealed that nausea was more common in Led + Sof ± R group and the difference was statistically significant. However, it was thought that this finding did not reflect an important condition because nausea was seen in very few patients. In the study by Welzel et al. (21), 42.7% of patients had at least one side effect. The rate of serious side effects in this study was 9.6%, and the rate of drug cessation due to serious side effects was 6.8%. Fatigue, itching and headache were the most common side effects. While the most common complaint in similar studies is weakness, we found itching as the most common side effect in our study. It should not be forgotten that ribavirin is present in treatment regimens, and any patient suffering from weakness should be evaluated for anemia and drug-related side effects.

In a multicenter study conducted by Calleja et al. (17) on patients with genotype 1, the rates of severe side effects and treatment discontinuation due to serious side effects were 5.5% and 1.5% in Led + Sof group, and 5.4% and 1.7% in PrOD group, respectively. Especially when evaluating the side effect, patients who do not receive ribavirin should be assessed with regard to anemia and TB elevation. In our study, 2 patients in the group receiving PrOD ± R could not complete the treatment because of the grade 3 TB elevation. One patient was receiving ribavirin while the other was not. Regardless of the treatment regimen, it was thought that AST, ALT, PLTs, WBC, albumin, INR and creatinine testing, especially Hb and TB values, were required.

In the study by Rodríguez Osorio et al. (20) on 120 patients aged over 65, the probability of side effects was 65%. The majority of patients with side effects were those who received PIs. The most common side effects included weakness, anemia, itching and high bilirubin levels. This study suggests that the elevation of TB levels in our study group receiving PrOD ± R may be related to the PI paritaprevir.

Since treatment regimens are given for 12 or 24 weeks, easy management of the side effects can be achieved. In addition, some studies show that treatment durations can be shortened to 4, 6 or 8 weeks, depending on patient characteristics. Furthermore, SVR rates were found to be too high for patients who could not complete the treatment. In our study, although 2 patients stopped treatment after 8 weeks of treatment, HCV-RNA levels were negative in the 12th week of SVR.

Study Limitations

The limitation of our study is that the study was a single center experience and only two types of drugs were used in the treatment.

Conclusion

The effectiveness of PrOD and Led + Sof combinations was close to 100% in patients with genotype 1 and it was assumed that HCV infection could be fully eradicated. Today, it should be remembered that antiviral treatment should be given in all patients with CHC infection and positive viral load, unless there are contraindications.

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Ethics

Ethics Committee Approval: The study was carried out in accordance with principles of the Helsinki Declaration of 1975 as revised in 2008, and with the approval number 08/05/2017/187 of the Gaziantep University Faculty of Medicine Clinical Research Ethics Committee.

Informed Consent: All patients provided written consent and study entry with all clinical investigations conducted according to the principles expressed in the Declaration of Helsinki.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Medical Practices: A.B., M.S., T.M., M.T.G., Concept: A.B., Y.B., A.E.Y., B.T.K., S.B., Design: A.B., Y.B., A.E.Y., B.T.K., S.B., Data Collection or Processing: A.B., Y.B., A.E.Y., B.T.K., S.B., A.D., K.U., M.S., M.N., T.M., Analysis or Interpretation: A.B., M.S., T.M., Literature Search: A.B., M.S., T.M., Writing: A.B., M.S., T.M.

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Long-term Kinetics of Alpha-fetoprotein in Chronic Hepatitis C Patients Treated with Direct-acting Antivirals and Possible Predictive Role of AFP Response to Treatment on Development of Hepatocellular Carcinoma

Direkt Etkili Antiviral Tedavisi Alan Kronik Hepatit C Hastalarında Uzun Süreli Alfa-fetoproteinin Kinetiği ve Tedaviye AFP Yanıtının Hepatoselüler Karsinom Gelişimini Öngörmedeki Muhtemel Rolü

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ABSTRACT

Objectives: To evaluate the post-treatment upto fourth-year kinetics of alpha-fetoprotein (AFP) in patients with chronic hepatitis C (CHC) treated with direct-acting antiviral (DAA) drugs.

Materials and Methods: In this retrospective, single-center study, 182 patients (124 female, 58 male) with CHC treated with DAA were included in the study. Biochemistry and AFP were recruited from the hospital database. The data at pre-treatment, 3rd and 48th month after the end of treatment were evaluated.

Results: Of the 182 patients, mean age was 58±12 (28-76), and forty-nine (27%) had cirrhosis. At month 3, the average decline of AFP was 35.6% (0.4-97.0). Early decline of AFP <8.7% was found to be a predictor for HCC development. Mean AFP was 7.7±9.2 ng/mL at pre-treatment and 3.8±2.7 at third month (p<0.001). The decline persisted at 48th month (3.6±2.4 ng/mL).

Conclusion: Early decline of AFP and persistence at fourth-year after DAA treatment was observed, except five cases developing HCC. Inadequate decline in AFP level found to be a possible predictor for HCC development. However, these results needs to be confirmed in large-scale multicenter cohorts. This study highlights the importance of AFP response to DAA treatment in identifying HCC risk, especially in patients with cirrhosis.

Keywords: Alpha-fetoprotein, chronic hepatitis C, direct-acting antivirals, hepatocellular carcinoma

ÖZ

Amaç: Doğrudan etkili antiviral (DAA) ilaçlarla tedavi edilen kronik hepatit C (KHC) hastalarında alfa-fetoproteinin (AFP) tedavi sonrası dördüncü yıl kinetiğini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif, tek merkezli çalışmada DAA ile tedavi edilen KHC'li 182 hasta (124 kadın, 58 erkek) çalışmaya dahil edildi. Hastane veri tabanından serolojik, biyokimyasal veriler ve hepatoselüler karsinomaya ilerleme bilgileri kaydedildi. Tedavi öncesi, tedavi bitiminden sonraki 3. ve 48. aydaki veriler değerlendirildi.

Bulgular: AFP seviyesinde tedavi sonrası 3. ay ortalama düşüş %35,6 (%0,4-97 aralığında) idi. Olguların %4,4'ünde AFP düzeyinde değişiklik olmazken, %8,2'sinde AFP yükselmesi gözlendi. HCC olguları hariç ortalama AFP 3. ayda 3,8±2,7, 48. ayda 3,6±2,4 idi (p=0,119). AFP'nin tedavi sonrası 3. aydaki düşme oranı %8,7'den daha az olanlarda HCC gelişimi anlamlı bulundu.

Sonuç: AFP düzeyi, olguların çoğunda DAA tedavisi bitiminde belirgin düşme göstermiş ve bu durum tedavi bitiminden 48 ay sonra da sebat etmiştir. Daha geniş kapsamlı verilere ihtiyaç olmakla beraber, bu çalışmanın verileri DAA tedavisi sonrası AFP'deki düşmenin yetersiz olmasının, sirotik hepatit C hastalarında HCC açısından daha yakın takip için bir uyarı olabileceğini desteklemektedir.

Anahtar Kelimeler: Alfa-fetoprotein, hepatit C, direkt-etkili antiviraller, hepatoselüler karsinoma

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Introduction

Chronic hepatitis C (CHC) is still a global cause of cirrhosis and hepatocellular carcinoma (HCC) (1). Alpha-fetoprotein (AFP), an onco-fetal glycoprotein with 59 amino acids and a half-life of five days may have mild elevations in CHC regardless of HCC (2). Early identification of HCC and early tumor stage determines the prognosis, thus close monitorization and evaluating AFP response are essential factors (3,4).

We aimed to examine the change in AFP levels following direct-acting antivirals (DAA) treatment and to determine the correlation of AFP change with biochemical parameters, aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis index based on four factors (FIB-4) scores.

Materials and Methods

We conducted a retrospective study of consecutive adult patients (older than 18 years) with CHC who received 12 or 24 weeks of DAA treatment between January 2015 and January 2017 in a tertiary hepatology clinic. Patients with CHC who received DAAs and under follow-up for at least 48 months. Patients with co-infection and who had HCC within 12 months of DAA treatment were excluded. Medical files were reviewed and the following data were recorded; 1) demographics, 2) co-morbidities, 3), underlying cirrhosis, 4) laboratory values including alanine aminotransferase (ALT), aspartate aminotransferase (AST), AFP, hepatitis C virus-RNA (HCV-RNA), HCV genotype (GT), and platelet (Plt) count, and hepato-biliary ultrasound. The treatment criteria were defined as CHC patients with Ishak fibrosis score ≥2 and /or hepatic activity score ≥2, patients with cirrhosis based on the reimbursement criteria of the Turkish Ministry of Health as of January 2015. The DAA treatment regimens included sofosbuvir + ledipasvi, ombitasvir + paritaprevir + ritonavir + dasabuvir, sofosbuvir and additional ribavirin in cirrhotic patients. The sustained viral response (SVR) was defined as the HCV-RNA negativity at the 3rd month of end-of-treatment (EOT). The SVR was defined as the HCV-RNA negativity at the 3rd month of EOT. The diagnosis of cirrhosis was based on biopsy, signs of portal hypertension, imaging and laboratory tests including ultrasound, transaminases, albumin, Plt, international normalized ratio and bilirubin.

The non-invasive fibrosis markers FIB4 score [(age x AST)/(Plt x √ALT)] and APRI score [(AST/upper limit of AST) X 100/Plt)] were calculated. FIB4 <1.45 indicates the absence of cirrhosis (with 90% negative predictive value for fibrosis), while the score between 1.45-3.25 is regarded as inconclusive and results >3.25 indicate cirrhosis (65% positive predictive value for advanced fibrosis). APRI <0.5 normal and ≥1.5 regarded likely as cirrhosis (5,6).

The study was approved by Ethics Committee İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 124, date: 17.05.2018).

Statistical Analysis

Statistical evaluation was done with SPSS v20 (IBM, Chicago). Numerical data are given as mean ± standard deviation (SD). The normality of distribution control was done by Kolmogorov-Smirnov. Categorical data were analyzed by chi-square or Fisher's exact tests. Student's t-test or Mann-Whitney U test was used for comparison of numeric values of two groups, and ANOVA or Kruskal-Wallis was used for more than 2 categories depending on normality of distribution. The cut-off point was calculated based on a receiver operator characteristic curve analysis. The results were given as mean ± SD. The $p<0.05$ was considered as the level of statistical significance.

Results

The study group consisted of 182 cases with HCV, mean age 58±12 (range: 28-76), 124 (68.1%) female, and all caucasian. SVR in the 12th week after the EOT was achieved in 98.4% of cases treated with DAAs. HCC developed in five patients with cirrhosis during a follow-up of 4 years. Pre-treatment (PreT) mean AFP level was 6.4±6.9 ng/mL in non-cirrhotic (n=133) and 11.1±13.1 ng/mL in cirrhotic cases (n=49) (p=0.021). Also, AFP level over 10 ng/mL was in 32.7% of the cirrhotic and 13.5% in non-cirrhotic patients. Initial, 3rd and 48th month AFP values were 7.5±9.2 ng/mL, 3.8±2.6 ng/mL, and 3.6±2.4 ng/mL, respectively (p=0.032).

The mean decline in AFP at the 3rd month compared to PreT was 33.3%±20.0% and 44.0%±22.0% for cirrhotic and non-cirrhotic cases, respectively (p=0.005). AFP level decreased in 159 (87.4%), increased in 15 (8.2%), and didn't change in 8 (4.4%) cases. The demographic and laboratory values are shown in Table 1.

Genotype distribution was as follows: GT1a 22 (12%), GT1b 148 (82%), GT2 4 (2%), GT3 4 (2%), GT4 4 (2%). Distribution of DAAs was sofosbuvir + ledipasvir (n=84), ombitasvir + paritaprevir + ritonavir + dasabuvir (PROD) (n=91), sofosbuvir (n=7), and additional ribavirin (n=67).

One non-cirrhotic case was non-responder and two cases relapsed (one cirrhotic). Five cirrhotic cases (4 responders and 1 relapser) developed HCC within 48 months of follow-up.

The cut-off for predicting HCC development in cirrhotic cases was 8.7% decline in AFP in our cohort (area under the curve 0.914, p=0.003, 0.818-1.000). Five cases developing HCC were female (n=3), GT1a (n=2), GT1b (n=3), non-responder (n=1), relapser (n=1), sofosbuvir based protocol (n=4), interferon-experienced (n=2), asthma (n=1), diabetes mellitus (n=3), hypertension (n=3), and chronic kidney disease (n=2).

Discussion

The pre-treatment level of AFP was found in a wide as 1-73 ng/mL in cirrhotic and 1-45 ng/mL in non-cirrhotic cases, with no evidence of HCC. The baseline AFP over 5.5 ng/mL was reported as 10%-48.2% of CHC patients in numerous studies (7). In our study AFP over 5.5 ng/mL was in 45.1% of cases. The AFP level was correlated with serum uric acid, steatosis, fibrosis, and low albumin levels (7).

In our study, the baseline AFP was not different between genotypes (p=0.110), CKD (p=0.149), diabetes mellitus (p=0.396), gender (p=0.343), but significantly higher in cirrhotic compared to non-cirrhotic (p=0.002). HCC cases had insignificantly higher baseline values of age, AFP, AST, ALT, HCV-RNA, Plt, APRI, and FIB-4 scores compared to the non-HCC group. In a study, males had lower post-treatment AFP, but still had the risk of HCC compared to females and the cut-off was reported lower as 3.5 ng/mL (8). Rapid decline of AFP in CHC during treatment may be due

Table 1. Demographic, clinical and laboratory data of chronic hepatitis C patients treated with direct acting antivirals

Variables	All cases	Cirrhotics	Non-cirrhotics	p*	HCC positive	HCC negative	p**
Total cases (n, %)	182	49 (27%)	133 (73%)	0.001*	5	177	0.001*
Gender F/M	124/58	35/14	89/44	0.162	3/2	121/56	0.692
Age	59±12	63±9	57±12	0.001*	70±5	59±12	0.041*
Baseline HCV-RNA**	6.4	7	6	0.508	11	6	0.158
HCV-RNA >6 mIU	78	23	55	0.499	4	74	0.089
SVR12	98.4%	98.0%	98.5%	0.801	80.0%	98.9%	0.001*
ΔAFP-0 vs 3rd m.	3.7±8.1	6.3±12.1	2.9±6.0	0.013*	-0.1±1.4	3.7±8.1	0.289
ΔAFP-3rd vs 48th m.	0.4±1.2	0.3±1.8	0.1±1.0	0.344	1010.0	0.14	0.000*
ΔAST-0 vs 3rd m.	31±36	51±48	24±29	0.001*	66±43	31±36	0.364
ΔAST-3rd vs 48th m.	0.2±1.2	0.3±12	0.1±10.0	0.945	-19±38	0.2±11	0.001*
ΔALT-0 vs 3rd m.	38±41	50±47	34±38	0.026*	25±32	38±41	0.640
ΔALT-3rd vs 48th m.	0.4±16	-2±15	1±16	0.233	22±49	0.4±16	0.001*
ΔAPRI-0 vs 3rd m.	0.6±1.1	1.5±1.8	0.3±0.5	0.001*	1.7±1.0	0.6±1.1	0.747
ΔAPRI-3rd vs 48th m	-0.5±0.8	0.1±0.5	-0.1±0.9	0.236	-0.5±1.2	-0.5±0.8	0.099
ΔFIB4-0 vs 3rd m.	2.9±3.1	6.5±4.2	1.8±1.1	0.001*	6.9±2.4	2.9±3.0	0.830
ΔFIB4-3rd vs 48th m	-0.5±1.0	-0.7±0.5	-0.3±1.1	0.122	-0.7±0.5	-0.5±1.0	0.968

*: Significant (p<0.05), **: Million IU, m: Months, F/M: Male/female, SVR12: Sustained viral response 12 weeks after treatment

to subsiding low-level inflammation in the liver, thus AFP may also be an acute phase reactant to ongoing liver inflammation.

In the recent decade, DAAs are increasingly efficacious in treating and raising the disease-related quality of life in CHC (9). One of the new emerging problems is the possible onset of post-treatment HCC, especially in patients with higher fibrosis (9,10). In our cohort, 2.74% of cases developed HCC. The HCC arising after DAA treatment is reported to have an aggressive prognosis (11). AFP normalization is found to be related to better prognosis (12,13). Even in patients without cirrhosis, Fib-4 scores ≥3.25 should be under follow-up for HCC (14). Older age is also another risk factor in SVR positive cases for HCC development (15). All five cases of HCC in our group were over 60 years old. The change of AFP in the 3rd month was 1.8% and 38.0% for cirrhotic with and without HCC, respectively (p=0.003). Serum AFP levels in pre-treatment and 48th month for each five HCC cases were changed 25 to 3,661 ng/mL, 9 to 917 ng/mL, 8 to 514 ng/mL, 18 to 21 ng/mL and 7 to 9 mg/dL.

In a study, AFP elevated 22.6% of cases and decreased in 77.4% after DAA treatment (16). A similar decline was also shown in interferon-alpha-based treatments (17,18). Lack of decrease in AFP was found to be a risk factor for HCC (19,20). Our study is compatible with this finding and additionally, a cut-off value for insufficient AFP decrease as 8.7% was a risk factor tor HCC development in cirrhotic and older patients.

In patients with CKD, AFP serum level was reported to have different kinetics (21). In our data, pre-treatment mean level (2.8±1.6 ng/mL) decreased to post-treatment (2.3±1.1 ng/mL) in CKD cases. AFP values were lower in CKD cases both pre- and post-treatment (p=0.000, p=0.032, respectively).

Study Limitations

The limitations of this study were the small number of HCC patients, retrospective pattern, lack of pre-treatment advanced imaging (22), genotype dominance of 1b, one ethnic group, the strength of the study was the availability of paired laboratory results of same laboratory standards and long-term surveillance for all cases.

Conclusion

In this CHC cohort DAAs resulted as 98,4% SVR at 12th week. The average change of AFP level was at 35% decline in all cases. In long-term surveillance, five cirrhotic cases with insufficient AFP response to treatment had developed HCC. Thus, despite to necessity for large-scale and multicenter data, insufficient AFP response to DAA treatment may be an alert for close monitorization of HCC.

Ethics Committee Approval: The study was approved by Ethics Committee İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 124, date: 17.05.2018).

Informed Consent: Since our study was retrospective, informed consent was waived.

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Research Article

53

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The Importance of Ischemia Modified Albumin in Chronic Hepatitis B and C

Kronik Hepatit B ve C'de İskemi Modifiye Albüminin Önemi

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ABSTRACT

Objectives: In this study, it was aimed to investigate the ischemia modified albumin (IMA) and the IMA/albumin ratio (IMAR) and the relationship between these two parameters with fibrosis in patients with chronic hepatitis B (CHB), hepatitis B e antigen negative chronic infection (HBI) and chronic hepatitis C (CHC).

Materials and Methods: This prospective study included 80 patients with CHB, 50 patients with HBI, 30 patients with CHC and 60 control groups. IMA level was measured using rapid colorimetric analysis developed (albumin-cobalt binding test). IMAR was calculated.

Results: Forty-two of the CHB cases were female and 38 were male (age range: 46.62±2.69). Thirty of the HBI patients were female and 20 were male (age range: 40.83±3.71). Ten of the cases with CHC were female, and 20 were male (age range: 41.35±3.58). Thirty-three of the control group were female and 27 were male (age range: 30.45±1.08). Serum IMA levels and IMAR, CHB, HBI, and CHC cases were statistically significantly higher than the control group ($p<0.05$). However, in terms of IMA, IMAR, no statistically significant difference was found in the between CHB, HBI and CHC cases. In CHB and CHC, IMA and IMAR were statistically significantly higher in those with significant fibrosis than those with mild fibrosis ($p<0.05$).

Conclusion: IMA and IMAR can be used as a marker in determining prognosis as an indicator of oxidative liver damage and in the evaluation of fibrosis (especially early detection of fibrosis).

Keywords: Chronic hepatitis B, HBeAg negative chronic infection; chronic hepatitis C, ischemia modified albumin, ischemia modified albumin/albumin ratio

ÖZ

Amaç: Bu çalışmada, kronik hepatit B (KHB), HBe Ag negatif kronik enfeksiyon (HBİ) ve kronik hepatit C (KHC) olgularında, iskemi modifiye albümin (İMA) ve İMA/albümin oranının (İMAR) tanı ve prognoz tayinindeki önemini ve bu iki parametrenin fibrozis ile olan ilişkisini araştırmak amaçlandı.

Gereç ve Yöntemler: Prospektif olan bu çalışmaya KHB'li toplam 80, HBİ'li 50, KHC'li 30 olgu ile 60 kontrol grubu alındı İMA seviyesi, hızlı kolorimetrik analiz (albumin-cobalt binding test) kullanılarak ölçüldü. İMAR hesaplandı.

Bulgular: KHB'li olguların 42'si kadın 38'i erkek (yaş aralığı: 46,62±2,69), HBİ'li olguların 30'u kadın, 20'si erkek (yaş aralığı: 40,83±3,71), KHC'li olguların 10'u kadın, 20'si erkek (yaş aralığı: 41,35±3,58), kontrol grubunun 33'ü kadın 27'si erkek (yaş aralığı: 30,45±1,08) idi. Serum İMA düzeyleri ve İMAR, KHB, HBİ, KHC olgularında, kontrol grubundan istatistiksel olarak anlamlı yüksekti ($p<0,05$). Ancak, İMA, İMAR açısından, KHB, HBİ ve KHC olguları arasında istatistiksel olarak anlamlı bir farklılık saptanmadı ($p>0,05$). KHB ve KHC'de, İMA ve İMAR, belirgin fibrozisi olanlarda hafif fibrozisi olanlardan istatistiksel olarak anlamlı yüksekti ($p<0,05$).

Sonuç: İMA ve İMAR, oksidatif karaciğer hasarının bir göstergesi olarak prognozun belirlenmesinde ve fibrozisin değerlendirilmesinde (özellikle; fibrozisin erken saptanmasında) bir belirteç olarak kullanılabilir.

Anahtar Kelimeler: Kronik hepatit B, HBeAg negatif kronik enfeksiyon, kronik hepatit C, iskemi modifiye albümin, iskemi modifiye albümin/albümin oranı

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Introduction

Chronic liver disease (CLD) is a liver pathology characterized by the gradual destruction of liver tissue over time; hepatitis B virus (HBV) and hepatitis C virus (HCV) viruses are the most common causes of CLD's morbidity and mortality worldwide (1). In hepatitis B e antigen (HBeAg) negative chronic infection (HBI), despite the risk of developing cirrhosis (LC) and hepatocellular carcinoma (HCC), these complications may not develop throughout their lives (2). Although albumin has many features such as antioxidant activity, and regulation of inflammatory response, it can affect the course of the disease and treatment results quantitatively and qualitatively, and is considered an important and negative prognostic factor (3).

The amino terminal end of the albumin molecule is the primary site for binding metal ions, cobalt and nickel, and under various conditions such as ischemia and oxidative stress (OS), the capacity of albumin to bind metals is reduced. This modified form of albumin, which is formed due to conformational change, is called ischemia modified albumin (IMA). Although IMA is a proven biomarker to increase in various OS-related diseases, the exact mechanism that leads to the formation of IMA is unknown. IMA is shown as a marker of ischemia and OS that occurs as a result of tissue hypoxia (4). In addition, it has been claimed that serum IMA level is associated with disease severity and may have prognostic use in chronic liver failure (5). Evaluation of the degree of necroinflammation and fibrosis in the liver is very important in the treatment decisions and follow-up of the patients (6).

In this study, it was aimed to investigate the importance of IMA and IMA/albumin ratio (IMAR) in diagnosis and determination of prognosis in chronic hepatitis B (CHB), HBI and chronic hepatitis C (CHC) cases and the relationship of these two parameters with fibrosis.

Materials and Methods

Patient Groups

This study is of 80 cases with CHB, 50 cases with HBI, 30 cases with CHC and 60 control group negative for hepatitis B surface antigen, anti-HCV and anti-human immunodeficiency virus, without a history of acute and chronic hepatitis and any chronic disease. Patients under 18 years of age, those with LC and HCC, those with chronic diseases (such as diabetes mellitus, coronary artery disease) were excluded from the study. CHB and CHC cases were divided into two groups as marked fibrosis (stage 3-4) and mild fibrosis (stage 1-2) (there were no stage 5,6).

Determination of Serum IMA Level and IMAR

Approximately 5 cc of blood was taken from the peripheral venous blood from the patients and separated into their serum by centrifugation. Serums were stored at -80 °C in a deep freezer. Serums were brought to room temperature and thawed on the working day. IMA level was measured using a rapid calorimetric analysis based on unbound Co measurement, developed by Bar-Or et al. (7), after incubation with the patient's serum. This test measures the cobalt binding capacity of albumin in the sample. The absorbances of the test mixtures were measured spectrophotometrically at 470 nm by the albumin-cobalt binding test and the calorimetric method. Results were obtained in about 30 minutes and are reported as absorbance units. In addition, the IMA/IMAR was calculated using the following formula: IMAR=IMA/serum albumin concentration (g/dL).

Biochemical tests of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin were routine analyzes performed in the laboratory with automatic analyzers. Liver biopsy specimens of CHB and CHC cases were scored using the Ishak histological scoring system (fibrosis was evaluated over 6). The study protocol followed the ethical guidelines of the 1975 Helsinki Declaration. Ethics committee approval was obtained from Fırat University Institutional Evaluation Committee (approval number: 24, date: 31.05.2018) and informed consent form was signed by the patients.

Statistical Analysis

Data analysis procedures were carried out using SPSS 22.0 (Chicago, USA) package statistics software. Kolmogorov-Smirnow and Shapiro-Wilk normality analysis was performed to determine the conformity of continuous variables to normal distribution. Student's t-test was used for the analysis of continuous variables conforming to the normal distribution, and the Kruskal-Wallis test was used for the analysis of variables that did not comply with the normal distribution. Pearson's chi-square test was used for comparisons between the two groups. Numerical data were expressed as mean ± standard deviation, and categorical data as %. One-Way ANOVA test was used in multiple comparisons. $P<0.05$ value was considered significant in statistical comparisons.

Results

Forty-two of the CHB cases were female and 38 were male (age range: 46.62±2.69). Thirty of the HBI patients were female and 20 were male (age range: 40.83±3.71). Ten of the cases with CHC were female, and 20 were male (age range: 41.35±3.58). Thirty-three of the control group were female and 27 were male (age range: 30.45±1.08). Serum ALT levels in CHB and CHC were statistically significantly higher than HBI and control groups (p=0.016). The demographic characteristics of CHB, HBI and CHC cases and the control group, the mean and p-values of the laboratory tests are summarized in Table 1.

No statistically significant difference was observed the patients with CHB, HBI, and CHC between serum IMA level and IMAR, and age (p=0.515, p=0.249, respectively) and gender (p=214, p=0.273, respectively). Also, there was no significant difference between IMA and IMAR and AST (p=0.858, p=0.143, respectively), ALT (p=0.539, p=0.326, respectively), AFP (p=0.289, p=0.304, respectively). Serum albumin levels were statistically significantly lower in CHB (3.81±0.04 g/dL), CHC (3.75±0.03 g/dL) and HBI (4.03±0.03 g/dL) than the control group (4.69±0.04 g/dL) (p=0.001). Serum IMA levels and IMAR, CHB, HBI, and CHC were statistically significantly higher than the control group (p=0.004 for IMA, p=0.001 for IMAR, respectively). However, in terms of IMA level and IMAR, no statistically significant difference was found in the comparison between CHB, HBI and CHC cases (p=0.072, p=0.213, respectively). Serum albumin, IMA levels and mean and p-values of IMAR of CHB, HBI, CHC cases and the control group are shown in Table 2.

In CHB and CHC cases, serum albumin levels were statistically significantly lower in those with significant fibrosis than those with mild fibrosis (p=0.044, p=0.012, respectively). Again, IMA and IMAR were statistically significantly higher in those with significant fibrosis than those with mild fibrosis (CHB; p=0.020, p=0.027, CHC, respectively; p=0.007, p=0.012, respectively). Albumin, IMA and IMAR values according to the degree of fibrosis in CHB and CHC cases are shown in Table 3.

Discussion

Hepatitis B and C viruses are two important viruses that cause serious consequences such as LC, fulminant hepatitis and HCC (8,9). Many studies have shown that IMA is the most important isoform of albumin (6,10). It has been reported that IMA concentration does not correlate with age and gender (11). In this study, there was no statistically significant difference between the IMA level and IMAR, and age and gender (p>0.05).

In a study, an increased plasma levels of IMA were observed in CHC cases and it was stated that high IMA concentrations may indicate chronic OS in CHC infection (12). In another study, it has been shown that IMA is not associated with other parameters more specific for the liver and ALT (4). In this study, there was no significant difference between IMA and IMAR and AST, ALT and AFP (p>0.05). Cakir et al. (5) showed that IMA increased in these cases and IMAR was associated with disease severity and liver fibrosis. They stated that as the albumin level decreases in patients with CLD, the IMA level will increase. In another study, it was recommended to use IMAR instead of IMA in patients with advanced liver disease (6).

A change of 1 g/dL in albumin causes a 2.6% change in the IMA level (11). However, the molecular events related to the structural changes that cause the change of serum albumin to IMA have not been fully elucidated (13). In this study, while there was a significant decrease in serum albumin levels in CHB, CHC and HBI compared to the control group, an increase in IMA level was observed (p=0.001). In addition, while there was a significant decrease in serum albumin levels in CHB and CHC compared to the HBI group, an increase in IMA level was found. These findings may be important in terms of demonstrating the importance of ischemia and related OS in liver inflammation due to viral hepatitis.

Another study showed that there is a significant increase in serum IMA levels and IMAR in CLD compared with healthy individuals. In a few cases, IMA has been shown to increase along with other parameters of OS. This suggests that a similar molecular

Table 1. Demographic characteristics of chronic hepatitis B, HBeAg negative chronic infection and chronic hepatitis C cases and the control group, mean values and p values of laboratory tests

	CHB	HBI	CHC	Control	p-value
Age	46.62±2.69	40.83±3.71	41.35±3.58	30.45±1.08	0.016
Gender (F/M)	42/38	30/20	10/20	33/27	0.063
AST (IU/L)	39.54±3.84	24.50±1.28	46.32±2.08	24.82±1.27	0.053
ALT (IU/L)	68.21±9.07	26.65±2.59	42.64±3.69	26.05±1.13	0.016
TOT BIL	0.53±0.06	0.39±0.03	0.52±0.05	0.32±0.02	0.122
AFP (µ/L)	3.25±0.18	1.98±0.16	3.40.±0.33	2.98±0.21	0.095
PTZ (sn)	11.58±0.17	10.97±0.64	11.70±0.19	11.30±0.10	0.107

F: Female, M: Male, AST: Aspartate amino transferase, ALT: Alanine amino transferase, AFP: Alpha fetoprotein, PTZ: Prothrombin time, TOT BIL: Total bilirubin, CHB: Chronic hepatitis B, CHC: Chronic hepatitis C, HBI: HBeAg negative chronic infection, HBeAg: Hepatitis B e antigen

Table 2. Mean and p-values of serum albumin, ischemia modified albumin and ischemia modified albumin/albumin ratios of chronic hepatitis B, HBeAg negative chronic infection and chronic hepatitis C and control group

	CHB	HBI	CHC	Control	p-value
Serum albumin (g/dL)	3.81±0.04	4.03±0.03	3.75±0.03	4.69±0.04	0.001
Serum IMA (ABSU)	0.171±0.01	0.181±0.01	0.190±0.01	0.088±0.01	0.004
IMAR (g/dL)	0.040±0.003	0.038±0.002	0.046±0.002	0.012±0.001	0.001

ABSU: Absorbance units, IMA: Ischemia modified albumin, IMAR: Ischemia modified albumin/albumin ratio, CHB: Chronic hepatitis B, CHC: Chronic hepatitis C, HBI: HBeAg negative chronic infection, HBeAg: Hepatitis B e antigen

Table 3. Comparison of albumin, ischemia-modified albumin levels, ischemia-modified albumin/albumin ratios according to the degrees of fibrosis in chronic hepatitis B and C cases

	Chronic hepatitis B			Chronic hepatitis C		
	Mild fibrosis (stage 1-2) (n=37)	Significant fibrosis (stage 3-4) (n=43)	p-value	Mild fibrosis (stage 1-2) (n=14)	Significant fibrosis (stage 3-4) (n=16)	p-value
Albumin	3.93±0.09	3.67±0.06	0.044	3.91±0.082	3.69±0.035	0.012
IMA	0.128±0.019	0.194±0.015	0.020	0.160±0.003	0.207±0.005	0.007
IMAR	0.029±0.005	0.044±0.004	0.027	0.040±0.004	0.047±0.003	0.012

IMA: Ischemia modified albumin, IMAR: Ischemia modified albumin/albumin ratio

event occurs in chronic hepatitis and that OS and free radical-mediated damage may play an important role in the development of liver failure (4,14). In our study, in line with the results of this study, serum IMA levels and IMAR, in CHB, HBI, CHC were found higher than the control group.

In a study serum IMA and IMAR levels were found to be significantly higher in patients with advanced fibrosis than those with low fibrosis. In addition, it has been stated that IMAR is more valuable than serum IMA concentration in distinguishing cases with mild and advanced fibrosis (6). In this study, serum IMA level and IMAR were significantly higher in those with severe fibrosis than those with mild fibrosis in CHB and CHC cases. This may show that IMA and IMAR can affect disease progression and can be used to evaluate fibrosis. This study is the first study in which serum IMA levels and IMAR values were investigated in cases with HBI according to our literature knowledge.

Study Limitations

There was no patient group with fibrosis 5 and 6 and HCC. The study had a small sample size, especially cases with CHC. Therefore, large-center studies with larger patient numbers are needed.

Conclusion

In this study, IMA levels and IMAR were found to be higher in CHB, HBI and CHC patients compared to the control group. In addition, in those with significant fibrosis in CHB and CHC, IMA level and IMAR were significantly higher than those with mild fibrosis. Early detection of fibrosis is necessary to prevent disease progression and appropriate treatment. IMA, IMAR can be used as a parameters in determining prognosis as an indicator of oxidative liver damage and in the evaluation of fibrosis (especially early detection of fibrosis). Perhaps, treatment methods aimed at preventing the formation of IMA by reducing OS may guide the development of new treatment methods in the future.

Ethics

Ethics Committee Approval: The study protocol followed the ethical guidelines of the 1975 Helsinki Declaration. Ethics committee approval was obtained from Fırat University Institutional Evaluation Committee (approval number: 24, date: 31.05.2018).

Informed Consent: Informed consent form was signed by the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.T., Desing: S.T., Data Collection or Processing: A.Ş., Analysis or İnterpretation: A.Ş., Literature Search: A.Ş., Writing: A.Ş., S.T.

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

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Research Article

57

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Hepatitis C Coinfection Among People Living with HIV in a University Hospital in İstanbul

İstanbul'da Bir Üniversite Hastanesinde HIV ile Yaşayan Bireylerde Hepatit C Koenfeksiyonu

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ABSTRACT

Objectives: Human immunodeficiency virus (HIV) has infected millions of people throughout the world and may co-exist with other infections due to common ways of transmission. In our study, we aim to assess the prevalence of hepatitis C virus (HCV) coinfection among people living with HIV (PLWH) as well as infection transmission ways, treatment responses of the treated patients.

Materials and Methods: Five hundred thirty PLWH were included in the study, monitored in our clinic between 2014 and 2020. Age, gender, education level, date of diagnosis and follow-up period, transmission ways, clinical observations and anti-HCV data of patients were retrospectively analyzed.

Results: Of the subjects 92.3% (n=489) were males, and 7.7% (n=41) were females. 1.7% (n=9) of patients were detected with anti-HCV positivity. 0.6% (n=3) of the anti-HIV positive patients had active hepatitis C infection. Anti-HCV positivity was found to be 65 times higher in injecting drug users.

Conclusion: There is no vaccine or post-exposure prophylaxis to protect against HCV. Therefore, HCV has to be monitored in follow-up visits for PLWH, risk factors should be identified, and the patients should be raised awareness of transmission and protection ways. Immediately started antiviral treatment when diagnosed with HCV. Antiviral therapy should be immediately started when HCV is diagnosed.

Keywords: HCV, HIV, coinfection

ÖZ

Amaç: Dünyada milyonlarca insanı etkileyen insan bağışıklık yetmezlik virüsü (HIV), ortak bulaş yolları nedeniyle başka enfeksiyon etkenleri ile birlikte olabilir. Çalışmamızda HIV ile yaşayan bireylerde hepatit C virüs (HCV) koenfeksiyon sıklığını, bulaş yollarını ve tedavi almış hastalarda tedavi cevabını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: 2014-2020 yılları arasında kliniğimizde takip edilen 530 HIV ile yaşayan birey çalışmaya alındı. Hastalara ait yaş, cinsiyet, eğitim düzeyi, tanı tarihi ve takip süresi, bulaşma yolları, klinik izlemleri ile anti-HCV verileri retrospektif olarak incelendi.

Bulgular: Olguların %92,3 (n=489) erkek, %7,7 (n=41) kadın idi. Hastaların %1,7'sinde (n=9) anti-HCV pozitifliği saptandı. Anti-HCV pozitif hastaların %0,6'sında (n=3) aktif hepatit C enfeksiyonu mevcuttu. Damar içi madde kullananlarda anti HCV pozitifliği 65 kat daha yüksek bulundu.

Sonuç: HCV'ye karşı koruma sağlayacak bir aşı veya temas sonrası profilaksi yoktur. Bu nedenle, HIV ile enfekte bireylerin takiplerinde HCV izlenmeli, risk faktörleri belirlenmeli, hastalar bulaş ve korunma yolları konusunda bilinçlendirilmelidir. HCV teşhisi konduğunda hemen antiviral tedaviye başlanmalıdır.

Anahtar Kelimeler: HCV, HIV, koenfeksiyon

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Introduction

In Turkey, there are 25,809 people living with HIV (PLWH) verified as of November 2020 (1). These people face several coinfections due to common transmission ways, including viral hepatitis B and C. Hepatitis C virus (HCV) main difference from hepatitis B is that it has no vaccine or post-exposure prophylaxis. In particular the individuals who have shared a contaminated needle and injection, and who made unprotected sexual intercourse are invariably at risk. With highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV)-based opportunistic enfections opportunistic infections were decreased, and life expectancy prolongation and higher quality of life were increased, whereas morbities and mortalities second to such infections–secondary to such infections as viral hepatitis C have remained critical (2). Several studies have reported that progression of liver disease is three times more likely in people with HIV/HCV coenfection-coinfection (3).

In our study, we aim to assess hepatitis C prevelance among PLWH we have followed up in our clinic, transmission ways and treatment responses of the treated patients.

Materials and Methods

Five hundred thirty PLWH were included in the study, followed up in Infectious Diseases and Clinical Microbiology at İstanbul Medeniyet University, Göztepe Training and Research Hospital, from January 2014 to September 2020. The data from patient files and electronic records were retrospectively reviewed, including the demographic information, HCV prevelances, transmission ways, treatment information, treatment results and clinical observations of the patients. ELISA was used for anti HCV serology, and polymerase chain reaction for HIV RNA.

Our study was approved by the Ethics Committee of İstanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2020/0457). All participants were informed about the study before it was conducted and their verbal consents were obtained.

Statistical Analysis

Number Cruncher Statistical System (Kaysville, Utah, USA) was used for statistical analyses. The datas were–the data were reviewed using descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum and maximum). Kolmogorov-Smirnov and Shapiro-Wilk tested normal distribution of quantitative data as well as graphical evaluations. For paired comparisons of the normally distributed quantitative data Student's t-test was used, and Mann-Whitney U test for paired comparisons of the non-normally distributed data was used. Pearson chi-square test, Fisher-Freeman-Halton exact test and Fisher's exact test were used for qualitative data. Significance level was defined as $p<0.05$.

Results

Between January 2014 and September 2020, 530 PLWH was studied; 92.3% (n=489) were males, and 7.7% (n=41) females. The median age of the patients was 37 (18 to 88), and the median length of follow-up was 4 years (0 to 6). 67.5% (n=330) of the patients were men who had sex with other men (MSM). The most prevalent way of HIV infection transmission was sexual intercourse; 62.3% (n=330) was homosexual, 31.7% (n=168) was heterosexual. Injecting drug use was detected for 1.3% (n=7). The distribution of descriptive characteristics of HIV-infected patients is shown in Table 1.

Anti-HCV positive was found in 1.7% (n=9) of the patients. The median age of the cases was 36 years (29 to 68), and the median length of follow-up was 4 years (0 to 5). Of these cases, 44.4% (n=4) were female, 55.6% (n=5) males. Injecting drug user (IDU) was at 33.3% (n=3).

Anti-HCV positive rates had no statistically significant difference depending on anti-HCV positivity rate was not statistically different according to mean ages, age groups, date of diagnosis, education level, length of follow-up, transmision way, being MSM, and CD4 T-lymphocyte count ($p>0.05$).

A statistically significant difference was found in anti HCV positive rates by gender ($p=0.003$; $p<0.01$). HCV positivity was found to be significantly higher in women. Anti-HCV was positive in four female patients. One of these patients had a history of operation and multiple blood transfusions, one had a history of injecting drug use.

For IDU, there were statistically significant difference in anti-HCV positive rates ($p=0.001$; $p<0.01$); IDU had significantly higher anti-HCV positive rate. The ODDS rate was found to be 64.62 (95% confidence interval: 11.81-353.6).

In Table 2, data of HIV patients were compared to those of HIV/HCV coinfected patients. In Table 2, data of HIV infected patients with and without HCV coinfection were compared. Of anti-HIV positive patients, 0.6% (n=3) had HCV-RNA positive. All of HCV-RNA positive patients were examined and all of them were genotip 3. Two of the patients were males and both were MSM and IDU. One of these patients was a Turkish citizen living abroad, who was found to have acute HCV infection and comorbid HIV infection. One patient was a female patient of foreign nationality and had a history of operation and multiple blood transfusions.

A patient used pegylated interferon alpha (Peg-IFN) plus ribavirin, and sustained one patient used Peg-IFN plus ribavirin, and had sustained virological response (SVR). Since the foreign patient did not have social security, she could not receive HCV treatment. Each patients continued to regularly use HAART. Cirrhosis and hepatocellular carcinoma were not observed in the patients during follow-up.

Discussion

The 2017 global hepatitis report of World Health Organization estimated that out of 71 million acute hepatitis C infected people throughout the world, 2.3 million were also HIV-coinfected (4).

Infection of HCV infection, like HIV, occurs vertically from the mother to the fetus and due to blood and blood components, sexual intercourse and injecting drug use. HIV HCV coinfection rates vary by country. It has been reported the coinfection rates were 12.16% in China (5), 25.6% in Bulgaria (6), 1% in Chile (7), 16.1% in the U.S. (8), and 13.8% in Greece (9), varying by geographical region, age group, risk group, and infection way. In addition, different studies from one country have showed that there were very significant differences depending on risk group. In Brasil, for example, a literature review reported that the rate was

Table 1. Distribution of descriptive characteristics of PLWH				
		n	%	
Age (years)	Min-max (median)	-	-	18-88 (37)
	Mean ± SD	-	-	39.34±12.03
	<35 years	216	40.8	-
	35-44 years	174	32.8	-
	45-54 years	74	14.0	-
	55-64 years	40	7.5	-
	≥ 65 years	26	4.9	-
Gender	Males	489	92.3	-
	Females	41	7.7	-
Length of follow-up (years)	Min-max (median)	-	-	0-6 (4)
	Mean ± SD	-	-	3.69±1.82
Education level	Primary school	27	5.1	-
	High school	39	7.4	-
	College	170	32.1	-
	Unknown	294	55.5	-
MSM (n=489 men)	MSM (-)	127	26.0	-
	MSM (+)	330	67.5	-
	Unknown	32	6.5	-
Transmission way	Heterosexual intercourse	168	31.7	-
	Homosexual intercourse	330	62.3	-
	Unknown	32	6.0	-
Injecting drug use	None	523	98.7	-
	IDU	7	1.3	-
CD4 count cell/mm^3	Min-max (median)	-	-	0-4731 (389)
	Mean ± SD	-	-	430.75±327.71
HIV-RNA IU/mL	Min-max (median)	-	-	2-100000000 (198500)
	Mean ± SD	-	-	3882043.9±46506767.5
Anti-HCV	Negative	521	98.3	-
	Positive	9	1.7	-
HCV-RNA (n=9)	Negative	6	66.7	-
	Positive	3	33.3	-

PLWH: People living with HIV, min: Minimum, max: Maximum, SD: Standard deviation, MSM: Men who had sex with other men, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, IDU: Injecting drug user

between 3.3% and 82.4% (10). For Turkey that rate has been found to remain between 0% and 19% (11,12,13,14,15,16,17,18,19). Furthermore, the current study reports that HCV prevelance is 1.7%, and active HCV infection 0.6%, similar to many previous studies conducted in Turkey.

In literature, it has been reported that HCV infection via heterosexual intercourse was rare (20). In a study, Vandelli et al. (21) studied 895 heterosexual monogamous pairs and found that HCV infection risk via sexual intercourse was little if any. Homosexual sexual intercourse has become one of the significant risk factors (22,23). The reason for the high level might be because of a false sense of security due to the HAART use and non-protected traumatized sexual intercourse. In our study, 33.3% (n=3) of the anti-HCV positive patients were MSM. One of these patients presented with hepatitis, nausea and vomiting and diagnosed with acute hepatitis C infection. The diagnosis of HIV was also made incidentally at the time of the acute HCV diagnosis.

In developed countries, injecting drug use is the key infection route of HCV (24). In a wide range of 4,306 HIV-infected patients, it has been reported that 25.1% of the patients had history of injecting drug use and were detected with HCV-positive in 78.5% of these patients. In Turkey, injecting drug use is not at the top of the list of HCV infection factors. It should be kept in mind that patients may make incomplete or false statements due to the fact that injecting drug use is illegal. In the current study, we showed that injecting drug use increases anti-HCV positive by 65 times. Sharing of syringes, injection applications under non-sterile conditions, unprotected sexual intercourse under the influence of

Table 2. Comparison of HIV patients and HIV/HCV coinfected patients Comparison of HIV infected patients with and without HCV coinfection

		Anti-HCV		p
		Negative (n=521)	Positive (n=9)	
		n (%)	n (%)	
Age (years)	Min-max (median)	18-881 (40)	29-68 (36)	[a]0.475
	Mean ± SD	42.73±13.35	45.18±12.62	
Age groups	<35 years	214 (41.1)	2 (22.2)	[b]0.406
	35-44 years	170 (32.6)	4 (44.4)	
	45-54 years	72 (13.8)	2 (22.2)	
	55-64 years	40 (7.7)	0 (0)	
	≥65 years	25 (4.8)	1 (11.1)	
Gender	Males	484 (92.9)	5 (55.6)	[c]0.003**
	Females	37 (7.1)	4 (44.4)	
Length of follow-up (years)	Min-max (median)	0-6 (4)	0-5 (4)	[d]0.489
	Mean ± SD	3.69±1.83	3.33±1.80	
Education level (n=236)	Primary school	26 (11.1)	1 (50)	[b]0.248
	High school	39 (16.7)	0 (0)	
	College	169 (72.2)	1 (50)	
MSM (n=457)	MSM (-)	125 (27.7)	2 (40.0)	[c]0.621
	MSM (+)	327 (72.3)	3 (60.0)	
Transmission way (n=498)	Heterosexual intercourse	162 (33.1)	6 (66.7)	[e]0.067
	Homosexual intercourse	327 (66.9)	3 (33.3)	
Injecting drug use	None	517 (99.2)	6 (66.7)	[c]0.001**
	IDU	4 (0.8)	3 (33.3)	
CD4 count cell/mm^3	Min-max (median)	0-4731 (388)	3-607 (410)	[d]0.550
	Mean ± SD	432.16±329.04	340.12±221.29	

[a]Student's t-test, [b]Fisher-Freeman-Halton exact test, [c]Fisher's exact Test, [d]Mann-Whitney U Test, [e]Pearson chi-square test, *p<0.05, **p<0.01, HIV: Human immunodeficiency virus, HCV: Hepatitis C virus, min: Minimum, max: Maximum, SD: Standard deviation, MSM: Men who had sex with other men, IDU: Injecting drug user

the substance may be the reason for this. It seems that patients with a history of injecting drug use should be evaluated in terms of HIV and HCV infection.

Anti-HCV positivity was found to be significantly higher in women in our study (n=4/41). Three patients were foreigners who were in Turkey for work. All of these patients stated that HIV transmission has happened sexually. Both HCV and HIV can be sexually transmitted. However, it should be kept in mind that some patients have a history such as surgery, multiple blood transfusions and may be transmitted by these ways.

Part of the HCV infected people spontaneously go through the disease while chronic infection develops in 75% to 85% of these patients. While some of the people infected with HCV have the disease spontaneously resolve, chronic infection develops in 75-85% of them. They could either remain asymptomatic or still have risks of cirrhosis, end-stage liver failure, and HCC progression. Studies have shown that gender, age, ethnicity, symptomatic acute infection and whether or not hepatitis B co-infection affect spontaneous HCV recovery, while HIV co-infection is one of the reasons that increase chronicity (25,26).

HIV-related guidelines, national or international, recommend that anti-HCV screening should be made for all HIV-positive individuals and continued if there are ongoing risk factors such as MSM, injection drug use and when HCV positive is detected the treatment should start. In the beginning of the threapy, due to HCV, drug interactions should be well considered in order to avoid hepatotoxic antiretroviral drug use. If viremia is detected by performing HCV RNA analysis, HCV genotype determination should be made in anti HCV positive patients. In follow-up of seronegative patients, HCV RNA should checked when unexplained elevation of liver enzyme is detected (27).

Also for the patients diagnosed with HCV infection, anti-HIV test should be required due to common transmission ways. In this study, HIV diagnosis of a patient was detected during his hospitalization due to acute hepatitis C infection.

Therefore, anti-HIV tests should be regularly performed for HCV positive patients having risky behaviors, and anti-HCV tests for HIV positive ones.

HIV/HCV coinfected people are more likely to have fibrosis, cirrhosis and related complications than only HCV positive ones, and thus early diagnosis and treatment become crucial (26,28,29). In a study including 1,176 anti-HCV positive patients in America, 34% of who were coinfected, it was observed that fibrosis stages of coinfected patients were similar to those of HIV negative

individuals 10 years older (30). In another study in which 23,441 HIV infected patient were monitored, it was found that 66.1% of 181 liver-related deaths had HCV positivity (31). In a cohort study performed in Sweden, it was showed that active HCV infection was present in 45% of deaths (32). In the present study, we observed that no patients developed cirrhosis during follow-up controls. We believe that for the HIV diagnosed patients at a young age, early detection of HCV positivity and immediate start to antiviral treatment can prevent progression of complications.

Anti-HCV positivity does not always prove the presence of active hepatitis C infection. Therefore, HCV-RNA should be considered, whether the individual have viremia or not. In this study, we found active infection in 3 of 9 patients were detected with anti-HCV positive. We could not start treatment two patients. We could not start treatment to two patients. A patient returned- one patient returned to his home country. One patient detected with HCV positivity was planned to administer direct-acting antiviral agents, however, the patient could not receive the treatment because she did not have social security. As a treatment, Peg-IFN and ribavirin was administered to one patient for 24 weeks, and HCV-RNA negativity was observed even in post-treatment follow-up at the 6th month and the patients had the SVR. It was thought that the high level of SVR in our patients high level of SVR in our patient which was defined as the level of HCV-RNA that could not be measured 6 months after the end of treatment, was due to reasons such as good adherance, young age and being Caucasian.

HCV seroprevalence was not found very high in our center and it is similar to other studies conducted in our country. One of the key factors of such low prevelance was lower frequency of injection drug use. The majority of the HIV-positive population being in the young age group, as well as early diagnosis of HCV and HIV and early initiation of treatment prevent possible complications.

Study Limitations

The limitation of the study is that it is a retrospective study, so all patient datas all patient's data were not available

Conclusion

PLWH are at risk due to HCV without vaccine and post-exposure prophilaxy. PLWH are at risk of HCV infection since there is no vaccine and postexposure prophylaxis. Patients should be made aware of transmision ways, regularly screened, and immediately started antiviral treatment when diagnosed with HCV.

Ethics

Ethics Committee Approval: Our study was approved by the Ethics Committee of Istanbul Medeniyet University, Göztepe Training and Research Hospital (approval number: 2020/0457).

Informed Consent: All participants were informed about the study before it was conducted and their verbal consents were obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: P.E., Desing: P.E., H.Ç., Data Collection or Processing: P.E., Analysis or İnterpretation: P.E., H.Ç., Literature Search: H.Ç., Writing: P.E., H.Ç.

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Evaluation of Knowledge Levels, Attitudes and Behaviors Among the Relatives of Patients Infected with Hepatitis B

Hepatit B Hasta Yakınlarının Bilgi Düzeylerinin, Tutumlarının ve Davranışlarının Değerlendirilmesi

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ABSTRACT

Objectives: To measure the knowledge level and evaluate the attitudes and behaviors of the relatives of patients with chronic hepatitis B.

Materials and Methods: This study was conducted in Ankara Atatürk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology. A self-explanatory questionnaire comprising was designed to evaluate and compare the knowledge, attitudes, and awareness of the participants regarding hepatitis B infection. The patients were followed up for at least one year with a diagnosis of hepatitis B virus (HBV) infection.

Results: The mean age of 106 relatives of patients was 40.6±11.8 years. The knowledge level of women about the disease, transmission routes, and protective measures was significantly better than men. The importance of receiving a vaccination and separating personal belongings that can be contaminated by blood was known by the majority (86.9% and 86.8%, respectively), but the vaccination rate was 49.1%. Age was inversely correlated with knowledge about transmission routes. The educational level had a positive impact on the knowledge level of relatives.

Conclusion: In the fight against HBV infection, informing the whole society, especially patients with HBV and their relatives, about transmission routes and prevention of HBV transmission is vital.

Keywords: Hepatitis B, patient relative, knowledge level, vaccination

ÖZ

Amaç: Kronik hepatit B'li hasta yakınlarının bilgi düzeyini ölçmek ve tutum ve davranışlarını değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma Ankara Atatürk Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği'nde yapıldı. Katılımcıların hepatit B enfeksiyonu ile ilgili bilgi, tutum ve farkındalıklarını değerlendirmek ve karşılaştırmak için açıklayıcı bir anket tasarlandı. Hastalar en az bir yıl süreyle hepatit B virüs (HBV) enfeksiyonu açısından izlendi.

Bulgular: Yüz altı hasta yakınının yaş ortalaması 40,6±11,8 yıldı. Kadınların hastalık, bulaşma yolları ve koruyucu önlemler hakkındaki bilgi düzeyleri erkeklerden önemli ölçüde daha iyiydi. Aşı yaptırmanın ve kan bulaşabilecek kişisel eşyaları ayırmanın önemi çoğunluk tarafından biliniyordu (sırasıyla; %86,9 ve %86,8), ancak aşılama oranı %49,1 idi. Yaş, bulaşma yolları hakkındaki bilgilerle ters orantılıydı. Eğitim düzeyi, akraba bilgi düzeyini olumlu yönde etkilemiştir.

Sonuç: HBV enfeksiyonu ile mücadelede tüm toplumu, özellikle HBV'li hastalar ve yakınları bulaşma yolları hakkında bilgilendirmek ve HBV bulaşının önlenmesi hayati önem taşımaktadır.

Anahtar Kelimeler: Hepatit B, hasta yakını, bilgi seviyesi, aşılama

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Introduction

The hepatitis B virus (HBV) infection is an important cause of morbidity and mortality as it causes both acute-chronic viral hepatitis and complications such as cirrhosis and hepatocellular cancer (HCC). Chronic HBV infection is the cause of more than half of HCCs which represent approximately 75-90% of all primary liver cancers. Besides, the incidence of cirrhosis in patients with untreated chronic hepatitis B is at least 40% (1). In our country, more than half of the liver transplantation cases performed between 2012-2016 were associated with viral hepatitis, especially HBV (2).

The low awareness, especially in the at-risk population that was born before the adoption of vaccination programs, may increase disease burden and death due to transmission and HBV complications (2). In Turkey, one out of three people over the age of 18 are estimated to have been infected with HBV, and it is thought that there are more than 2 million adults with hepatitis B surface antigen (HBsAg) positivity. Only about 12% of these people were found to be aware of their condition (3). In our country, since HBV infection is the endemic and horizontal transmission is prominent, relatives who share the same house with the patients are at risk for transmission. It will be effective to reduce the prevalence of HBV by identifying missing and inaccurate information about HBV in society, especially in patients and their relatives, and increasing the level of knowledge among people, and organizing educational approaches to create attitude and behavior change (4). In our country, it is known that the vaccination rate of the high-risk population is around 5% (4).

This study aimed to evaluate the level of knowledge and attitudes of the first-degree relatives who share the same house with patients in terms of their knowledge regarding disease definition, modes of transmission, risk factors, prevention methods, and consequences of the disease.

Materials and Methods

Study Group

The study included 106 volunteers who were older than 18 years of age and shared the same house with an HBsAg-positive patient to which they were related (first-degree). Only one relative of patients was included in the study group. The patients were admitted to the Ankara Atatürk Training and Research Hospital between 01.06.2014-01.07.2014 and were followed up for a duration of at least one year at our center.

Ethical Issues

This study was approved by the Institutional Ethics Review Committee of Ankara Yıldırım Beyazıt University Faculty of Medicine. The relatives of the patients were informed, and verbal and written informed consent was obtained from them before they took the questionnaire.

Study Instrument

A self-explanatory questionnaire comprising of 24 questions was designed to evaluate and compare the knowledge, attitudes, and awareness of the participants regarding hepatitis B infection. The questionnaires were completed under observation without any intervention. The content of the questionnaire was created by scanning national and international publications and the disease-related questions we received from patients. The questions were open-ended, but in some questions, options were given to determine the views of the participants. The questionnaire was comprised of the following sections:

- Demographics: age, gender, education, socioeconomic status,
- Knowledge of HBV: sources, self-assessment, knowledge items,
- Attitudes and behaviors towards HBV,
- Disease concerns and difficulties.

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS, Chicago, IL, USA). In the study, numerical data were shown with mean and standard deviation, and categorical data were shown with frequency and percentages. Chi-square tests were used for categorical data comparison between independent groups, and the Kruskal-Wallis test was used for multiple group analysis for ordinal data. The internal consistency of the questionnaires used in the study was evaluated with Cronbach's alpha value. In all statistical analyses, obtaining a p-value <0.05 was considered statistically significant.

Results

Sociodemographic Characteristics

A total of 106 relatives, 63 (59.4%) females and 43 (40.6%) males were included in the study. The mean age of the participants was 40.6±11.8 years.

Awareness

The responses of the participants to the questions that measured their level of awareness are shown in Table 1.

In our study, women were more aware that hepatitis B was an infectious disease affecting the liver (p=0.001) and a contagious disease (p=0.039) than men.

Knowledge Level

The responses of the participants to the questions that measured their level of knowledge are shown in Table 2.

Women had more information about the risk of transmission to relatives (93.7%, p=0.012), protection methods (vaccination: 100%, p<0.001; separation of personal items with blood contact: 95.2% p=0.002), complications (death: 49.2%, p=0.015; liver transplantation 31.7%, p=0.023) and treatment purpose (stopping viral replication: 76.2%, p<0.001), while men had higher rate of the misinformation that hepatitis B could turn into hepatitis C spontaneously (93%, p<0.001). Participants under the age of 30 were more aware that hepatitis B was an infectious disease (86.4%, p=0.004) and could be transmitted through vertical (100%, p=0.001) and sexual transmission (72.7%, p<0.001).

The knowledge that inactive carriage was contagious and required follow-up was greater in those under 30 and over 50 years of age (100%, p=0.001). All participants over the age of 50 knew that treatment aimed to stop viral replication (p=0.003), and the disease could cause cirrhosis (p=0.007). Persons with higher education had more knowledge about the aim of reducing viral

Table 1. Distribution of participants' awareness level about HBV infection

	n	%
What does hepatitis B infection mean?		
It is a microbial disease affecting blood	34	32.1
An important disease in which the liver is affected by a germ	81	76.4
Icterus is seen	62	58.5
It is an infectious disease	62	58.5
What other hepatitis germs do you know other than hepatitis B?		
Hepatitis A	65	61.3
Hepatitis C	98	92.5
Hepatitis D	30	28.3
Does the liver regenerate in patients with chronic hepatitis?		
Yes	45	42.5
No	48	45.3
Does hepatitis occur only with hepatitis germs?		
Yes	53	50
No	38	35.8
Can hepatitis B spontaneously return to hepatitis C?		
Yes	75	70.8
No	22	20.8
Is it necessary to have icterus for a person to have hepatitis?		
Yes	41	38.7
No	55	51.9

HBV: Hepatitis B virus

Table 2. Distribution of participants' knowledge level about HBV infection

	n	%
Can people infected with hepatitis B become only "silent carriers"?		
Yes	89	84
No	10	9.4
A person, who has been informed that s/he is a silent carrier, does not need to be followed and does not transmit the disease, is that correct?		
Yes	20	18.9
No	83	78.3
Are the relatives of patients at risk for hepatitis B infection?		
Yes	92	86.8
No	14	13.2
What are the modes of transmission?		
Contact with patient blood	106	100
During sexual activity	78	73.6
During surgery	88	83
During dental treatment	90	84.9
During childbirth	77	72.6
Acupuncture, tattoo, during piercing	80	75.5
With the common use of instruments in contact with blood in the barbershop	92	86.8
Kissing on the lips	40	37.7
Sharing kitchen utensils with infected person	29	27.4
With mouth and nose secretions caused by sneezing	37	34.9
With mosquito bite	33	31.1
With phlegm, sweat, tears, breast milk	29	27.4
Sharing the same environment with the patient	27	25.5
Shaking hands with infected person	14	13.2
Respiratory tract	27	25.5
Shared toilet, bathroom, with clothes, kitchen utensils	25	23.6
With stress	21	19.8
What are the ways to prevent hepatitis B?		
Separation of personal items with blood contact, such as toothbrushes and nail clippers	92	86.8
Vaccination	95	89.6
Single partner sexual activity	42	39.6
Using a condom	42	39.6
Washing foods with water	60	56.6
Using bottled water	26	24.5
What is the prognosis for hepatitis B?		
Cirrhosis of the liver	96	90.6
Liver cancer	48	45.3
Death	42	39.6
Liver transplantation	44	41.5
Does hepatitis B need to be monitored in a health facility?		
Yes	106	100
No	0	0
Is there any medication for chronic hepatitis B infection?		
Yes	77	72.6
No	26	24.5
If there is a treatment, what are the aims?		
Stopping the replication of virus and inactive it	62	58.5
Stopping the progression of the disease	77	72.6
Preventing hepatitis B turns into icterus	60	56.6
Preventing liver failure	39	36.8
Eliminating the disease completely	32	30.2
Can a person infected with hepatitis B donate blood?		
Yes	0	0
No	106	100

HBV: Hepatitis B virus

replication through treatment (69.1%, p=0.01) and stopping the progression of disease (81.8%, p=0.017). Also, they were more knowledgeable about the sexual transmission (using condoms: 56.4%, p=0.001; single partner sexual activity: 49.1%, p=0.012), when compared to those with lower education.

Sources of Information

Although the most common source of information was physicians for all groups, the rate of those who applied to the internet for information was higher in the group under 30 years of age (59.1%, p<0.001) and with a high level of education (38.2%, p=0.001) (Table 3).

Attitudes and Behaviors

The responses of the participants to the questions that measured their attitudes and behaviors are shown in Table 4. The rate of those who had HBV screening was lower in the group with higher education level (p=0.002).

Table 3. Distribution of information sources reported by participants.

	n	%
Where did you get information about hepatitis B?		
Doctor	82	77.4
Internet	29	27.4
Family	13	12.3
Newspapers, magazines	4	3.8

Table 4. Distribution of participants' attitude and behavior

	n	%
Did you get a hepatitis screening test?		
Yes	96	90.6
No	10	9.4
Would you be more afraid if your relative had hepatitis C or D instead of hepatitis B?		
Yes	74	69.8
No	29	27.4
Which of the following did you do when you learned that your spouse/sexual partner had hepatitis B?		
Blood screening test	72	67.9
Vaccination	52	49.1
I avoided living in the same house	0	0
I avoided sexual intercourse	11	10.4
Using condoms	14	13.2
After learning about the disease, I decided not to have children.	0	0
Which of the following situations occurred because of your relative with hepatitis B?		
I'm anxious to share the same house	8	7.5
I am very afraid that the disease can be transmitted to my children/grandchildren	18	17
I immediately had the test to see if I had the germ	55	51.9
I hesitate to have sexual intercourse	11	10.4
I have health concerns about her/his life	52	49.1

Discussion

HBV infection is a global public health problem. In our country, vaccination and education studies in the prevention of infection are important since HBV infection is the endemic and horizontal transmission is prominent (5). This study aimed to measure the knowledge level of respondents concerning HBV infection and to determine their risk perceptions and attitudes. The patients in the study were followed by our clinic for more than a year. When the answers given to the questions measuring the level of knowledge about HBV were examined, 76.4% of the participants knew that hepatitis B was an infectious disease affecting the liver and 84.0% knew that inactive carriage could be seen. In a similar study conducted by Şenol (6) with the relatives of people with chronic hepatitis B in İstanbul, 90.4% of the participants stated that HBV was an infectious disease, 94.2% of them stated that inactive carriage could be seen, and 80.8% of them stated that the carriers could transmit the disease to others (6). In another study conducted by Poyrazoğlu et al. (7) in Kayseri, 41.1% of relatives stated that hepatitis was a liver disease and an infectious disease, while 61.6% of them stated that the carriers could transmit the disease to others.

It is known that 15-20% of chronic hepatitis B cases may progress to icterus and HCC (8,9). In our study, 90.6% of the participants knew that the complications could lead to icterus, 45.3% to HCC, 41.5% to liver transplantation, and 39.6% to death. In the study of Şenol (6), they found that 82.7% of the relatives knew that hepatitis B could cause icterus and HCC. In the study of Poyrazoğlu et al. (7), 93.8% of the relatives of patients (patients with hepatitis B and C) stated that hepatitis could cause icterus and 39.3% of them stated that the disease could cause cancer. In a study conducted by Cheung et al. (10) with Chinese and Southeast Asians living in Canada, 68% of the participants were aware of HBV while more than 60% did not know the relationship between HBV and icterus or cancer. Our study and other studies conducted with relatives of patients showed that the level of knowledge about complications was higher in relatives than in the general population. The reason for this can be that relatives of patients have more information about hepatitis B due to various concerns including their own health.

While 90.6% of the patients' relatives had undergone screening tests, only 49.1% of them received the vaccination, even though 89.6% of the participants had knowledge about the protective effects of vaccination. Similar to our study, in the study of Şenol (6), it was found that 32.7% of the people who should be vaccinated against HBV had not applied for vaccinations. It is rather interesting to see that, even though the importance of vaccination is so well understood, a significant proportion of individuals choose not to get vaccinated-despite being at high risk for transmission. In the study conducted by Bulut et al. (11), the percentage of individuals completing the HBV vaccination schedule was 63.3%, and 12.1% of individuals did not even begin vaccination. In the same study, it was found that compliance with the vaccination schedule increased statistically with age (11). When the reasons for people not getting vaccinated were examined, the most common reasons were indifference, negligence, and lack of information (12). The vaccination rates of the risky population in our country are estimated to be around 5%-an alarming figure by any standard.

Therefore, it is important to organize training and educational approaches that encourage vaccination in both health professionals and at-risk groups (4).

In Turkey, in studies investigating the level of HBV-related information, it has emerged that there is an insufficient level of knowledge. Gökmenoğlu et al.'s study of dentistry students, an important risk group, showed that the level of knowledge was insufficient (1). However, in the same study, it was shown that the level of knowledge is better in the advancing classes with awareness and education studies. Again, in a study conducted by Özen in our country, it was reported that the level of knowledge is not sufficient even in hepatitis carriers (2). In reports from various underdeveloped countries, it has been observed that the level of knowledge and awareness of HBV in dental healthcare professionals (3), pregnant women (4), and healthcare professionals (5) are not sufficient. However, it is seen that all these deficiencies can be increased with various training programs and awareness programs. In our study, even in a group that is expected to have a high level of awareness about the disease, the insufficient level of knowledge shows that it is important to keep people informed about the issue.

Study Limitations

The limitations of our study are the relatively small number of patients, the fact that the questions were answered based on self-reporting, and the validity and reliability analysis of the questions asked were not performed. The other important limitation is that the data in the current study is relatively old and the statements and comments could be changed over time.

Conclusion

According to the findings of our study, the relatives of patients with HBV seem to have incomplete information about hepatitis B, while vaccination rates were found to be low. It is suggested that health professionals should give more importance to the education of patients and their relatives, especially during patient follow-up. In the fight against HBV infection, informing the whole society, especially patients with HBV and their relatives, about transmission routes and prevention of HBV transmission are vital. Our study is important because it is the first relatively large-scale study conducted with patient relatives in our country. However, multicenter studies with higher patient counts are needed to identify deficiencies in the society about hepatitis B, in order to address the lack of knowledge in the community and to provide education that will lead to behavioral changes.

Ethics

Ethics committee approval: This study was approved by the Institutional Ethics Review Committee of Ankara Yıldırım Beyazıt University Faculty of Medicine.

Informed Consent: Informed consent was obtained from them before they took the questionnaire.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K.K., İ.H., M.A.T., Concept: A.K.K., R.G., M.A.T., Design: A.K.K., R.G., M.A.T., Data Collection or Processing: A.K.K., G.R.Y., R.G., Analysis or Interpretation: A.K.K., İ.H., M.A.T., Literature Search: A.K.K., İ.H., M.A.T., Writing: A.K.K., R.G., F.E., İ.H., G.R.Y., M.A.T., Final approval: A.K.K., R.G., F.E., İ.H., G.R.Y., M.A.T.

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The Knowledge Level and Behavior of Patients with HBV Regarding HBV Infection and Prevention

HBV'li Hastaların HBV Enfeksiyonu ve Önlenmesine İlişkin Bilgi Düzeyi ve Davranışı

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ABSTRACT

Objectives: To determine the knowledge of hepatitis B infected patients and their behaviors regarding hepatitis B virus (HBV) infection and vaccination.
Materials and Methods: This study was conducted in Ankara Atatürk Training and Research Hospital, Department of Infectious Diseases. A total of 402 patients followed for one year or more were included in the study.
Results: Seventy-seven percent of the patients knew that HBV affects the liver, 64.2% of the patients were aware that HBV was an infectious disease and the possibility of inactive carriage was known by 91% of the patients. Although almost all patients were aware of the transmission routes, they were found to assume that transmission rates could be high even in circumstances where the risk of transmission was actually very low. Vaccination and its effects were recognized by all of the patients, as well as the possibility for progression to cirrhosis. Seventy-six percent of the patients were aware of treatments for HBV infection.
Conclusion: In this study, the knowledge and awareness level of the patients was considered to be good overall, despite the fact that there were some gaps in patient knowledge. We believe that these positive findings were associated with the educational activities in our clinic.
Keywords: Hepatitis B, knowledge, prevention

ÖZ

Amaç: Hepatit B ile enfekte hastaların bilgilerini ve hepatit B virüs (HBV) enfeksiyonu ve aşılama ile ilgili davranışlarını belirlemektir.
Gereç ve Yöntemler: Bu çalışma Ankara Atatürk Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları Kliniği'nde yapılmıştır. Çalışmaya bir yıl veya daha uzun süre takip edilen toplam 402 hasta dahil edildi.
Bulgular: Hastaların %77'si HBV'nin karaciğeri etkilediğini biliyordu, hastaların %64,2'si HBV'nin bulaşıcı bir hastalık olduğunun farkındaydı ve inaktif taşıyıcı olma olasılığını %91'i biliyordu. Neredeyse tüm hastalar bulaşma yollarının farkında olsalar da, bulaşma riskinin gerçekten çok düşük olduğu durumlarda bile bulaşma oranlarının yüksek olabileceğini varsaydıkları bulundu. Aşılama ve etkileri, siroza ilerleme olasılığı tüm hastalar tarafından fark edildi. Hastaların yüzde yetmiş altısı HBV enfeksiyonu tedavisinden haberdardı.
Sonuç: Bu çalışmada, hasta bilgilerinde bazı boşluklar olmasına rağmen, hastaların bilgi ve farkındalık düzeylerinin genel olarak iyi olduğu kabul edildi. Bu olumlu bulguların kliniğimizdeki eğitim faaliyetleri ile ilişkili olduğuna inanıyoruz.
Anahtar Kelimeler: Hepatit B, bilgi, önleme

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Introduction

Despite being a vaccine-preventable disease, Hepatitis B is a common public health problem throughout the world. The global prevalence of hepatitis B surface antigen (HBsAg), a surface antigen of the hepatitis B virus (HBV) which shows the presence of infection, ranges from 3% to 6%; however, prevalence varies greatly according to geographical region and vaccination success (1).

In Turkey, one out of three people over the age of 18 has been infected with HBV at some point in their life, and it is thought that there are more than 2 million adults with HBsAg positivity. Only about 12% of these people were found to be aware of their condition (2,3). According to this result, HBV awareness in our country can be considered to be quite low.

Prevention is the most important precaution for HBV infection. Many people who do not have symptoms and signs do not consider themselves to be at any risk for Hepatitis B. Therefore, patient education that may increase the likelihood of avoidance and vaccination behaviors, will play a crucial role in the prevention of disease spread. The second step is to increase and maintain the level of community immunity (herd immunity). The third step is to strengthen the surveillance of the disease. This will ensure timely, accurate and consistent reporting of diagnosed cases. The fourth step is to prevent the transmission of the disease. The fifth step is to increase accessibility to appropriate treatment options, thus reducing disease-related mortality (4,5,6). In order to achieve these goals, not only healthcare workers but also patients should be sufficiently educated about Hepatitis B infection.

In this study, we aimed to determine the knowledge and behaviors of patients infected with hepatitis B.

Materials and Methods

Study Group

The study included 402 patients with hepatitis B infection who were followed for a duration of at least one year between June 2014 and July 2014 at Ankara Atatürk Training and Research Hospital, Clinic of Infectious Diseases and Clinical Microbiology. The importance and requirements of the study were explained verbally to all patients followed at our center and written informed consent was obtained before sampling from all individuals that accepted to participate.

Ethical Issues

This study was approved by the Institutional Ethics Review Committee of Ankara Atatürk Training and Research Hospital in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Study Instrument

A self-explanatory questionnaire comprising of 24 questions was designed to assess and compare patients' knowledge and attitudes regarding hepatitis B infection. The questionnaires were completed under observation without any intervention. The content of the questionnaire was created by scanning national and international publications with regard to the questions we usually receive from patients followed at our department. The questions were open-ended, but in some questions, options (multiple-choice) were given to learn the views of the participants. The questionnaire was comprised of questions that assessed the following:

- Demographic: age, gender, education, socioeconomic status,
- Current disease status,
- Knowledge of Hepatitis B: Sources, self-assessment, knowledge items,
- Attitudes and behaviors towards disease,
- Disease concerns and difficulties.

Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (Chicago, IL, USA). In the study, numerical data were shown with mean and standard deviation, and categorical data were given with frequency (n) and percentages. Chi-square tests were used for categorical data comparisons while the Kruskal-Wallis test was used for multiple group analyses of ordinal data. The Cronbach's alpha value, which shows the consistency of the questionnaire, was found to be 0.588. In all statistical analyses, obtaining a $p<0.05$ value was considered to demonstrate statistical significance.

Results

We included 402 patients (258 males and 144 females) into our study, mean age was 37.9±11.3 years.

Most of the patients learned that they had HBV infection during blood donation (n=300, 74.6%).

All (402 patients, 100%) knew that hepatitis B infection could progress to cirrhosis, 372 patients (92.5%) knew that it could progress to liver cancer, 288 patients (71.6%) were aware of the possibility of death due to HBV infection (Table 1, 2). The rate of correctly answering this question was statistically higher in patients who were diagnosed 0-5 years ago (41.1%) than those who were diagnosed more than 5 years ago (p=0.036). A large majority of patients (366, 91%) also had knowledge that individuals could carry the infection as silent carriers.

In the study group, 120 (29.9%) attended physician visits every 3 month. Patients who attended visits every 3 months were more likely to know that HBV infection affects the liver, that their relatives were at risk for infection, and that the disease had drug treatments, compared to patients who attended physician visits at longer intervals (p=0.045, p=0.040, p=0.042, respectively).

The most recognized transmittance patterns by patients were: dental treatment (n=402, 100%), kissing (n=402, %100) and blood route (n=396, 98.5%) (Table 3).

The frequency of knowing about preventive measures were as follows: separation of toothbrushes and nail clippers (n=402, 100%), vaccination (n=402, 100%), single-partner sexual life (n=402, 100%). In addition, patients were found to believe that washing food (100%) and using bottled water (100%) were important for the prevention of disease transmission (Table 4).

Patients were mostly educated about hepatitis B infection by their physicians (n=390, 97%), while the internet was also an important source of information which was reported by 264 (65.7%) of the patients.

The family members of 336 patients (83.6%) were screened for HBV after the disease was diagnosed in their relative. All of

Table 1. Distribution of patients' knowledge about HBV infection		
	n	**%**
What is hepatitis B infection?		
It is a microbial disease affecting blood	150	37.3
An important disease in which the liver is affected by a germ	312	77.6
Icterus is seen	120	29.9
It is an infectious disease	258	64.2
Can people infected with hepatitis B become "silent carriers"?		
Yes	366	91.0
No	36	9.0
Are the relatives of patients at risk for hepatitis B infection?		
Yes	348	86.6
No	48	11.9
Is there any medication for chronic hepatitis B infection?		
Yes	306	76.1
No	96	23.9
Can hepatitis B infection be treated with diet?		
Yes	294	73.1
No	108	26.9
HBV: Hepatitis B virus		

Table 2. Patients' knowledge of prognosis of HBV infection		
Sequelae of infection	**n**	**%**
Cirrhosis of the liver	402	100.0
Liver cancer	372	92.5
Death	288	71.6
Liver transplantation	378	94.0
HBV: Hepatitis B virus		

Table 3. Distribution of patients' knowledge about HBV transmission		
	n	**%**
Mode of transmission		
Contact with patient blood	396	98.5
During sexual activity	366	91.0
During surgery	384	95.5
During dental treatment	402	100.0
During childbirth	396	98.5
Acupuncture, tattoo, during piercing	396	98.5
With the common use of instruments in contact with blood in the barbershop	396	98.5
Kissing with infected person	396	98.5
Contact with body fluids	396	98.5
Sharing the same environment with the patient	396	98.5
Shaking hands with infected person	402	100.0
Respiratory tract	396	98.5
Shared toilet, bathroom, with clothes, kitchen utensils	396	98.5
With stress	396	98.5
With the common use of insulin needle	402	100.0
HBV: Hepatitis B virus		

the patients (n=402,100%) stated that they believed their relatives should be vaccinated to prevent hepatitis B infection. The most common negative behavior reported by patients was avoidance or refusal of medical intervention by medical personnel in the emergency medicine setting (n=210, 52.2%), which was followed by people avoiding handshaking or kissing (n=210, 52.2%) (Table 5).

Gender, age, education and income were found to have no effect on the knowledge level of our study group (p>0.05 for each).

Discussion

HBV infection is accepted as the leading cause of hepatocellular cancer (HCC) worldwide. In case-control studies, the risk of HCC in individuals with chronic HBV infection is reported to increase between 5 and 15 times, although it varies with regard to the effects of other risk factors. Hepatic cirrhosis is present in 70-90% of individuals who develop HCC on the basis of HBV infection, but HCC may develop without cirrhosis in HBV infection (7,8). In a study conducted in Chinese and Southeast Asians, 68% of the participants stated that they were aware of HBV, but more than 60% did not know the relationship between HBV and cirrhosis and cancer. It has been shown that the level of knowledge about HBV infection increases with advanced age, education level and the use of media in health education (9). In studies conducted with different occupational groups in our country, the rates of those who were aware that hepatitis B could progress to cirrhosis and HCC were respectively, 13.1% and 8.3% among barbers and 88.7% and 75.3% among midwives. In a previous study in our clinic, these rates were found to be 85.7% and 65.7%, respectively (10).

In the literature, individuals were reported to believe that the disease could be transmitted by breast milk, saliva, sweat, tears, kissing, sneezing and handshaking (11,12,13). The presence of these erroneous notions is the source of unnecessary worries in the society and also the problems experienced by these patients in social life. Similarly, in our study, although all patients knew the correct routes of transmission, the proportion of patients with similar false information was quite high. In a previous study at our clinic, we had found that 75.2% of patients were aware that the separation of personal items such as toothbrushes and nail clippers were necessary measures to prevent HBV infection. In the current study, all patients were found to know that hepatitis B could be prevented by vaccination. In the previous study at our clinic, this percentage was 63.8% (10), indicating that the education carried out by our clinic had been effective.

Studies have shown that those who are in close contact with patients diagnosed with hepatitis B and those who live in the same household are persons at high risk of developing the disease

Table 4. Distribution of patients' knowledge about HBV infection prevention

	n	%
Prevention of transmission		
Separation of personal items with blood contact, such as toothbrushes and nail clippers	402	100.0
Vaccination	402	100.0
Single partner sexual activity	402	100.0
Using a condom	402	100.0
Avoid contact with blood and body secretions of infected persons	402	100.0
Washing foods with water	402	100.0
Bottled water	402	100.0

HBV: Hepatitis B virus

Table 5. Negative attitudes and behaviors exposure by the patients

Have you encountered negative attitudes and behaviors related to your illness?		
Yes	210	52.2
No	192	47.8
Have you encountered negative attitudes and behaviors in your family?		
Yes	48	11.9
No	354	88.1
What are the negative attitudes and behaviors you have encountered?		
My colleagues didn't want to share the same environment with me	60	14.9
Most people avoided shaking hands or kissing me.	210	52.2
My family is trying to keep my grandchildren and/or children away from me	54	13.4
My dentist declined me treatment	90	22.4
Emergency medical staff did not want to/hesitated to provide treatment	210	52.2
A large notice indicating that I was positive for HBV was placed on my bed when I was treated as an in-patient	66	16.4

HBV: Hepatitis B virus

and that these people should be screened regularly (5,14,15). In a study conducted on the relatives of patients with hepatitis B in our country, it was found that 23.1% of the patients' relatives had not undergone screening. In the same study, it was found that 32.7% of the participants who had to be vaccinated after having a screening test and 25% of the participants whose spouses had hepatitis B were not vaccinated to prevent hepatitis B infection (16). In our study, 16.4% of the patients reported that their family members had not undergone screening tests. However, all of the patients stated that their relatives should be vaccinated in order to prevent the disease from spreading. In the previous study at our clinic, 95.8% of patients had stated that their family members should undergo screening tests (10).

Studies conducted with different segments of the national and international community have shown that a great many participants have incomplete or incorrect information about hepatitis B infection prevention and transmission routes. Nevertheless, these studies have been shown that education and awareness studies contribute to infection prevention and vaccination (17,18,19). Similarly, when we compare the results of our previous study with the current study, we believe that our patients' HBV knowledge and awareness have increased as a result of effective training.

For the assessment of patient knowledge levels in our country should include the conduct of large-scale multi-center studies to determine the level of knowledge of patients with HBV and the general population. Considering the extreme numbers of Syrian immigrants in our country, it is essential that such studies should be conducted as soon as possible. The results of greater studies can improve the chance to perform sufficient and targeted education in the diverse populations that are present in our country.

Study Limitations

The limitations of our study are that the patient was obtained from a single center, the questions were answered on the basis of the self-reporting, and the validity and reliability analysis of the questions asked were not performed.

Conclusion

Hepatitis B is a preventable and curable disease. Increasing the level of knowledge about the disease and vaccination studies can both reduce the incidence of the disease and prevent negative attitudes and behaviors faced by the patients.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Review Committee of Ankara Atatürk Training and Research Hospital in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Informed Consent: Informed consent was obtained from them before they took the questionnaire.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K.K., İ.H., M.A.T., Concept: A.K.K., R.G., M.A.T., Design: A.K.K., R.G., M.A.T., Data Collection or Processing: A.K.K., G.R.Y., R.G., Analysis or Interpretation: A.K.K., İ.H., M.A.T., Literature Search: A.K.K., İ.H., M.A.T., Writing: A.K.K., R.G., F.E., İ.H., G.R.Y., M.A.T., Final approval: A.K.K., R.G., F.E., İ.H., G.R.Y., M.A.T.

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Research Article

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The Importance of Vitamin D Deficiency as a Potential Marker Among Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında Potansiyel Belirteç Olarak D Vitamini Eksikliğinin Önemi

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ABSTRACT

Objectives: We aimed to identify the potential role of vitamin D_3 among patients with chronic hepatitis B (CHB) in Birjand, Iran.

Materials and Methods: In this case-control study, 292 patients were selected with CHB and 304 healthy subjects as control groups in the outpatient clinic of the infectious diseases department between January 2018 and December 2019. We quantified the levels of total vitamin D_3 in serum samples of them. Logistic statistical analysis was applied at the significance level of 5%.

Results: The mean age and serum vitamin D_3 level of the study and control groups were; 39.9±12.3 years, 43.0±9.3 years and 17.76±5.53 ng/mL, 22.07±2.41 ng/mL, respectively. So, a significant difference between means of vitamin D_3 serum in the two groups was observed (p>0.05). The prevalence of vitamin D_3 deficiency was higher among patients with hepatitis B virus (63.0%) than the healthy group (32.9%). Frequency distribution of serum vitamin D_3 levels showed a significant difference between the two groups (p=0.001). The risk of vitamin D_3 deficiency was significantly more than the healthy group (odds ratio: 3.17, p<0.001).

Conclusions According to the results; a high risk of vitamin D_3 deficiency related to CHB was found in this city. Future studies are warranted to consider the impact of vitamin D supplementation in CHB.

Keywords: Vitamin D_3 level, liver disease, chronic HBV infection

ÖZ

Amaç: İran, Birjand'daki kronik hepatit B (KHB) hastalarında vitamin D_3'ün potansiyel rolünü belirlemeyi amaçladık.

Gereç ve Yöntemler: Bu olgu-kontrol çalışması için, Ocak 2018 ile Aralık 2019 tarihleri arasında enfeksiyon hastalıkları bölümü polikliniğinden KHB'li 292 hasta ve kontrol grubu olarak 304 sağlıklı denek seçildi. Bunların serum örneklerindeki total vitamin D_3 düzeylerini belirledik. Lojistik istatistiksel analiz %5 anlamlılık düzeyinde uygulanmıştır.

Bulgular: Çalışma ve kontrol gruplarının yaş ortalamaları ve serum vitamin D_3 düzeyleri sırasıyla; 39,9±12,3 yıl, 43,0±9,3 yıl ve 17,76±5,53 ng/mL, 22,07±2,41 ng/mL idi. İki grup arasında serum vitamin D_3 ortalamaları arasında anlamlı bir fark gözlendi (p>0,05). Vitamin D_3 eksikliği prevalansı KHB'li hastalarda (%63,0) kontrol grubuna göre (%32,9) yüksekti. Vitamin D_3 seviyelerinin frekans dağılımı iki grup arasında anlamlı farklılık gösterdi (p=0,001). Vitamin D_3 eksikliği riski control grubuna göre anlamlı derecede fazlaydı (olasılık oranı: 3,17, p<0,001).

Sonuç: Sonuçlara göre; bu şehirde KHB'ye bağlı yüksek vitamin D_3 eksikliği riski bulundu. Her ne kadar gelecekteki çalışmaların KHB'de D vitamini takviyesinin etkisini dikkate alması garanti edilse de. Gelecekteki çalışmaların KHB'de D vitamini takviyesinin etkisi üzerine olması beklenmektedir.

Anahtar Kelimeler: Vitamin D_3 düzeyi, karaciğer hastalığı, kronik HBV enfeksiyonu

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Introduction

The liver is the main place for vitamin D_3 synthesis, where 25-hydroxylation occurs (1). Vitamin D_3 plays an appearing role in metabolic liver diseases. There is evidence about the interrelationship between vitamin D_3 and different chronic liver diseases owing to its immunomodulatory role (2,3). About 240 million individuals are infected with hepatitis B virus (HBV) chronically all over the world (4).

It has been shown that vitamin D_3 has very important biologic effects (5,6). Vitamin D_3 levels can affect the immune system and host response to HBV infection.

But, the association between vitamin D_3 metabolism and chronic hepatitis B (CHB) is less well characterized yet (7).

Different studies suggested low levels of vitamin D_3 are associated with high levels of HBV replication in CHB patients recently. Although, a study found a positive relationship between hepatitis B surface antigen (HBsAg) seroclearance and vitamin D_3 levels (8).

Also, another one showed a significant relationship between higher levels of HBV replication and low levels of vitamin D_3 in CHB infection (9). In addition, the role of vitamin D_3 may also affect disease progression in patients with HBV infection.

According to the mentioned contents, it was assumed that vitamin D_3 level may be one of the responsible agents for the very low serum levels of CHB patients. So, the purpose of this study was to specify the risk, associated factors, and symptoms related to vitamin D_3 deficiency among CHB patients compared to healthy individuals in Birjand.

Materials and Methods

This case-control study was carried out in Khorasan Jonoobi province of Iran in 2019 in the outpatient clinic of the infectious diseases department.

Sampling

In this study, 292 patients with CHB (HBsAg positive, anti-HBs negative), were randomly selected according to the calculated sample size by the following formula with a power of 90%. In addition, 304 natural immunized persons (HBsAg negative, anti-HBs has normal liver enzymes who have not received antiviral treatment were included. the healthy group was selected from collected samples of the master plan of the province (26).

$$n = \left[\frac{\frac{z_{1-\alpha}}{2} + z_{1-\beta}}{0.5 \ln\left(\frac{1+r}{1-r}\right)} \right] + 3$$

Vitamin D_3 Level Classification

Total vitamin D_3 levels were measured in the serum samples. Based on the World Health Organization, a level of 30 ng/mL or above is considered as vitamin D_3 sufficiency (10). Then, vitamin D_3 status was classified as normal (≥30 ng/mL), insufficient (20-29.9 ng/mL), and deficient (<20 ng/mL).

Laboratory Tests

For laboratory tests, 10 ccs of venous blood were taken from patients and healthy controls. The serum levels of vitamin D_3 were measured using a COBAS e411 analyzer, manufactured by Mannheim Roch diagnostic Gmbh in Germany, with the Elecsys kit (REF0589413). Other tests were performed on patients and healthy controls according to laboratory routines. Levels of alanine transaminase (ALT), aspartate transaminase (AST), (glycated hemoglobin) hemoglobin A1C (HbA1C) and bilirubin levels of liver enzymes were measured by the ARCHITECT I system biochemical auto-analyzer. Levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood sugar (FBS), and body mass index (BMI) were also measured.

The inclusion criteria for CHB patients were: patients who were admitted to the infectious diseases outpatient clinic with the diagnosis of CHB with the approval of the infectious specialist according to clinical and serological signs, willingness to participate in the study, didn't receive supplementation or injection of calcium and vitamin D_3 in the last six months and also with age ≥18 years. In addition, 304 healthy subjects without a history of hepatitis B disease were selected as healthy control group 26.

Patients' and healthy controls exclusion criteria include severe renal disease, history of cardiovascular disease, co-infection with cancer, pregnancy, diabetic disease, thyroid disorders, other viral hepatitis (hepatitis C virus, hepatitis D virus, human immunodeficiency virus), and other causes of liver disease such as alcohol consumption.

Variables of interest were: age, sex, BMI, and clinical symptoms such as FBS, glycated HbA1C, blood pressure, and HBsAg.

Ethics Approval

This study was approved by the Birjand University of Medical Sciences (BUMS) Ethics Board Committee (approval number: IR.BUMS.REC.1398.324).

Statistical Analysis

Descriptive statistics were used to describe the data, chi-square test was applied to determine the difference of symptoms related to vitamin D_3 deficiency between the study groups. Also, logistic regression was done to specify the relationship between considered variables and vitamin D_3 deficiency in two groups. All analysis was done by SPSS version 22.0. The significance in all of these tests was two-tailed with a 5% significance level.

Results

Out of the all subjects who participated in the study, 48.6% were male in the case group; with a mean age 29±5.3; and 52.2% female with mean age (31.5±7.8); also, of the 304 healthy subjects, 22.1% male; mean age 23.1±7.7, and 77.8% female with mean age 29.1±11.7. So; the distribution of gender was similar in the patients' group (Table 1). Healthy controls were younger than patients but no significant difference between them was observed ($p>0.05$). So that, the mean age of the CHB and control groups were, 32.9±12.3 years and 28.18±11.21 years, respectively. There was no significant difference in HbA1C level between genders, 5.71% vs 5.43% ($p=0.343$) (Table 1).

The mean of vitamin D_3 serum levels in the CHB and control groups were; 17.76±5.53 ng/mL, 22.07±2.41 ng/mL, respectively with significant differences (p=0.031). When categorized as deficient, insufficient, and sufficient. Then among the healthy subjects, vitamin D_3 levels were classified as 32.9%, 25.96%, and 41.15%, respectively.

Of 292 patients, 184 (63.1%), 56 (19.2%), and 52 (17.8%) had vitamin D_3 deficiency, insufficiency, and sufficient vitamin D_3 serum levels, respectively. The prevalence of vitamin D_3 deficiency was high among CHB patients (63.1%) as well as in healthy individuals (32.9%). Vitamin D_3 levels frequency distribution showed a significant difference in the two groups (p=0.001) (Table 2).

There is a negative correlation between vitamin D_3 levels and BMI and HbA1C in patients. Also, a positive correlation was noticed between age and vitamin D_3 levels, but none of these have significant values in the control group (p>0.05) (Table 3).

The results of the comparison of laboratory characteristics of CHB patients and healthy controls showed that the mean of ALT in patients was 32.82 IU/mL (8-117) and AST was 32.21 IU/ML (10-167). Of the all patients in total (21.04%) had ALT and (17.54%) had AST higher than 40 IU/ML while in the healthy group, only 15% had ALT and 5% had AST higher than 40 IU/mL. Also, there was a significant difference in ALT and AST between the two groups (p=0.001). Based on this result, between variables such as LDL, HDL, and BMI, age, sex, and vitamin D_3 levels; was observed no significant difference.

According to the logistic regression results, the risk of vitamin D_3 deficiency in men is 45% higher than in women which is not statistically significant [odds ratio (OR): 1.54, p=0.114). Among the patients, 75.3% were urban and 24.7% were rural residents. The distribution of vitamin D_3 deficiency in rural people is more than in urban population, which is significant in both groups (OR: 2.321, p=0.004). There was no significant difference in the BMI distribution between the two groups (p=0.13). In general, 47.3% of patients had a desirable weight, 35.5% had overweight and 8.2% had a BMI of more than 30 (Table 4).

Discussion

This study was conducted for the first time in this province (a region in the East of Iran) regarding vitamin D_3 pattern in patients with CHB and also to investigate factors associated with vitamin D_3 deficiency in CHB in comparison with the healthy group. In a period (1990-2010), the prevalence of vitamin D_3 deficiency was studied in Iranian society, and according to the results, in all regions; both sexes had moderate and significant vitamin D_3 deficiency (11).

Nghiem et al. showed that vitamin D_3 deficiency existed in many CHB patients and this deficiency had a relationship with the complications and outcome of the disease. Decreased liver function due to HBV-induced injuries to liver cells can be one of the causes of vitamin D_3 deficiency in CHB (12,13).

The results of this study showed that different degrees of the prevalence of vitamin D_3 deficiency existed among patients and healthy controls. The duration of exposure to sunlight exposure is an important factor in the changes in vitamin D_3 levels (14).

Table 1. The baseline characteristics of CHB group by sex

	Male	Female	p-value
HbA1C (mmol/mol)	5.71±1.24	5.43±1.11	0.343
BMI (kg/m²)	25.6±3.1	24.7±2.9	0.595
Age (year)	23.33±7.76	29.79±11.77	0.033
BP1[1] (mmHg)	120.38±1.7	110.96±2.0	0.243
BP2[2] (mmHg)	79.91±1.0	76.68±0.861	0.084
FBS[3] (mg/dL)	97.08±24.5	121.44±123.82	0.131

CHB: Chronic hepatitis B, HbA1C: Hemoglobin A1C, BMI: Body mass index, BP1[1]: Blood pressure (systolic), BP2[2]: Blood pressure (diastolic), FBS[3]: Fasting blood sugar

Table 2. Distribution frequency of serum vitamin D level in the study groups

Group	n	Serum vitamin D level		
		Deficiency (n, %)	Insufficiency (n, %)	Sufficient (n, %)
Patients	292	184 (63.1)	56 (19.2)	52 (17.8)
Control	304	100 (32.9)	79 (26.0)	125 (41.15)

Table 3. Correlation between serum vitamin D levels and assessed variables in the study groups

Variables	Serum vitamin D			
	Case		Control	
	r	p	r	p
Age (year)	0.371	0.07	0.159	0.189
BMI (kg/m²)	-0.039	0.69	0.106	0.382
HbA1C (mmol/mol)	-0.04	0.78	-	-

BMI: Body mass index, HbA1C: Hemoglobin A1C

Table 4. Results of logistic regression for risk of vitamin D deficiency against the variables of interest in the study groups

Variables	Vitamin D Deficiency		Odds ratio (95% CI)	p-value
	Yes	No		
Male	182 (62.7%)	150 (48.1%)	OR: 1.540	0.114
Female	110 (37.3%)	154 (51.9%)	*	-
Urban	197 (70.9%)	175 (62.1%)	*	-
Rural	95 (29.1%)	129 (37.9%)	2.321 (1.31-4.11)	0.004
Mean ± SD	24.39±4.60	25.26±3.79		-
Normal (18.5-24.9)	47.3%	44.4%	*	-
Overweight (25-29.9)	35.5%	40.04%	0.72 (0.568-1.07)	0.135
Obese (>30)	8.2%	11.1%	0.86 (0.38-1.93)	0.081
BP1	12.28±1.29	11.42±1.3	0.39 (0.16-1.78)	0.363
BP2	7.49±0.971	7.23±0.368	0.09 (0.031-0.41)	0.671
18-24	23 (8.6)	22 (9.3)	0.12 (0.58, 1.07)	0.133
25-34	76 (25.9)	64 (18.3)	0.997 (0.565-1.759)	0.091
35-44	84 (29.3)	91 (28.1)	1.21 (0.84, 1.98)	0.073
45-54	44 (15.5)	72 (21.7)	1.079 (0.851-1.367)	0.341
55-64	35 (12.1)	39 (11.6)	1.015 (0.691-1.492)	0.282
>65	21 (7.1)	18 (3.9)	*	-
CHB	184 (63.1)	45 (36.9)	3.17 (1.521-5.913)	-
Control	100 (32.9)	204 (67.1)	*	-

CI: Confidence interval, SD: Standard deviation, CHB: Chronic hepatitis B, BP1: Blood pressure (systolic), BP2: Blood Pressure (diastolic)

In some studies, vitamin D_3 levels were found to be inversely proportional to HBV-DNA viral load and a sufficient level of vitamin D_3 (15).

Previous studies showed the association between D_3 level and CHB (16,17,18), this study was in line with these studies too (19).

In this study, vitamin D_3 insufficiency/deficiency accounted for 82.1% of patients, which was similar to the reported prevalence from Japan and Germany (20,21). However, these results indicate that the relatively high prevalence of vitamin D_3 deficiency is similar to another study (22). It might be because sunshine hours differ among various latitudes as sunlight-related ultraviolet rays are the substantial factor for vitamin D_3 synthesis (22). However, this study showed that there was no association between the serum vitamin D_3 level and biological factors in both study groups. This failure could be due to variations in the subject's age, HBV genotype, and racial background.

BMI higher than normal is considered to be an effective factor in the level of vitamin D_3 stores (23). In this study, however, no significant relationship was found between serum levels of vitamin D_3 and BMI. This result was different from other studies (21,22).

The current study, showed no association between the biochemical parameters and the serum vitamin D_3 level by sex. It is obscurant whether vitamin D_3 deficiency is effective in CHB. We assume that sunlight exposure time might be short in the healthy subjects since they might go out less frequently than patients with CHB.

A high prevalence of vitamin D_3 insufficiency in healthy individuals, as well as CHB patients, can be associated with consuming poor foods in vitamin D_3 and lower sun exposure. Also, the results of Tabrizi et al. (21) as a systematic review study showed a high prevalence of vitamin D_3 deficiency among the Iranian population. The main reason for the higher vitamin D_3 deficiency prevalence in these people may be due to spending more time at home, and the clothing that may result in reduced vitamin D_3 synthesis. Also, the vitamin D_3 content is low in the Iranian diet (24).

In the published records on the prevalence of vitamin D_3 deficiency showed that vitamin D_3 deficiency prevalence was significantly different based on geographical regions in the Iranian population (10). In this study, however, vitamin D_3 deficiency was not correlated with liver function parameters significantly, probably due to that vitamin D_3 serum levels are affected by multiple factors. Roughly, one billion people worldwide apparently are vitamin D_3 deficient (11,25). In line with a previous study (3), our results confirm an inverse correlation between BMI and HbA1C loads and vitamin D_3 levels in the patients' group.

Study Limitations

Some limitations of this study were: influencing of several factors on serum vitamin D_3 levels; such as seasonal variation, diet, and geographical habitation. However, any information about these affecting factors for study subjects was not available. Another limitation is that vitamin D_3 may be an additional factor for the clinical outcomes of HBV infection and its interaction with vitamin D_3 receptor on the pathogenesis of HBV infection needs to be explored further. However, this study could not demonstrate the relevance between assessed variables and serum level vitamin D_3, partially due to having only a few patients with advanced liver fibrosis.

Conclusion

Our study findings reveal that probably this studied population suffers from an insufficiency of vitamin D_3. This indicates the need to consume foods rich in vitamin D_3, require higher sun exposure, or vitamin D_3 supplementation should be recommended in this area. It is noteworthy that although vitamin D_3 deficiency is apparent in patients, this deficiency is also a noticeable difference with healthy people. Therefore, supplementation of vitamin D_3 with the initial dose should be recommended and initiated.

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Ethics

Ethics Committee Approval: This study was approved by the Birjand University of Medical Sciences (BUMS) Ethics Board Committee (approval number: IR.BUMS.REC.1398.324).

Informed Consent: Written consent was obtained from the all of patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.O., M.Z., Concept: F.O., M.Z., Desing: F.O., M.Z., Data Collection or Processing: M.Z., Analysis or İnterpretation: F.O., M.Z., Literature Search: F.O., M.Z., Writing: F.O., M.Z.

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Research Article

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Assessment of Stigma Exposure Status of Patients with Hepatitis B Infection

Hepatit B Enfeksiyonu olan Hastalarda Yaşanılan Zorlukların Değerlendirilmesi

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ABSTRACT

Objectives: Although stigma is well defined in people with a chronic disease or condition, it has not been studied much in individuals infected with hepatitis B virus (HBV). The study is one of the first descriptive individual studies conducted on this subject in our country. Our aim in this study was to evaluate the stigma experiences and concerns of individuals living with HBV, their sharing of their illness with the environment, and the state of being affected by their social relationships.

Materials and Methods: Patients with hepatitis B surface antigen positivity who were admitted to the infectious diseases outpatient clinic were surveyed through face-to-face interviews. Epidemiological data, stigma experiences and anxiety states, people with whom they shared their illness, the reasons for not sharing, the impairment of social relations were questioned.

Results: It was found that 19.5% of 390 individuals infected with HBV who participated in our study were "exposed" to stigma in various ways, and 27.4% were "worried" about experiencing this condition. In research, 19.9% of women, 41.4% of university graduates, and 34.8% of divorced or widowers were found to experience higher stigma (p=0.002, p=0.02 and p<0.001, respectively). It was determined that 56.7% of the participants did not share their illnesses, and this need increased with stigma experiences and anxiety. It was found that individuals mostly shared their disease status with their first-degree relatives (p<0.001).

Conclusion: The fact that individuals infected with HBV experience different forms of stigma or experience anxiety suggests that there is a need to investigate these conditions and develop treatment interventions.

Keywords: Hepatitis B infection, stigma, awareness

ÖZ

Amaç: Stigma, kronik hastalığı veya durumu olan kimselerde iyi şekilde tanımlanmış olmasına rağmen hepatit B virüsü (HBV) ile enfekte bireylerde çok fazla araştırılmamıştır. Çalışma bu konu hakkında ülkemizde yapılan ilk tanımlayıcı bireysel çalışmalardan biridir. Bu çalışmada amacımız, HBV ile yaşayan bireylerin stigma deneyimleri ve kaygılarının, hastalıklarını çevreyle paylaşma ve sosyal ilişkilerinin etkilenme durumunun değerlendirilmesidir.

Gereç ve Yöntemler: Enfeksiyon hastalıkları polikliniğine başvuran hepatit B yüzey antijeni (+) bireylerle yüz yüze görüşme yoluyla anket yapıldı. Epidemiyolojik veriler, hastaların stigma deneyimleri ve kaygı durumları, hastaların hastalıklarını kimlerle paylaştıkları, paylaşmama nedenleri ve sosyal ilişkilerin etkilenmesi sorgulandı.

Bulgular: Çalışmamıza katılan HBV ile enfekte 390 bireyin %19,5'inin çeşitli şekillerde stigmaya "maruz kaldığı", %27,4'ünün ise bu durumu yaşamaktan "kaygı duyduğu" bulundu. Araştırmada kadınların %19,9'unun, üniversite mezunlarının %41,4'ünün, boşanmış/dul olan bireylerin %34,8'inin daha yüksek oranda "stigma" yaşadığı belirlendi (sırasıyla; p=0,002, p=0,02 ve p<0,001). Katılımcıların %56,7'sinin hastalıklarını paylaşmadığı, stigma deneyimleri ve kaygı durumuyla birlikte bu ihtiyacın arttığı belirlendi. Bireylerin hastalık durumlarını en çok birinci derece yakınları ile paylaştıkları tespit edildi (p<0,001).

Sonuç: HBV ile enfekte bireylerin farklı şekillerde stigma deneyimleri veya kaygı yaşadıklarının tespit edilmiş olması, bu durumların araştırılması ve iyileştirme müdahalelerinin geliştirilmesine ihtiyaç olduğunu düşündürmüştür.

Anahtar Kelimeler: Hepatit B enfeksiyonu, stigma, farkındalık

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Introduction

Hepatitis B virus (HBV) infection is a global public health problem and continues to be important (1,2,3). According to the report of the World Health Organization (WHO), it is reported that one million people die every year due to viral hepatitis, and since 2000 there has been an increase of 22% in deaths. WHO aims to reduce the number of HBV infections by 90% and mortality by 65% for 2030 and determines strategies for this purpose. One of these strategies is to ensure that individuals are diagnosed by generalizing HBV examinations and to prevent social transmission by treating them when necessary (4,5,6,7). However, the situation or anxiety of individuals encountering stigma in various ways in their environment due to being diagnosed with HBV may create some obstacles in ensuring the success of these strategies.

These unpleasant conditions, which are assessed in different conditions and patients, have not been studied much in HBV-infected individuals (8,9,10,11). Stigma (stigmatization, labeling); is a social unacceptance situation and has been expressed in various ways. On the one hand, it is defined as a social and cultural process, on the other hand, it is considered as a state of deviation from normal and a complex individual/social time period (12,13). Stigma may be associated with feelings of shame, blame, fear, anxiety, depression, and lower quality of life (HCQ) among people living with chronic hepatitis B (CHB). Stigma against individuals can also appear as discrimination. Discrimination, on the other hand, has been stated by the institutions as negative actions such as refusing the employment of people with certain characteristics and preventing access to health services, with basic concepts such as race and sexuality at the forefront. It has been reported that negative attitudes and behaviors towards individuals can be seen in many environments such as family, relatives, immediate environment, social environment, work environment, and health institutions (8,13,14,15,16). The state of anxiety is a situation that occurs with the threat or perception of a threat of body or mind that is real or imaginary and it can be frequently observed in individuals with chronic infections (17).

Some of the individuals with HBV infection because of their anxiety about exposure to stigma in various ways or encountering this situation; they do not have screening or diagnostic tests, they need to hide their diseases, and even some of those who are diagnosed do not have their treatment and follow-up (10,11,18,19). Depending on these situations, patients can both endanger their own health and play a role in social contagion by causing the spread of infection. Individuals may also present with late complications of HBV infection, such as hepatocellular cancer, cirrhosis, and liver failure, due to delays in treatment (3,20).

Our aim is to assess the experiences of stigma or anxiety in patients with HBV infection, the reasons for sharing or not sharing their HBV infection, their social relations, and knowledge-awareness in our own clinic. The study is a pilot study that also aims to control and determine the obstacles to the disease in individuals living with HBV.

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Materials and Methods

Study Design and Setting

The study was conducted as a descriptive cross-sectional study at Recep Tayyip Erdoğan University Faculty of Medicine and Training and Research Hospital between 2018-2020, with face-to-face interviews with HBV infected individuals who applied to the infectious diseases and clinical microbiology outpatient clinic, who agreed to participate in the questionnaire. The patients were informed in detail about the study. After the questionnaire patients were informed by the Guidelines for Prevention and Treatment of CHB.

The Criteria for Inclusion in the Study

Volunteer patients aged 18 years or older who were infected with HBV were included. Individuals with hepatitis B surface antigen (HBsAg) (+), HBV-DNA level 2,000 IU/mL and below were accepted as HBV carriers, and those with 2,000 IU/mL and above as chronic HBV infection.

Instruments-data Collection

The questionnaire questions were developed depending on the literature (8,10,21). The questionnaire was composed of questions questioning the demographic characteristics of the patients (age, gender, education, place of residence, marital status, alcohol, cigarette or drug addiction, stage and duration of the disease, presence of HBV infection in the family, knowledge of the transmission routes and complications of HBV infection), the status of sharing their illnesses due to being diagnosed with HBV infection, the reasons for not sharing, their life experiences due to stigma-discrimination, and their anxiety. Verbal consent was obtained from the participants by explaining the content of the study before the questionnaire. The questions in the study were divided into groups as sharing the disease behavior, experiencing stigma discrimination, or anxiety due to the disease, and social relations (answers were arranged according to the 4-point Likert scale).

Ethics

Before starting the study, written permission from the institution their search was conducted in, and approval from Recep Tayyip Erdoğan University Non-Invasive Clinical Researches Ethical Board (decision number: 2020/129) were taken.

Statistical Analysis

The data of the study were assessed with IBM SPSS 23.0 (Chicago, USA) software. The compliance of the variables to normal distribution was checked with the Kolmogorov-Smirnov test. Descriptive statistics (percentage, frequency, median) and chi-square analysis were used to assess the data. Statistically $p<0.05$ was taken as the significance level.

Results

Of the 390 patients included in the study; 51.5% were women (n=201), the median age was 42 (19-98) years, and the median

duration of the disease was found to be 10 (1-35) years. It was determined that 77.2% (n=301) of the participants were married, 50% (n=195) had primary school education and 39.5% (n=154) lived in the city center, and 73.6% (n=287) had HBV in their families. Demographics details of the participants are given in Table 1. When the transmission routes are questioned to assess the knowledge of individuals infected with HBV, it was determined that 10.5% (n=41) of the participants did not know that virus is transmitted by blood, 7.9% (n=31) by sexual transmission, 30.8% (n=120) by vertical transmission from mother to baby, 6.2% (n=24) of the participants did not know that the virus could be transmitted with the special items used in the nail clipper-barber, 37.4% (n=146) with the use of common items such as plates, glasses, forks. It was found that 92.8% (n=362) of the individuals did not know about the disease before being infected with HBV, 17.9% (n=70) did not know that the disease could progress to cirrhosis and 43.1% (n=168) did not know that the disease could turn into hepatocellular cancer.

When the participants' sharing status of their sickness was assessed according to their epidemiological characteristics, while the highest share rate in all groups was determined as with family members, first degree relatives (mother, father, spouse, and children) with 99.2% (n=388), the least sharing rate was determined as with work/social environment with 60% (n=232). In terms of gender, it was observed that females shared their status at a higher rate than males and that they most often said to their first-degree relatives, and it was found to be statistically significant (p=0.03). While no statistically significant difference was observed in the fields of education and profession regarding sharing the illness with their relatives, a statistically significant difference was observed in the place of residence and marriage status (p-values: 0.14, 0.35, 0.04, 0.03, respectively). The epidemiological characteristics of the individuals and the distribution and statistical comparison of the people with whom they share the diagnosis of HBV infection are given in Table 2. It was determined that 34 of the individuals living with HBV shared their illness with everyone around them and the others were selective. It was determined that all participants shared their disease status mostly with their first degree relatives and it was found to be statistically significant (p<0.001).

HBV infected individuals were divided into three groups according to their stigma exposure; was determined that the first group (n=76 and 19.5%) was "exposed" to stigma in various ways, the second group (n=107 and 27.4%) did not experience this situation but felt anxiety, and the third group (n=207 and 53.1%) did not experience any of these situations. Sharing status of the patients according to their situation of treating with stigma is given in Table 2. When the participants' non-sharing of HBV infections were examined, it was found that two patients did not share their illness with anyone (231 and 59.2%), and they did not share their illness with various individuals around the participant. The reasons for not sharing were roughly grouped into 3 groups; it was determined for the first group (n=76 and 19.5%) as "being exposed to at least one of various stigma conditions", for the second group as anxiety of being exposed to at least one of the stigma states (n=107 and 27.4%), and for the third group as no need to say-not wanting to others to know the special condition (n=48 and 12.3%).

Among the participants, 19,9% (n=40) of women, 41,4% of university graduates (n=12), and 34,8% of divorced or widower (n=24) were found to experience higher stigma related victimization, which was statistically significant (p=0.002, p=0.02 and p<0.001,

Table 1. Demographic characters of the participants

	n	%		n	%
Gender			**Education**		
Male	189	48.5	Illiterate	67	17.2
Female	201	51.5	Primary school	195	50.0
Profession			High school	99	25.4
Officer	52	13.3	University	29	7.4
Private	73	19.0	**Settlement**		
Farmer	20	5.1	City center	154	39.5
Housewife	164	41.8	District	148	37.9
Unemployed	72	18.5	Village	88	22.6
Student	9	2,3			
Marital status			**Having family member with hepatitis**		
Married	301	77.2	Unknown	25	6.1
Never married	69	17.7	Hepatitis B	287	73.6
Single (divorced od widower)	20	5.1	Hepatit C	78	20.3
Stage of diseases			**Who is aware of the disease?**		
Inactive carriers	343	87.9	Parents/spouse/child	388	99.2
Chronic active hepatitis	45	11.5	Relative/neighbor	291	74.4
Cirrhosis and hepatocellular cancer	2	0.6	Coworker/social friend	232	60.0

Table 2. The epidemiological characteristics of the participants and the distribution of the people with whom they shared their diagnosis of HBV infection*

		Parents/ spouse/child	Relatives/ neighbor	Coworker/social friend	p
		n (%)	n (%)	n (%)	
Gender	Male (n=189)	188 (99.4)	131 (69.3)	107 (56.6)	0.03
	Female (n=201)	200 (99.5)	159 (79.1)	127 (63.2)	
Education	Literate (n=67)	65 (100)	48 (71.6)	39 (58.2)	0.14
	Primary school (n=195)	194 (99.5)	142 (72.8)	119 (61.0)	
	High school (n=99)	98 (98.9)	78 (78.8)	59 (59.5)	
	University (n=29)	29 (100)	21 (72.4)	17 (58.6)	
Profession	Officer (n=52)	52 (100)	41 (78.8)	47 (90.4)	0.35
	Private (n=73)	72 (98.6)	56 (76.7)	58 (79.4)	
	Farmer (n=20)	20 (100)	20 (100)	10 (50.0)	
	Housewife (n=164)	164 (100)	156 (95.2)	147 (89.6)	
	Unemployed (n=72)	71 (98.6)	47 (65.3)	44 (61.1)	
	Student (n=9)	9 (100)	5 (55.6)	6 (66.7)	
Settlement	City center (n=154)	153 (99.3)	143 (92.9)	143 (92.9)	0.04
	District (n=148)	147 (99.3)	132 (89.2)	112 (75.6)	
	Village (n=88)	88 (100)	83 (94.3)	71 (80.7)	
Marital status	Married (n=301)	300 (99.7)	231 (76.7)	180 (59.8)	0.03
	Never married (n=69)	68 (98.6)	42 (60.9)	41 (59.4)	
	Single (divorced od widower) (n=20)	20 (100)	17 (85.0)	10 (50.0)	
Stage of diseases	Chronic active hepatitis (n=45)	45 (100)	38 (84.4)	33 (73.3)	0.25
	Inactive carriers (n=343)	341 (99.4)	251 (73.3)	200 (58.3)	
	Cirrhosis and hepatocellular cancer (n=2)	2 (100)	2 (100)	2 (100)	
Stigma/ discrimination	No (n=207)	207 (100)	188 (90.8)	161 (77.8)	<0.001
	Anxious people(n=107)	106 (99.1)	51 (47.7)	51 (47.7)	
	Yes (n=76)	75 (98.7)	22 (28.9)	51 (67.1)	

respectively). The relation of stigma/experiencing discrimination with epidemiological data is given in Table 3.

When the exposure situations are investigated to private level, they found as experiencing at least one of the situations of "being excluded from the environment, getting reaction, being deceitful, embarrassed, judged" (n=28 and 34.2%), people staying away from themselves (n=6 and 7.9%), not eating their meals, plates fork-spoon (n=10 and 13.2%), not being admitted to a dormitory (n=4 and 5.2%), not being hired or being fired (n=28 and 34.2%). Absence of employment and dismissal status was determined as not being hired as a cook (n=10 and 35.7%), not being asked to act as a babysitter (n=8 and 28.6%), not being admitted to a police school (n=7 and 25%), not being hired as a cleaning staff (n=3 and 10.7%).

When the anxiety states of the participants based on their experiences are examined, the presence of "anxiety about transmitting the disease to someone else, anxiety that the person to marry will experience discrimination due to the disease" (n=142 and 36.4%, n=107 and 27.4%) with the highest frequency, respectively and the least frequently "anxiety about discrimination while receiving health care" were found (n=324 and 83.1%). The variables related to the anxiety states of individuals infected with HBV and the data regarding the influence of social relations are given in Table 4.

In the study, it was found that HBV-infected individuals were most frequently affected by coworker relationships (n=30 and 26.1%).

Discussion

Stigma has been frequently investigated in patients with physical-mental disorders, drug addiction, alcoholism, tuberculosis, HIV and HCV, etc. chronic diseases (9,11,18,22). However, studies conducted in patients with HBV infection are less worldwide (8,23,24,25). Studies conducted in our country are limited in number and are not investigated alone in individuals living with HBV (23,24,25). In the study we conducted in order to see the profile of HBsAg (+) people in Rize province and to determine the problems

Table 3. Analysis of patients exposed to stigma/discrimination according to their epidemiological characteristics

		No n (%)	Experiencing anxiety n (%)	Yes n (%)	p
Gender	Male	86 (45.5)	67 (35.4)	36 (19.0)	0.002
	Female	121 (60.2)	40 (19.9)	40 (19.9)	
Education	Literate	43 (64.2)	17 (25.4)	7 (10.4)	0.02
	Primary school	105 (53.8)	51 (26,2)	39 (20.0)	
	High school	50 (50.5)	31 (31.3)	18 (18.2)	
	University	9 (31.0)	8 (27.6)	12 (41.4)	
Profession	Officer	32 (61.5)	8 (15.4)	12 (23.1)	<0.001
	Private	35 (47.9)	27 (37.0)	11 (15.1)	
	Farmer	11(55.0)	8 (40.0)	1 (5.0)	
	Housewife	104 (63.4)	33 (20.1)	27 (16.5)	
	Unemployed	22 (30.6)	29 (40.3)	21 (29.2)	
	Student	3 (33.3)	2 (22.2)	4 (44.4)	
Settlement	City center	82 (53.2)	36 (23.4)	36 (23.4)	0.17
	District	73 (49.3)	50 (33.8)	25 (16.9)	
	Village	52 (59.1)	21 (23.9)	15 (17.0)	
Marital status	Married	176 (58.5)	78 (25.9)	47 (15.6)	<0.001
	Never married	10 (50.0)	5 (25.0)	5 (25.0)	
	Single (divorced od widower)	21 (30.4)	24 (34.8)	24 (34.8)	
Sharing with relatives	Parents/spouse/child	206 (99.5)	105 (98.1)	76 (100)	<0.001
	Relative/neighbor	188 (90.8)	51 (47.7)	51 (67,1)	
	Coworker/social friend	161 (77.8)	22 (20.6)	51 (67.1)	
Hepatitis in the family	Unknown	11 (44.0)	11 (44.0)	3 (12.0)	0.48
	Hepatitis B	153 (53.3)	73 (25.4)	61 (21.3)	
	Hepatit C	43 (55.1)	23 (29.5)	12 (15.4)	

and deficiencies, it was determined that exposure to stigma in our patients was not at all low. This situation made us think that stigma should be cared for in individuals living with HBV in the society and solutions should be investigated.

In the society in studies; it has been stated that stigma can be observed in many different situations such as exclusion, stigmatize, discrimination, disclosure, rejection, accusation, trial, stigma, distancing, reaction, etc (8,11,26,27,28). In addition, it has been reported that there are victimizations in different areas, especially in social relations, access to health services, education and business environment (9,10,26,27,29,30,31). In the study of Tran (32), it was found that the treatment management of patients due to being late due to stigma anxiety became difficult, in the review of Ellard and Wallace (18), indigenous Australian people did not have screening and diagnostic tests due to prejudices, did not take protective measures, and did not have the HBV vaccine sufficiently. These patients may come up with late complications of the disease in the future. WHO reported that at least 60% of liver cancer cases developed due to delay in treatment due to the failure of performing hepatitis diagnosis tests on time (3,20). In our study, the majority of the patients stated that they did not have information about HBV infection before diagnosis, so the absence of a test due to stigma could not be examined. The fact that they were not asked whether the follow-up and treatment status due to stigma were disrupted after the diagnosis was seen as an important limitation of our study.

In studies, it was stated that individuals often tend not to share their diseases in order to avoid any exposure related to stigma (19,21,28,33,34). Mohamed et al. (30) reported that 33.5% of HBV-infected individuals hesitated to explain their disease in order not to experience stigma and 93.6% of them shared their condition only with their families. Wallace et al. (27) found in their investigations that participants selectively shared their infection status to protect themselves and their families. In our study, it was

Table 4. Participants' anxiety and life experiences due to being diagnosed with hepatitis B

	Never (%)	Sometimes (%)	Frequently (%)	Always (%)
Variables of social relationships and life experiences*				
Disease affecting parents' relationships negatively (n=322)	302 (93.8)	9 (2.8)	10 (3.1)	1 (0.3)
Negatively affecting relationships with spouse (n=313)	289 (92.3)	10 (3.2)	8 (2.1)	6 (1.9)
Negatively affecting sexual life (n=321)	294 (91.6)	16 (5.0)	10 (3.1)	1 (0.3)
Negatively affecting relationships with kids (n=242)	235 (97.1)	5 (2.1)	1 (0.4)	1 (0.4)
Negatively affecting relationships with relatives (n=280)	254 (90.7)	17 (6.1)	7 (2.5)	4 (0.7)
Negatively affecting relationships with neighbors (n=224)	182 (81.3)	21 (9.4)	19 (8.5)	4 (0.8)
Negatively affecting social relationships (n=293)	192 (65.5)	51 (17.4)	41 (14.0)	9 (3.1)
Negatively affecting relationships with coworkers (n=115)	75 (65.2)	10 (8.7)	30 (26.1)	-
Experiencing limitations in business life (n=189)	162 (85.7)	22 (11.6)	3 (1.6)	2 (1.1)
Explanatory variables related to the anxiety latent variable				
Anxiety about the course of the disease	135 (34.6)	111 (28.5)	104 (26.7)	40 (10.3)
Anxiety of transmitting the disease to others	102 (26.2)	101 (25.9)	142 (36.4)	45 (11.5)
Anxiety about being embarrassed because of illness	280 (71.8)	60 (15.4)	38 (9.7)	12 (3.1)
Anxiety of experiencing stigmatization- discrimination with the person to marry	38 (9.7)	80 (20.5)	107 (27.4)	165 (42.3)
Anxiety about discrimination while receiving health care	324 (83.1)	18 (4.6)	31 (7.9)	17 (4.4)
Anxiety of experiencing stigmatization-discrimination in business environment	309 (79.6)	35 (8.9)	35 (8.9)	10 (2.6)
Anxiety of experiencing stigmatization-discrimination in the social environment	289 (74.1)	51 (13.1)	41 (10.5)	9 (2.3)
Anxiety about being punished for illness	283 (72.6)	57 (14.6)	41 (10.5)	9 (2.3)

*More than one answer was given to the questions and rates were determined based on the answers given

determined that the participants were selective when sharing their diseases, 25.6% of them did not share their disease information with their close relatives and neighbors, 40% with their work and social environment, and two people did not share their disease information with anyone.

In our study, it was found that individuals who were both exposed to stigma and experienced exposure anxiety tend not to share their illnesses frequently. Among the reasons for not sharing, not being hired or dismissed situation or anxiety came to the fore and this situation brought to mind the necessity of raising awareness and prioritizing improvement on this issue. Similar to our study, it was observed that this situation is at the top of the exposures outside of our country. In most of the studies, it has been reported that one of the places where individuals share their illness the least is the work environment and it has been stated that individuals generally avoid disclosing that they are infected due to reasons such as not being hired or being fired (8,10,21,30,33,35,36). This situation made us think that stigma may cause material and moral problems in individuals infected with HBV, and this situation should be considered.

Studies have shown that the degree of stigma experiences and the areas affected by them may show a social difference, and their exposure may be more common among certain populations, epidemiologically, culturally, religiously, and ethnically (9,11,18,27,36). Despite the national HBV anti-discrimination laws and regulations in China, stigma-based discrimination continues to be widespread in many settings, including patients living with CHB, the workplace, educational institutions, healthcare centers, and the community (21). In another study performed, it was reported that 29% of Vietnamese living in Chicago thought that people with HBV could be discriminated against at work, at school, and 21% of them believed that HBV carriers could be denied health services (8). The stigma was also observed in the statements of the participants in our study, where the patients were exposed to negative behaviors such as not being eaten from the food they cooked, avoiding hugging, not being cared for babies, not being asked to be employed, getting away from them, not being taken to the dormitory. However, unlike other studies, this exposure has been found to be quite low in healthcare services.

In our country, it was not possible to assess the situation, since there is no study in which stigma was examined and studied alone in individuals infected with HBV in our country. In the study we conducted in our own province, it was determined that 19.5% of the participants were exposed to at least one of the stigma-discrimination situations in various ways and these people shared less of their illness with their environment, and it was found to be statistically significant (<0.001). In addition, another important point that draws our attention is that the participants' anxiety about being exposed to stigma-discrimination was found to be higher than their exposure. When asked about the concerns of individuals infected with HBV, the fact that it was determined that the anxiety of transmitting the disease to other individuals came to the fore, may

have contributed primarily to this situation. However, the limitation of our study is that only HBV-infected patients were assessed and that the knowledge and attitudes of those living around them were not examined. It is thought that studies conducted with the participation of all individuals, whether infected or not, would put the problems experienced better.

In the literature, it has been stated that the stigma-discrimination against individuals with HBV is mostly related to the lack of knowledge and awareness about the transmission routes, prevention and treatment of the infection (8,11,20,28). In a study conducted in Ghana, it was observed that the opinion that the patients were "cursed" due to their religious beliefs was prevalent due to the thought that HBV infection caused a highly contagious, severe disease and it was not known that there was a treatment (36). Again, in studies conducted in Canada and China, it has been reported that the information on the transmission routes of HBV is not very good. In the questionnaire study applied to all Vietnamese living in Chicago, it was reported that 44% of the participants stated that individuals infected with HBV should avoid close contact such as hugging or kissing. Again, in some studies performed, it was determined that the patients and the people around them avoid physical contact, daily activities, avoid sharing their food and belongings, etc., and experience discrimination-exposure (8,9,21,33).

It has been reported that awareness about hepatitis infection in our country is not very good, with a low rate of 12% (6). In our study, the fact that it was determined that 92.8% of the individuals did not have an idea about the disease before they were infected, although there was a very large family history in the participants, and when the individuals were surveyed, 146 (37,4%) of them stated that they had hepatitis contagiousness even in situations such as food sharing and use of common items, and 120 (30.8%) of them were not known to be transmitted from mother to baby, and the awareness of other transmission routes was not found to be 100%, showed that awareness and consciousness were not very good in our own patients. However, since our study was conducted only on individuals infected with HBV and not on non-infected individuals, it cannot be generalized to the whole society. This is an important limitation of our study, and it made us think that studies involving all individuals should be conducted. Identifying the deficiencies as a society and applying educational interventions without discriminating individuals can be much more beneficial for the improvement of awareness and consciousness.

Studies examining the relationship between educational status and experiencing one of the stigma states in HBV-infected patients are limited in the literature. In a study conducted among immigrants in Beijing, although there is an inverse relationship between high education level and stigma-discrimination, different studies reported that stigma-discrimination anxiety increases as the education level increases (8,10,21,33). The fact that it was found in our study that the most stigma-discriminated people were university graduates and that these people had difficulties in getting a job made us think that there were serious insufficiencies in the approach to individuals with HBV infection in the society and the need to take some legal measures.

In the studies, it was found that individuals do not want to have a screening test for hepatitis B infection because they are afraid of being deprived of social isolation due to information poverty in countries with poor immigrants, especially in communities with low education levels (8,31,35). In the observational study of Vu et al. (37), they stated that Chinese and Vietnamese immigrants did not want to have a screening test due to many reasons such as not being able to find a job, not being able to rent a room, not being able to make friends because they live together in small rooms, they are reluctant to tell about their diseases, and vaccination rates are low. It is very important for individuals infected with HBV to be afraid of getting diagnosis or to hide their diseases after diagnosis, not to follow-up and treatment, as well as endangering their own health as well as spreading the virus and causing public transmission. Especially in people living as immigrants, the presence of a contagious infectious disease may trigger exposure to stigma. The rate of immigrants in our province is very low and there is no immigrant participant in our study. Since our country has been receiving immigrants quite frequently in recent years, it can be better assessed whether cultural and linguistic differences affect stigma and discrimination by planning studies in which these groups would include.

In the study, it was found that individuals infected with HBV are exposed to stigma in various ways, especially opportunities such as recruitment, and their awareness and consciousness are not very good. However, it is thought that the stigma was not observed prominently in all areas of the society would be related to individuals' selectively sharing their diseases with their environment or hiding their diseases.

Determining the difficulties experienced in individuals with HBsAg (+) may contribute to HBV prevention strategies. Access to HBV screening and diagnostic tests, vaccination and preventive standard methods should be increased, and development of the complications should be prevented by treating patients. Countries should determine the stigma situations that will affect each of these steps separately according to their ethnic structure, and take relevant measures to ensure recovery. In line with this purpose, efforts should be made to reach accurate and accessible information to the whole society through training seminars, press and media, and efforts should be made to raise awareness with legal protection, treatment and support systems throughout the country and to improve the health and well-being of individuals.

Study Limitations

The study is performed in tertiary hospital in a province of the Eastern Black Sea region of Turkey, Rize and not all HBV infected individuals in the province were reached. In the study, only the stigma status in infected individuals was examined, and other causes affecting the quality of life, such as depression, were not investigated. Other limitations of the study include the absence of a case-control group and the lack of use of a scale. It is thought that there is a need for randomized controlled studies that reflect the country in which the number of data is much higher. The difficulties and adverse situations experienced have been investigated only in people living with HBV and cannot be generalized to the whole society. It was thought that assessing the studies that investigated the perspective and knowledge levels of the people around the infected individual would be more beneficial for educational interventions and raising awareness.

Positive Aspects

As far as we know, the study is the first descriptive study in our country in which only stigma was investigated in individuals infected with HBV, and it is a pilot study conducted to reveal the problems experienced in our city. Identifying deficiencies can be helpful in planning regulations. However, multi-center studies should be planned and supported by studies reflecting the country in general.

Conclusion

It has been observed that stigma is not negligible in hepatitis B infection, and it persists at various levels in individuals infected with HBV. It is thought that there is a need for plannings that reflect the society in general, include different ethnic groups, identify problems and carry out solution-oriented public works, and provide consultancy services.

Ethic

Ethics Committee Approval: Before starting the study, written permission from the institution their search was conducted in, and approval from Recep Tayyip Erdoğan University Non-Invasive Clinical Researches Ethical Board (decision number: 2020/129) were taken.

Informed Consent: Verbal consent was obtained from the participants by explaining the content of the study before the questionnaire.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.E.Y., İ.B.., Design: İ.Y.E., U.K., A.E., Data Collection or Processing: A.Y.Y., U.K., Analysis or Interpretation: A.Y.Y., Literature Search: U.K., A.E., Writing: İ.E.Y., İ.B., U.K., A.E.

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Insulin Resistance in Patients with Chronic Hepatitis B Virus Infection: A Case-control Study

Kronik Hepatit B Virüsü Enfeksiyonu Olan Hastalarda İnsülin Direnci: Bir Olgu Kontrol Çalışması

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ABSTRACT

Objectives: It was aimed to compare the rate of insulin resistance (IR) in patients with chronic hepatitis B virus (CHB) infection with the general population.

Materials and Methods: The files of the patients were retrospectively examined. Patients testing for insulin and fasting blood glucose were included. For detecting IR, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was used. All patients were divided into 2 groups in terms of HOMA-IR. All data were compared between two groups. The rate of IR was compared with the general population.

Results: Forty-seven were female and the mean age was 38. Seventy-one had hepatitis B e antigen (HBeAg)-negative CHB infection, 44 had CHB and 5 had HBeAg-positive CHB infection. IR was detected in 47 patients. The rates of IR were similar between females and males. The rates of IR was 38% in HBeAg negative CHB infection, 36.4% in CHB and 80% in HBeAg positive CHB infection. The rate of IR in patients with CHB infection was found to be 39% in our study.

Conclusion: This study showed higher rate of IR in patients with CHB infection than in the general population and thus these patients should be carefully monitored in terms of the occurrence of IR and diabetes mellitus.

Keywords: Insulin resistance, hepatitis B, metabolic syndrome

ÖZ

Amaç: Kronik hepatit B virüsü (KHB) enfeksiyonu olan hastalarda insülin direnci (İR) oranının genel popülasyonla karşılaştırılması amaçlanmaktadır.

Gereç ve Yöntemler: KHB enfeksiyonu olan hastaların dosyaları geriye dönük olarak incelendi. Çalışmaya insülin ve açlık kan şekeri düzeyleri ölçülen hastalar dahil edildi. İR'yi tespit etmek için Homeostatik Model Değerlendirmesi (HOMA-İR) indeksi kullanıldı. Tüm hastalar HOMA-İR açısından 2 gruba ayrıldı. Tüm veriler iki grup arasında karşılaştırıldı. KHB enfeksiyonu olan hastalardaki İR oranı genel popülasyon ile karşılaştırıldı.

Bulgular: Hastaların 47'si kadındı ve ortalama yaş 38 (aralık: 20-65) idi. Yetmiş bir hastada hepatit B e antijeni (HBeAg) negatif KHB enfeksiyonu, 44'ünde KHB ve 5'inde HBeAg pozitif KHB enfeksiyonu vardı. Kırk yedi hastada İR tespit edildi. İR oranları kadın ve erkek arasında benzerdi. İR oranları; HBeAg negatif KHB enfeksiyonu olanlarda %38, KHB olanlarda %36,4 ve HBeAg pozitif KHB enfeksiyonu olanlarda %80 bulundu ve bunlar istatistiksel olarak anlamlı değildi. Çalışmamızda KHB enfeksiyonu olan hastalarda İR oranı %39 olarak bulundu.

Sonuç: Bu çalışma, İR'nin KHB enfeksiyonu olan olgularda genel popülasyona göre daha yüksek oranlara sahip olduğunu ve bu nedenle bu hastalarda İR ve diabetes mellitus oluşumunun dikkatle izlenmesi gerektiğini göstermiştir.

Anahtar Kelimeler: İnsülin direnci, hepatit B, metabolik sendrom

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Introduction

Metabolic syndrome (MS) is a cluster of conditions including central obesity, hypertension, glucose abnormality and dyslipidemia (1). It is associated with an increased risk of heart diseases, diabetes mellitus (DM) and the development of cancer (2). Though the pathogenesis of MS remains uncertain, insulin resistance (IR) has been considered a key mechanism (3). Also, IR is a main contributing factor of MS and DM.

Hepatitis B is one of the most common infection in the world and may cause complications including cirrhosis, liver failure and hepatocellular carcinoma (HCC) (4). Both hepatitis B and MS are common health problems. In general population, the prevalence of combined chronic hepatitis B (CHB) infection and MS is around 0.99%-1.74% (5,6,7). However, this rate varies depending on whether the area is endemic for HBV infection or MS. Furthermore, the coexistence of both diseases increases the risk of cirrhosis and HCC.

Recently, an experimental study showed that hepatitis B X protein impairs the hepatic insulin signaling pathway and that CHB infection is found to be related to IR (8). A clinical study also suggest that hyperinsulinemia develops in CHB infection and CHC virus (CHC) infection (9). This association has been understood in CHC infection but the relationship between CHB infection and IR is still remained unclear (10,11). In this study, the rate of IR in patients with CHB infection is compared with that in the general population.

Materials and Methods

This study was conducted between December 2016 and January 2018 in infectious diseases and clinical microbiology department. Of cases with CHB infection, the files of the patients were retrospectively examined. Since our study was a retrospective design, ethical approval and patient consent were not obtained. Patients testing for insulin and fasting blood glucose (FBG) were included. Their age, sex, height, body weight and body mass index (BMI), hepatitis B virus (HBV) DNA level, FBG, fibrosis score, hepatitis activity index (HAI), alanine aminotransferase, insulin level were determined. The height and weight of all patients were recorded and BMI was calculated. For detecting IR, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was calculated by using FBG and insulin values and "FBG (mg/dL) X fasting insulin (μU/mL)/405" formula of 120 patients. All patients were divided into the 2 groups in terms of IR; 1) case group (HOMA-IR ≥2.5 mg/dL) and 2) control group (HOMA-IR <2.5 mg/dL). HBV infection was defined according to European Association for the Study of the Liver 2017 Clinical Practice Guidelines (12). Patients with known DM, cirrhosis and HCC were excluded from the study. All subjects were also negative for anti-hepatitis C virus (HCV), delta infection and human immunodeficiency virus. All data were compared between two groups. The rate of IR in the patients included in our study was compared with that in the general population.

Statistical Analysis

SPSS 21.0 program was used for all statistical analysis. Chi-square test was used for categorical data. Pearson's chi-square test results were accepted. In order to determine the presence of parametric data, normal distribution was examined by Kolmogrov-Smirnov test. For data showing normal distribution, Student's t-test was used and $p<0.05$ was considered statistically significant.

Results

Of the 120 patients, 47 were female and the mean age was 38 (range: 20-65). Detailed characteristics of the patients shown in Table 1. Seventy-one had hepatitis B e antigen (HBeAg)-negative CHB infection, 44 had CHB; 9 patients had HBeAg positive and 25 patients were on anti-viral treatment) and only five had HBeAg-positive CHB infection. IR was detected in 47 patients. The rates of IR were similar between female (38.4%) and male (40.4%). The rates of IR; 38% in HBeAg-negative CHB infection, 36.4% of CHB and 80% of patients in HBeAg-positive CHB infection were found and these were not statistically significant. There was no statistically significant in IR according to the DNA levels of the patients. Five patients were weak (BMI: <18.5), 44 were normal weight (BMI: 18.5-24.9), 47 were overweight (BMI: 25-29.9) and 24 were obese (BMI >30). The rates of IR were 40% in weak patients, 25% in normal weight, 47% in overweight, and 50% in obese patients. The results were statistically significant between the groups. Of the 38 patients underwent biopsy, moderate-to-advanced fibrosis (F: 3-6) was detected in 8 patients and mild fibrosis (F: 0-2) was observed in the remaining 30 patients. HAI and fibrosis score were not statistically significant for IR. All statistical results were shown in Table 2.

Discussion

IR is an important factor for MS and DM. CHC infection is well known to be associated with IR and increased risk of DM. In contrast, IR in CHB infection has not been clearly defined. Previous studies showed that IR in CHB infection was not different from healthy controls (13,14). In 296 non-diabetic subjects, at the first health examination, the incidence of DM or glucose intolerance was found to be similar between HBV carriers and non-HBV controls,

Table 1. Detailed characteristics of the patients according to insuline resistance

Sex (female, n)	**47**
Age (year)	38.96±11.57
Body weight (kg)	74.04±18.60
Body height (cm)	167±8.82
Body mass index (kg/m^2)	26.47±6.26
Hepatitis activity index	5 (1-12)
Fibrosis score	2 (0-4)
Alanine aminotransferase (U/L)	38.30±20.10
Fasting blood glucose (mg/dL)	89.19±20.72
Insulin level (mU/L)	12.47±6.68
HbA1C (%)	5.60±0.82
HbeAg negativity (n)	110
HOMA-IR	2.96±2.16
HBV-DNA level (IU/mL)	57 (0-1140000000)

HbA1C: Hemoglobin A1C, HbeAg: Hepatitis B e antigen, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HBV: Hepatitis B virus

Table 2. All results according to insuline resistance

	HOMA-IR ≥2.5 (47)	HOMA-IR <2.5 (73)	p
Sex (Female)	**19**	**28**	**0.48**
Age (year)	39.82±13.53	38.82±10.44	0.94
Body weight (kg)	75.38±12.47	73.13±22.22	**0.02**
Body height (cm)	165.64±8.82	168.51±8.94	0.83
Body mass index (kg/m^2)	27.37±3.54	25.84±7.66	**0.01**
Hepatitis activity index	7 (1-11)	4 (2-12)	0.06
Fibrosis score	2 (0-4)	2 (0-4)	0.76
Alanine aminotransferase (U/L)	39.45±17.90	37.50±22.03	0.08
Fasting blood glucose (mg/dL)	98.82±28.32	82.56±9.92	**0.001**
Insulin level (mU/L)	18.47±6.80	8.80±2.43	**0.001**
HbA1C (%)	6.15±1.01	5.22±0.34	**0.001**
HbeAg negativity (n)	42	68	0.34
HBV-DNA level (IU/mL)	1470 (0-1140000000)	15 (0-156000)	0.08

HbA1C: Hemoglobin A1C, HbeAg: Hepatitis B e antigen, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, HBV: Hepatitis B virus

showing that asymptomatic CHB infection did not increase the risk of DM but unlike our study, IR was not investigated among the subjects (15). Contrary to relevant study comparing subjects with recovery from hepatitis B and CHB infection with those of disease-free, a study showed that CHB infection was correlated with IR and has shown that patients with CHB infection may need to monitor the development of IR and DM (16). Also, in a systematic review examining chronic viral hepatitis and metabolic derangement, HCV infection is positively associated with IR and hepatic steatosis (17). In contrast, in this article, HBV infection is inversely associated with lipid metabolism, and exhibits no conclusive association with IR or the risk of DM. Taken together, the relationship between HBV and IR is uncertain (14).

Similar to our results, in a study from Turkey, no significant relationship was seen between IR and HBV-DNA levels and IR was observed more frequently in these patients compared to the general population (18). In a study from south Korea reviewing hepatitis B surface antigen (HBsAg) and anti-HCV Ab among study participants, unlike our study, IR was not evaluated, and it found that serologic evidence of HBV and HCV infection was associated with the prevalence of diabetes (19). Furthermore, Ye et al. (20) found CHB had a risk of developing IR, especially higher in CHB patients with non-alcoholic fatty liver disease.

IR is defined as a subnormal biological response to normal insulin concentrations (21). It most frequently occurs in association with obesity, but can result from many causes including stress, medications, pregnancy. As consequences of obesity-related IR, it includes impaired glucose tolerance, impaired fasting glucose, type 2 DM, and increased insulin requirements in type 1 DM (22). As expected, in this study, increased weight and BMI, high FBG, elevated insulin level and high hemoglobin A1C were found statistically significant for IR.

IR is seen in 25% of healthy population, 60% of those with impaired glucose tolerance and 60-75% of patients with type 2 DM (23). The rate of IR was found to be 39% in our study. This rate was slightly higher than the healthy population.

Study Limitations

The study has some limitations. It was a retrospective study and had low number of patients and some data were missing. Because this study was cross-sectional, it was difficult to conclude a causal relationship between HBV infection and IR. For valuable clinical data, this study may be generalized across Turkey.

Conclusion

This study showed IR has higher rate in cases with chronic HBV infection than in the general population and thus these patients should be carefully monitored the occurrence of IR and DM but further studies are needed to clarify this challenge.

Ethics

Ethics Committee Approval: Retrospective study.
Informed Consent: It was obtained.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ö.F.T., Desing: B.M., İ.İ.B., Data Collection or Processing: S.Y.K., Analysis or İnterpretation: N.S., Literature Search: A.K., Writing: A.K.

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Research Article

93

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Evaluation of Portal Venous Flow as a Non-invasive Method for Diagnosing Liver Fibrosis in Patients with Chronic Hepatitis B

Kronik Hepatit B'li Hastalarda Karaciğer Fibrozunun Teşhis Edilmesi İçin Non-invaziv Bir Yöntem Olarak Portal Venöz Debinin Değerlendirilmesi

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ABSTRACT

Objectives: This study aimed to evaluate the relationship between portal venous flow (PVF), which could be measured non-invasively with Doppler ultrasound, and the degree of fibrosis obtained by biopsy in patients with chronic hepatitis (CHB).

Materials and Methods: The study included 133 patients with CHB. During the Doppler evaluation, PVF was calculated in addition to routine measurements. The patients were divided into two groups according to the degree of fibrosis based on the biopsy results: F0 and F1 (first group) and F2, F3 and F4 (second group). The Doppler ultrasound findings obtained from all patients were compared with the pathology results.

Results: The mean PVF was measured as 688.38±608.2 mL/minute. An inverse correlation was detected between PVF and liver fibrosis degree (p<0.0001, Spearman's correlation coefficient 0.47). In the receiver-operating characteristic analysis, the area under the curve was 71.1% (95% confidence interval: 55.6%-83.6%). The cut-off value for PVF was calculated as 480 mL/minute, at which it had a sensitivity of 57.8% and specificity of 100%.

Conclusion: We considered that the decrease we showed in PVF in our study could be used as a non-invasive evaluation method in the differentiation of mild and significant fibrosis in non-cirrhotic patients.

Keywords: Chronic hepatitis B, Doppler ultrasonography, non-invasive fibrosis test

ÖZ

Amaç: Bu çalışmada, kronik hepatit B (KHB) hastalarında non-invaziv olarak Doppler ultrason ile ölçülebilen portal venöz akım (PVA) ve biyopsi ile elde edilen fibrozis derecesi arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya KHB hastası 133 hasta dahil edildi. Doppler değerlendirmesi sırasında rutin ölçümlere ek olarak PVA hesaplandı. Hastalar biyopsi sonuçlarına göre fibrozisin derecesine göre F0 ve F1 (birinci grup) ve F2, F3 ve F4 (ikinci grup) olmak üzere iki gruba ayrıldı. Tüm hastalardan elde edilen Doppler ultrason bulguları patoloji sonuçları ile karşılaştırıldı.

Bulgular: Ortalama PVA 688,38±608,2 mL/dakika olarak ölçüldü. PVA ile karaciğer fibrozisi derecesi arasında ters korelasyon saptandı (p<0,0001, Spearman korelasyon katsayısı 0,47). ROC analizinde eğrinin altında kalan alan %71,1 idi (%95 güven aralığı: %55,6-%83,6). PVA için cut-off değeri 480 mL/dakika olarak hesaplandı ve bu değerde duyarlılığı %57,8 ve özgüllüğü %100 idi.

Sonuç: Çalışmamızda PVA'da gösterdiğimiz azalmanın, sirotik olmayan hastalarda hafif ve anlamlı fibrozisin ayrımında non-invaziv bir değerlendirme yöntemi olarak kullanılabileceğini düşündük.

Anahtar Kelimeler: Kronik hepatit B, Doppler ultrasonografi, non-invaziv fibrozis testi

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Introduction

Clinical manifestations due to hepatitis B virus (HBV) emerge as an important global health problem, and the most common of these conditions is chronic hepatitis B (CHB). In CHB patients, the treatment decision is made according to HBV-DNA and alanine aminotransferase (ALT) levels, and the degree of necroinflammation and degree of fibrosis in the liver biopsy. A liver biopsy is the gold standard in evaluating liver fibrosis; however, due to complications, such as pain, bleeding, and pneumothorax, variable pathology interpretations, and these risks being repeated in each biopsy required, researchers have begun to seek non-invasive tests for detecting fibrosis (1,2,3,4,5,6).

Doppler ultrasonography (US) is a widely accepted imaging method due to its easy accessibility, non-invasiveness, reproducibility when desired, and low cost, despite possible errors in the evaluation of chronic hepatitis patients and differences between practitioners. A Doppler US assessment is widely used in the follow-up of chronic hepatitis patients to obtain useful information about hepatic parenchymal morphology and hemodynamic changes (7,8).

Although there are trials and studies on the use of non-invasive fibrosis markers in patients with chronic hepatitis C, the data on the use of these markers in CHB patients remain limited (9,10,11,12,13). This study aimed to determine whether portal venous flow (PVF) detected by Doppler US was related to the degree of fibrosis obtained from percutaneous biopsies in CHB patients.

Materials and Methods

This study was conducted with the approval of the Clinical Research Ethics Committee of our university (approval number: 9/15, date: 18.06.2020). A prospective diagnostic accuracy study was conducted in our hospital between December 2018 and December 2019, involving 133 CHB patients. All patients provided written informed consent.

The inclusion criteria were being aged 18-70 years and having a diagnosis of chronic hepatitis serologically related to HBV according to the biopsy result. Patients that were hepatotoxic and those using drugs that could cause hemodynamic changes in liver Doppler flow were excluded from the study. Further excluded were patients with coagulation disorders or heart failure, and pregnant women.

Automatic pistol needle biopsies (16 W x 15 cm, ESTACOR to, GEOTEK Medical, Ankara, Turkey) were performed through intercostal access under ultrasound guidance in the interventional radiology unit. The patients' demographic characteristics, ALT and HBV-DNA levels, platelet counts, and pathology reports were obtained from the electronic hospital files and by screening epicrises.

In order to clinically evaluate the chronic hepatitis stage and correlate it with the Doppler data, the patients were divided into two groups according to the degree of fibrosis: the first group that did not have significant fibrosis (F0 and F1) (n=42) and the second group with a high degree of fibrosis (F2, F3 and F4) (n=91). In liver biopsies, the histopathological evaluation was made according to the METAVIR scoring system.

All 133 patients were examined with Doppler and grayscale US using a 2-5 MHz frequency convex ultrasound probe (Canon Aplio 500, Canon Medical System Corporation, Tokyo, Japan). The patients underwent the ultrasound evaluation in the supine position in the morning after fasting for 10 to 12 hours. All ultrasounds were performed by the same radiologist. All segments of the liver were examined with grayscale and Doppler US. Patients with structural abnormalities in hepatic vascular structures and focal parenchymal lesions were excluded from further analysis. Ultrasound parameters were obtained within one week after the biopsy procedure. Doppler portal vein parameters were obtained during apnea at the beginning of inspiration to avoid changes caused by deep inspiration. The smallest possible pulse repetition frequency setting was chosen to minimize measurement errors. Care was taken to ensure that the angle between the ultrasound beam and the vein to be examined was always below 60. Portal vein measurements were performed at the inferior vena cava level with the least variability between practitioners, using an intercostal and subcostal approach. To calculate PVF, the mean portal venous velocity and cross-sectional area were measured in the transverse plane. PVF was automatically obtained from these values as a function of the Doppler device.

Statistical Analysis

Statistical analyses were performed using the SPSS, version 15 (SPSS Inc, Chicago, IL). The Kolmogorov-Smirnov test was used to evaluate the conformance of continuous variables to normal distribution. Descriptive statistics were expressed as mean, standard deviation, frequency and percentages. During statistical analysis, the correlation between Spearman's rank correlation coefficient and data was evaluated. A p-value of less than 0.05 was considered statistically significant.

Results

Of the 133 patients included in the study, 88 were men and 45 were women. The mean age of all patients was calculated as 41.82±12.48 years. ALT levels in seven men and four women were above the cut-off value of 35 IU/L. The fibrosis value indicated F2 to F4 level of fibrosis in 91 patients. In 42 patients, the fibrosis value was reported as F0 or F1; i.e., low degree of fibrosis. Portal and splenic vein diameters were calculated as 10.56±1.64 and 4.7±1.64 mm, respectively. The mean PVF was measured as 688.38±608.2 mL/min. The descriptive, laboratory and pathology findings of the sample are shown in Table 1, and portosystemic hemodynamic parameters in Table 2.

There was no statistically significant correlation between the histological activity index and hemodynamic parameters of the patients. In the correlation evaluation between the PVF and liver fibrosis degree of the patients, a statistically significant

Table 1. Descriptive, laboratory and pathology results

	Mean	Standard deviation
Age	41.82	12.49
Platelet count (10^3/μL)	218.91	58.06
Alanine aminotransferase (U/L)	30.56	15.15
Fibrosis degree	2.22	0.74
Histological activity index	7.67	2.49

inverse relationship was found (p<0.0001, Spearman's correlation coefficient: 0.47). Apart from this, there was no correlation between the portosystemic hemodynamic parameters and the degree of fibrosis. The p-values of the correlation analysis between the pathological and portosystemic hemodynamic data of the patients are shown in Table 3. We used the ROC curve to determine the PVF cut-off value in the diagnosis of significant liver fibrosis in CHB patients. In this analysis, the area under the curve was 71.1% (95% confidence interval: 55.6%-83.6%). The cut-off value for PVF was calculated as 480 mL/min, at which this parameter had 57.8% sensitivity and 100% specificity (Figure 1).

Discussion

HBV infection is one of the leading causes of chronic liver disease worldwide (14). The aim of HBV treatment is to prevent HBV replication, decrease necroinflammatory activity, and stop the progression of fibrosis. The evaluation of the degree of liver fibrosis in HBV patients plays a key role for better clinical management since the treatment decision is usually made according to the degree of necroinflammation (15). It is also very important to evaluate the early stages of liver fibrosis, especially in patients with chronic viral hepatitis because the prognosis is mainly determined by the degree of fibrosis (16). Despite its contraindications and complications, a liver biopsy is still considered as the gold standard for defining the degree of liver fibrosis and guiding treatment (17).

Many new laboratory and imaging methods are being investigated for a non-invasive evaluation of liver fibrosis (17). Doppler US is a non-invasive method for evaluating liver hemodynamics and can be easily performed at the same time as routine upper abdominal US. However, due to limited data and conflicting results (18,19,20,21), the clinical role of Doppler measurements in evaluating non-cirrhotic liver disease remains controversial (18,19,22,23,24). In this regard, Doppler US methods have been the subject of several publications (18,24,25). These methods include the measurement of maximum and minimum velocities of the portal vein, PVF, congestive index, and portal venous index (15).

In the pathology of liver diseases within the range of chronic hepatitis to decompensated cirrhosis, there are various changes, such as hepatocellular inflammation, necrosis, development of regenerative nodules, collagen deposition, and lobule reconstruction. These pathological changes may result be gradual, with increasing intensity at each stage, with the increase in resistance to the portal vein, a decrease in its velocity, and an enlargement of its diameter. The enlargement of the portal vein diameter can counteract the reduction in portal vein velocity, and thus a certain degree of stability can be achieved in PVF to maintain hepatic perfusion (26).

Modifications occur in the usual architecture of the liver associated with sinusoidal vascular impairment due to HBV infection. As a result, various degrees of liver inflammation and fibrosis are known to occur. These changes can theoretically lead to alterations in intrahepatic and extrahepatic vascular impedance, which can be detected by the Doppler examination of the portal vein, hepatic vein, and hepatic artery. Several Doppler ultrasound parameters have been investigated to identify hemodynamic changes in the liver, but there is still no consensus on which option is best for determining the degree of liver fibrosis (27,28,29).

In a study by Su et al. (26), a statistically significant difference was found between the control group and chronic hepatitis patients, as well as between chronic hepatitis and compensated cirrhotic patients in terms of the portal vein diameter and velocity, but no difference was observed in terms of PVF. Similarly, Zheng et al. (30), evaluating cirrhotic patients, reported that the degree of fibrosis was associated with the portal vein diameter and velocity, splenic vein diameter, and spleen size; however, they did not detect any relationship between PVF and fibrosis. The most important difference between these previous studies and our study is that we did not include cirrhotic patients in our sample. In other studies in the literature that did not evaluate cirrhotic patients, Rocha et al. (15) and Bernatik et al. (24) showed no relationship between the degree of fibrosis and portal vein velocity and flow, but the sample sizes of both studies were much lower than the previously mentioned works. In contrast, we found a statistically significant negative correlation between PVF and liver fibrosis in our study. We calculated the cut-off value of PVF as 480 mL/min in differentiating between patients with mild and significant fibrosis. The extent to which and the order in which fibrosis, inflammation, and steatosis

Table 2. Portosystemic hemodynamic results

	Mean	Standard deviation
Portal vein diameter (mm)	10.56	1.64
Portal venous flow (mL/minute)	688.38	608.21
Splenic vein diameter (mm)	4.70	1.64
Spleen size	102.91	16.77

Table 3. P-values obtained from Spearman's correlation test

	Fibrosis	Histological activity index
Portal vein diameter	0.465	0.620
Portal venous flow	0.003*	0.922
Splenic vein diameter	0.746	0.212
Spleen size	0.627	0.324

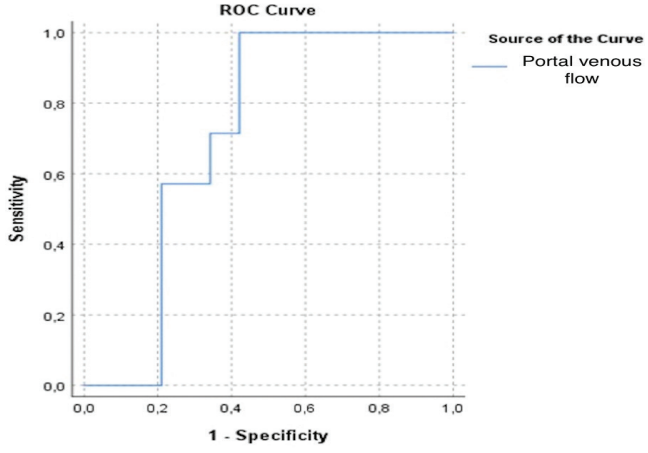

Figure 1. ROC curve for portal venous flow
ROC: Receiver-operating characteristic

can alter arterial and venous hepatic vascular patterns before cirrhosis remain controversial (15). Therefore, we consider that this decrease in PVF, which we detected in our sample that did not include cirrhotic patients, can be used as a non-invasive evaluation method in the differentiation between mild and significant fibrosis. However, this recommendation should be supported by studies conducted with larger case series. Nevertheless, none of the threshold parameters obtained by non-invasive laboratory or imaging methods has good diagnostic performance. In the literature, it has been stated that using at least two of these non-invasive laboratory tests simultaneously are useful in the evaluation and follow-up of the fibrosis degrees of CHB patients. Thus, the use of markers obtained by Doppler US, especially PVF together with laboratory markers can provide significant contributions. Further studies with a high number of patients evaluating both laboratory and imaging markers together will be important in terms of elucidating this situation.

Study Limitations

Our study also had certain limitations: first, the number of patients was relatively small, and second, all measurements were undertaken by a single person only once. Therefore, we did not evaluate intraobserver and interobserver agreement. Considering the user-dependent nature of this process, it is inevitable that there would differences between the measurements of different radiologists, and even between those performed by the same radiologist at different times.

Conclusion

There is a consistent and growing need for easily reproducible tests for the effective diagnosis of significant hepatic fibrosis. Studies comparing the efficacy of liver biopsy and non-invasive tests guide the development and implementation of new techniques. This study concludes that Doppler US can help identify CHB patients with significant fibrosis.

Ethics

Ethics committee approval: This study was conducted with the approval of the Clinical Research Ethics Committee of our university (approval number: 9/15, date: 18.06.2020).

Informed Consent: All patients provided written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.K., Ş.Ö.D., T.P., Concept: U.K., Ş.Ö.D., T.P., Design: U.K., Ş.Ö.D., T.P., Data Collection or Processing: U.K., Ş.Ö.D., T.P., Analysis or Interpretation: U.K., Ş.Ö.D., T.P., Literature Search: U.K., Ş.Ö.D., T.P., Writing: U.K., Ş.Ö.D., T.P.

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Research Article

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Results of Viral Hepatitis and Human Immunodeficiency Virus Screening in Afghan Irregular Migrants: A Cross-sectional Study (2011-2019)

Afgan Düzensiz Göçmenlerin Viral Hepatit ve İnsan Bağışıklık Yetersizliği Virüsü Enfeksiyonu Tarama Sonuçları: Kesitsel Çalışma (2011-2019)

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ABSTRACT

Objectives: The aim of the study was to present human immunodeficiency virus (HIV) and hepatitis A, B, and C seroprevalence data in Afghan irregular migrants.

Materials and Methods: This retrospective cross-sectional study was conducted in Erzurum, which had two of Turkey's 28 immigration removal centers, and included 9,197 Afghan irregular migrants of all ages referred to the hospital between January 2011-2019. Continuous data were presented as median (minimum-maximum) values; categorical variables were expressed as frequency (percentage) values.

Results: Seropositivity rates were 5.5% for hepatitis B surface antigen (HBsAg), 1.6% for hepatitis C virus, 94.3% for hepatitis A virus (HAV), and 0.2% for HIV. Rates of HBsAg, anti-hepatitis B core antibody immunoglobulin G (anti-HBc IgG), and anti-HAV positivities were significantly lower in the 0-15 age group, while the rate of anti-HBs positivity was significantly higher in the 0-15 and ≥41 age groups. In the 7,196 immigrants who underwent all three hepatitis B tests (HBsAg, anti-HBs, and anti-HBc IgG), infection was detected in 7.0%, while 87.5% had never encountered hepatitis B or been vaccinated against hepatitis B.

Conclusion: Epidemiological studies on migrant populations are necessary to protect public health in the host country. As there is limited information pertaining to these groups in the literature, having access to health data will be beneficial for physicians who provide medical care to this group.

Keywords: Community health, hepatitis, HIV, irregular migrant, migrant health

ÖZ

Amaç: Afgan düzensiz göçmenlerin hepatit A, B, C ve insan bağışıklık yetmezliği virüsü (HIV) enfeksiyonu seroprevalanslarının sunulması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif kesitsel çalışma, ülkede bulunan 28 geri gönderme merkezinden ikisine sahip olan Erzurum ilinde yürütüldü ve çalışmaya Ocak 2011-2019 tarihleri arasında hastaneye sevk edilen tüm yaşlardan 9.197 Afgan düzensiz göçmen dahil edildi. Sürekli veriler ortanca (en küçük-en büyük), kategorik değişkenler frekans (yüzde) olarak sunuldu.

Bulgular: Hepatit B yüzey antijeni (HBsAg) seropozitifliği %5,5; hepatit C virüs seropozitifliği %1,6; hepatit A virüs (HAV) seropozitifliği %94,3 ve HIV seropozitifliği %0,2 olarak tespit edildi. HBsAg, anti-hepatit B çekirdek antikoru immünoglobulin G (anti-HBc IgG) ve anti-HAV pozitiflik sıklığı 0-15 yaş grubunda anlamlı olarak daha düşük; anti-HBs pozitiflik sıklığı 0-15 ve ≥41 yaş gruplarında anlamlı olarak daha yüksek bulundu. Hepatit B (HBsAg, anti-HBs ve anti-HBc IgG) testlerinin her üçünün de yapıldığı 7.196 göçmende ise hepatit B enfeksiyonu %7,0 sıklıkta bulunurken, göçmenlerin %87,5'inin hepatit B ile karşılamadıkları ve/veya hepatit B'ye karşı aşılanmadıkları görülmüştür.

Sonuç: Göçmen nüfus, ev sahibi ülkede toplum sağlığı için epidemiyolojik incelemeler gerektiren bir gruptur. Literatürde bu gruplar ile ilgili verilerin sınırlı olduğu da göz önüne alındığında özellikle bu gruba tıbbi bakım sağlayan hekimlerin sağlık verilerine sahip olması faydalı olacaktır.

Anahtar Kelimeler: Toplum sağlığı, hepatit, HIV, düzensiz göçmenler, göçmen sağlığı

Karaşahin EF, Karaşahin Ö, Akdemir Kalkan İ. Results of Viral Hepatitis and Human Immunodeficiency Virus Screening in Afghan Irregular Migrants: A Cross-sectional Study (2011-2019). Viral Hepat J. 2021;27:98-102.

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Introduction

Turkey is used as a transit route by irregular migrants because it lies at the intersection of Asia, Europe, and Africa and acts as a bridge from politically and economically underdeveloped states to affluent Western countries. Turkey may also be the immigration target country for citizens of some nations. Irregular migrants are those who enter a country illegally and stay illegally, or enter legally but stay beyond the time legally permitted.

With a population of more than six million, Afghans comprise the largest irregular migrant group worldwide. Afghanistan has high infant mortality (37.1%) and mortality rates in children under the age of five (62/1,000) and has been ravaged by a decades-long civil war (1). Afghans are also the second largest group of irregular migrants to Turkey, after Syrians (2). According to data from the Directorate General of Migration Management affiliated with the Turkish Ministry of the Interior, the number of Afghan irregular immigrants in Turkey reached 12,248 in 2014, 45,259 in 2017, and 20,486 by June 2020. In the first five months of 2020, a total of 57,505 irregular immigrants were detained (2).

Regional and age- and sex-specific prevalence studies of infectious diseases should be evaluated in order to prevent and control outbreaks that may result from the movements of irregular migrants and to plan vaccination programs. However, due to the situation in Afghanistan, there are no comprehensive data on the prevalence of viral hepatitis and human immunodeficiency virus (HIV) infections there.

The aim of the present study was to present data regarding the seroprevalence of hepatitis A, B, C, (HAV, HBV, HCV) and HIV infection according to age and sex among Afghan irregular immigrants in a province that is one of the migrant entry points into Eastern Turkey.

Materials and Methods

This cross-sectional study was conducted in the Erzurum province, which has two of Turkey's 28 immigration removal centers. The total combined capacity of these centers is 1,500 people. According to data from the General Directorate of Migration Management, Erzurum is one of the seven provinces with the highest numbers of irregular migrants (over 5,000) detected as of the end of 2019 (2). The present study included 9,197 Afghan irregular migrants of all ages referred to the hospital from these two centers between January 2011 and January 2019. The results of HIV and HA, HB, and HC screening tests were recorded retrospectively. This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (approval number: 2020/04-49, date: 17.02.2020). Informed consent of patients couldn't obtain due to retrospective design of study.

Irregular Migrant Practices in Turkey

Apprehended irregular migrants are detained in the aforementioned "removal centers" until deportation. In these centers, migrants first undergo free health examinations and vaccinations (e.g., measles, hepatitis B, oral poliovirus, combination). If any of the migrants have health needs that exceed the health care capacity of the removal center, they are referred to hospitals and receive free treatment. During admission to the hospital, migrants are screened for infectious diseases such as viral hepatitis (HAV, HBV, HCV) and HIV, the incidence of which are known to increase due to irregular migration (2).

Definitions

The following definitions based on HBV serological indicators were used (3):

- Hepatitis B infection: hepatitis B surface antigen (HBsAg) and anti-hepatitis B core antibody immunoglobulin G (anti-HBc IgG) positive;
- Natural immunity: HBsAg negative, anti-HBc IgG and anti-HBs positive;
- Acquired immunity: HBsAg and anti-HBc IgG negative, anti-HBs positive;
- Never exposed to HBV: HBsAg, anti-HBc IgG, and anti-HBs negative.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY). Continuous data were presented as mean ± standard deviation and median (minimum-maximum) values, categorical variables were expressed as frequency (percentage) values. The significance of differences between the groups was evaluated using chi-square test. We also conducted Bonferroni correction for the post hoc chi-square analysis. $P<0.05$ was considered statistically significant.

Results

Of the 9,197 Afghan migrants included in the study, 8,195 (89.1%) were male. The mean age was 23.12±9.67 years and the median age was 21 (0-86) years.

The distribution of HBsAg, anti-HBc IgG, anti-HBs, anti-HCV, anti-HAV, and anti-HIV screening results of the irregular migrants are presented in Table 1.

Table 1. Distribution of HIV and hepatitis A, B, and C screening results of Afghan irregular migrants

	Number screened	Positive n (%*)	Negative n (%*)
HBsAg	8,999	505 (5.5)	8,494 (94.4)
Anti-HBs	8,932	2,171 (24.2)	6,761 (75.7)
Anti-HBc IgG	7,196	700 (9.7)	6,496 (90.3)
Anti-HCV	9,036	146 (1.6)	8,890 (98.4)
Anti-HAV	859	810 (94.3)	49 (5.7)
Anti-HIV	8,131	16 (0.2)	8,115 (99.8)

*Row percentage, HIV: Human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, Anti-HBc IgG: Anti-hepatitis B core antibody immunoglobulin G, HCV: Hepatitis C virus, HAV: Hepatitis A virus

The distribution of HA, HB, and HC and HIV screening results by age groups is presented in Figure 1. The frequency of HBsAg, anti-HBc IgG, and anti-HAV positivity was significantly lower in the 0-15 age group compared to other age groups (p<0.001). The rate of anti-HBc IgG seropositivity was significantly higher in the ≥41 age group compared to other age groups (p<0.001; p=0.017; p=0.042, respectively). The frequency of anti-HBs positivity was significantly higher in the 0-15 and ≥41 age groups compared to the 16-25 and 26-40 age groups (p<0.001), but did not differ significantly between the 0-15 and ≥41 age groups (p>0.05).

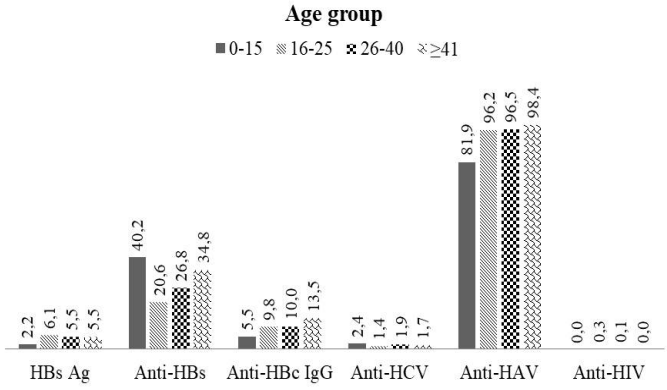

Figure 1. Distribution of the HIV and hepatitis A, B, and C screening results of Afghan irregular migrants by age group (seropositivity, %)

There are 826 (9.0%) people in 0-15 age group; 6050 (65.8%) people in 16-25 age group; 1774 (19.3%) people in 26-40 age group; and 547 (5.9%) people in ≥41 age group, HBsAg: Hepatitis B surface antigen, HBc IgG: Hepatitis B core antibody immunoglobulin G, HCV: Hepatitis C virus, HAV: Hepatitis A virus, HIV: Human immunodeficiency virus

The results of HIV and HA, HB, and HC screening among Afghan irregular migrants according to sex are presented in Table 2. Rates of HBsAg, anti-HBc IgG, and anti-HAV positivity were significantly higher, while anti-HBs positivity was significantly lower among males (p<0.001 for all). HBsAg, anti-HBs, and anti-HBc IgG testing was performed on 7,196 migrants to evaluate HBV infection and immune status (Table 3). Of the irregular migrants found to be anti-HIV-positive, two had HBV coinfection, four had natural immunity to HBV, and 10 had never been exposed to HBV. HBV coinfection was detected in nine (6.2%) of the anti-HCV-positive migrants.

Discussion

A quarter century of civil war and political instability has impoverished Afghanistan, leading the Afghan people to lose hope for political and economic recovery and migrate elsewhere to start a new life. According to data from the General Directorate of Migration Management, 446,578 Afghan irregular migrants have been apprehended in Turkey since 2014 (2). The present study examined viral hepatitis and HIV seroprevalence data obtained during general health examinations of detained Afghan irregular migrants.

Data regarding the seroprevalence of hepatitis and HIV in Afghanistan are limited. One study reported low HIV (0.063%) and HCV (0.82%) seroprevalence among 4,750 members of the Afghan national army (4). Of 125,832 blood samples in central blood banks and branches tested between 1989 and 2005, HBsAg and HCV seroprevalence rates were reported to be 1.76% and 0.63%, respectively (5). In the 2019 report from the World Health Organization (WHO) Afghanistan office, it was estimated that there were 5,900 HIV-positive Afghans in 2017 (6). The WHO has

Table 2. Distribution of HIV and hepatitis A, B, and C and screening results of Afghan irregular migrants according to sex

	Sex, n (%*)		p
	Male	Female	
HBsAg	486 (6.1)	19 (2.0)	<0.001
Anti-HBs	1,886 (23.7)	285 (29.6)	<0.001
Anti-HBc IgG	653 (10.2)	47 (6.1)	<0.001
Anti-HCV	128 (1.6)	18 (1.8)	0.540
Anti-HAV	710 (95.0)	100 (86.0)	<0.001
Anti-HIV	16 (100)	-	-

*Positivity percentage in the given sex group, HIV: Human immunodeficiency virus, HBsAg: Hepatitis B surface antigen, Anti-HBc IgG: Anti-hepatitis B core antibody immunoglobulin G, HCV: Hepatitis C virus, HAV: Hepatitis A virus

Table 3. Distribution of hepatitis B virus infection and immune status among Afghan irregular migrants by age

HBV infection/immune status	0-15 years (n, %*)	16-25 years (n, %*)	26-40 years (n, %*)	≥41 years (n, %*)	Total (n, %*)
HBV infection	17 (3.0)	362 (7.4)	97 (7.2)	29 (7.1)	505 (7.0)
Natural immunity	10 (1.8)	71 (1.5)	23 (1.7)	23 (5.7)	127 (1.8)
Acquired immunity	57 (10.1)	74 (1.5)	39 (2.9)	31 (7.6)	201 (2.8)
Isolated anti-HBc IgG positivity	4 (0.7)	46 (0.9)	15 (0.8)	3 (0.7)	68 (0.7)
Never exposed to or vaccinated against HBV	474 (84.3)	4,322 (88.7)	1,179 (87.1)	320 (78.8)	6,295 (87.5)

*Positivity percentage in the given age group, HBV: Hepatitis B virus, Anti-HBc IgG: Anti-hepatitis B core antibody immunoglobulin G

reported based on national statistics that the prevalence of HIV is below 0.1% among those 15-49 years of age (7).

Common risk factors for HBV, HCV, and HIV infection include sharing injection equipment, reusing medical equipment and needles in healthcare institutions without appropriate sterilization, and transfusion of unscreened blood and blood products (8,9,10). As the prevalence of viral hepatitis and HIV infection is higher among risk groups than the general population, these groups must be assessed separately. For example, a study done in donors will not reflect the general population, as individuals at high risk for HIV and hepatitis were evaluated and excluded with a questionnaire at the time of blood donation.

Migrants may have a different risk of HBV infection than the general population. Members of this group may also adopt other high-risk behaviors such as drug addiction that can put populations at risk for infectious diseases. In addition, collective and unhygienic living conditions further increase risk (11,12). On the other hand, it is known that migrants leave their home countries because they tend to avoid violence and have the means and opportunity to do so because of their higher socioeconomic status (12,13).

HIV, HCV, and HBsAg seroprevalence rates were determined to be 3.0%, 36.6%, and 6.5%, respectively, in a study of 464 intravenous drug users, who comprise an important risk group in Afghanistan (11). A meta-analysis of the literature evaluating risk groups between October 2003 and 2011 showed that the seroprevalence of HBsAg was 1.9% among 132,981 people screened for HBV and that of HCV was 1.1% among 132,500 screened (14). In another meta-analysis evaluating HC seroprevalence, the prevalence was 0.7% in the general population and 32.6% among intravenous drug users (15). The HBsAg seroprevalence among Afghan immigrants in the USA in the periods 1979-1991 and 2007-2008 was 4.1% and 5.0%, respectively, and was 60.8% (45/74) among Afghan refugees in Dalaki, Iran (12,13,16). In 2003, the HBsAg seroprevalence among Afghan migrants in Belochistan, Pakistan was found to be 8.3% (n=903) (17). These differences were attributed to the fact that immigrants able to reach the USA were of higher socioeconomic status and the USA likely had better health practices (10,12). In contrast, the high HBsAg seroprevalence among migrants in Belochistan was associated with unsafe intravenous drug use (13,16). For Afghan nationals in Iran, it has been stated that the HBsAg seroprevalence is unexpectedly high and health screenings should be conducted before placing migrants in camps.

The HBsAg seroprevalence in our study was higher than that in studies of the general population in Afghanistan and similar to the results of Afghan immigrants in the USA. The seroprevalence rates of HBV, HCV, and HIV infections were found to be lower than those previously reported in high-risk groups but higher than in the general population. This has been interpreted as an indicator that migrants constitute a risk group for these infections (12,16,17).

Between 1990 and 2005 in the central Asian and Caucasus countries, it was determined that the approximate HBsAg seroprevalence was 5% among young adults and decreased with age (18). We also observed in the present study that HBsAg seropositivity was highest in the 16-25 age group and decreased in the older age groups. In another study, the HBsAg seroprevalence in children under the age of five was found to be 0.3% and showed a sharp increase (1.8%) over the age of 15 (14). Similarly, the HBsAg seroprevalence in our study was lowest under the age of 15 compared to other groups. In contrast, anti-HBs positivity was higher in those under the age of 15 compared to the other age groups. This may be a result of vaccination programs started for those under 15 years of age. In the WHO health profile assessment of Afghanistan, the HB vaccination rate among one-year-olds was reported to be 71.0% in 2013 (19). However, the acquired immunity detected in our study for children under the age of 15 (10.1%) was very low compared to WHO data. In those over 40 years of age, both anti-HBc IgG and anti-HBs positivity were found to be higher than in the other age groups. We believe this is a result of natural immunity increasing with age in individuals who were not vaccinated against HBV and were susceptible to the disease.

In our study anti-HBc IgG positivity is low compared to HBsAg positives. Anti-HBc IgG can be found positive in the absence of HBsAg in most patients with acquired immunity. In a small proportion of these patients, isolated anti-HBc can also be detected in plasma. Apart from that, in those infected with HBV, HBsAg may be negative due to the point mutation in the precor region. All these donors have a high level of anti-HBc (20). This difference is thought to arise from here.

In another study, the prevalence of HCV infection gradually decreased after 60 years of age. It has been emphasized that this may be due to lack of economic power leading to reduced physical mobility and fewer examinations of older adults (21). In our study, we detected no age-based difference in HCV infection. Our data showed that all of the HIV-infected migrants were in the 15-40 age group, which is the most common period for infection.

Anti-HIV, HBsAg and anti-HCV seroprevalences of Afghan refugees were found to be 0%, 3.71% and 2.06%, respectively, in a study carried out with migrants in Erzincan province in our region. Seroprevalences in both studies were similar, with minor differences attributed to the sample size of the studies (727 vs 9,197) (22).

HAV is a common infectious agent worldwide, but the prevalence depends on local health conditions. HAV can be transmitted through contaminated water, food, and with close contact via the fecal-oral route. In low- and middle-income countries, HAV infection is usually asymptomatic in childhood and adults generally have immunity (10). It has been shown that HAV infection is common and that environmental and socioeconomic factors play an important role in its transmission. While 50% of the under-5 population was found to be anti-HAV-positive, it was shown that this rate increased rapidly with age and reached 100% among those over the age of 15 in Ethiopia (23). Our findings that hepatitis A positivity was lowest in the 0-15 age group support these data. Considering that the data in our study were based on the results of screening performed at the start of their migration, it can be assumed that the adults were infected with HAV before emigrating from Afghanistan. On the other hand, the low anti-HAV seropositivity rate in the under-15 population could be stemming from the lack of access to vaccines in this age group.

Study Limitations

The fact that this study was conducted on a specific group using retrospective data can be considered a limitation. However, the inclusion of a large sample population is an important advantage

of the study. Similarly, the analysis of different age groups provides important information both about active disease and immunization status.

Conclusion

The migrant population represents an important group that requires epidemiological study to ensure public health in nearly every country. As there are limited information pertaining these groups in the literature, having health data will be especially beneficial for physicians who provide medical care to this group. In addition, these data will facilitate immunization of these sensitive groups and thereby potentially reduce outbreaks and treatment costs for countries such as Turkey, where all migrant health expenses are covered by the state.

In our province, Afghans constitute this particular immigrant group. In line with the results of our study, it is understood that this group is susceptible to HBV and HAV infections. For this reason, it is important for Afghans to complete their vaccination quickly when they first come together with the health service.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (approval number: 2020/04-49, date: 17.02.2020).

Informed Consent: Informed consent of patients couldn't obtain due to retrospective design of study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.F.K., Design: E.F.K., Data Collection or Processing: Ö.K., Analysis or Interpretation: E.F.K., Literature Search: Ö.K., Writing: E.F.K., Ö.K., İ.A.K., Critical Review - İ.A.K.

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

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103

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Evaluation of HBsAg, Anti-HCV, Anti-HIV Seroprevalence and Perinatal Outcomes in Pregnant Women

Gebe Kadınlarda HBsAg, Anti-HCV, Anti-HIV Seroprevalansının ve Perinatal Sonuçların Değerlendirilmesi

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ABSTRACT

Objectives: Vertical transmission of hepatitis B virus, hepatitis C virus, (HBV, HCV) and human immunodeficiency viruses (HIV) infections is an important public health problem. The aim of this study was to determine the rates of hepatitis B, anti-HCV and anti-HIV seropositivities in pregnant women in a city and to evaluate the infections in terms of perinatal outcomes.

Materials and Methods: In this retrospective study, 8,464 patients who gave birth in obstetrics and gynecology clinic were recorded. Seropositivity rates of pregnant women were investigated according to the results of hepatitis B surface antigen (HBsAg), HCV antibody and anti-HIV antibody. The rates were determined according to years and perinatal results and statistical comparison was made.

Results: HBsAg seropositivity in pregnant women included in the study was 2.8 % (n=55) in 2015, 2.2% (n=52) in 2016, 2.3% (n=47) in 2017 and 2.2% (n=49) in 2018. The 4 year average was found to be 2.3% (n=203). There was no significant difference between the years (p>0.05). Among all our patients, 4-year mean anti-HCV seropositivity was 0.57% (n=49) and there was no difference between years (p>0.05). Anti-HIV seropositivity was found to be 0.09% on average, and there was no statistically significant difference over the years (p>0.05).

Conclusion: Since hepatitis B, which is a preventable viral disease, has a risk of transmission during delivery and if it is transmitted to the fetus, it may lead to fatal complications at later ages, it is necessary to screen all pregnant women in terms of HBsAg seropositivity and to include it in an antepartum planning program to protect and treat newborns from infection. Although the transmission rate of HCV is low in the society, considering its clinical course, screening of HCV

ÖZ

Amaç: Hepatit B virüsü, hepatitis C virüsü (HBV, HCV) ve insan immün yetmezlik virüsleri (HIV) enfeksiyonlarının dikey bulaşması önemli bir halk sağlığı problemidir. Bu çalışmadaki amaç bir ildeki gebelerde hepatit B, anti-HCV ve anti-HIV seropozitiflik oranlarını belirlemek ve enfeksiyonları perinatal sonuçlar açısından değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmada kadın hastalıkları ve doğum kliniğinde doğumu gerçekleştirilmiş 8,464 hasta kayıt altına alınmıştır. Gebelerde seropozitiflik oranları, hepatit B yüzey antijeni (HBsAg), HCV antikoru ve tespit edilen anti-HIV antikoru sonuçlarına göre araştırıldı. Yıllara göre ve perinatal sonuçlara göre oranlar belirlenip istatistiki karşılaştırma yapıldı.

Bulgular: Çalışmaya alınan gebelerde HBsAg seropozitifliği 2015 yılında %2,8 (n=55), 2016 yılında %2,2 (n=52), 2017 yılında %2,3 (n=47) ve 2018 yılında ise %2,2 (n=49) bulunmuş olup 4 yıllık ortalaması %2,3 (n=203) olarak hesaplanmıştır. Yıllar arasında anlamlı bir farklılık gözlenmemiştir (p>0,05). Tüm hastalarımız içinde dört yıllık ortalama anti-HCV seropozitifliği %0,57 (n=49) olup yıllar arasında fark bulunmadı (p>0,05). Anti-HIV seropozitifliği ortalama olarak %0,09 olarak saptanmış olup yıllara göre istatistiki anlamda bir farklılık izlenmemiştir (p>0,05).

Sonuç: Önlenebilir bir viral hastalık olan hepatit B'nin doğum esnasında bulaş riski olduğundan ve fetusta bulaş olursa ilerleyen yaşlarda ölümcül komplikasyonlara yol açabileceğinden tüm gebelerin HBsAg seropozitifliği açısından taranması ve bunun bir antepartum planlama programına dahil edilmesi yenidoğanların enfeksiyondan korunması ve tedavi edilmesi için gereklidir. HCV'nin toplumda bulaş oranı düşük bir düzeyde olmasına karşın klinik

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ABSTRACT

together with HIV in risky groups and pregnant women antibody positivity is considered important for the health of the society and newborns.
Keywords: Seroprevalance, pregnancy, HBsAg, anti-HCV, anti-HIV, perinatal outcomes

ÖZ

seyri dikkate alındığında riskli gruplarda ve gebelerde HIV ile birlikte taranması toplum ve yenidoğan bebeklerin sağlığı için önemli görülmektedir.
Anahtar Kelimeler: Seroprevalans, gebelik, HBsAg, anti-HCV, anti-HIV, perinatal sonuçlar

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections seen worldwide are still important infectious diseases today. Hepatitis is the most common infection in our country and HBV, which is the leading one, is a major health problem (1,2). Although there are many ways of transmission of hepatitis B, it is a viral agent that can be transmitted most frequently with infected body fluids, through permucosal or percutaneous contact. Viral encounter can occur between individuals living in the same house through sexual or parenteral transmission, with vertical transition from mother to baby, and horizontal transmission (3). Since almost half of the carriers receive HBV in the perinatal period, transmission from mother to baby draws attention as an important way of transmission of this virus (4). Perinatal transmission is rarely seen after birth, and it is known that 5-10% is transplacentally. Transition from mother to baby usually occurs during birth and 70-90% of these babies can be chronic carriers (5). In our country, which is in a moderately endemic region and has an hepatitis B surface antigen (HBsAg) seroprevalence rate of 3.9-12.5%, regional differences can be observed (6).

It is known that millions of people around the world have HCV infection. It has been reported that the risk of transmission to the baby is less than 5% in mothers who are positive after the HCV-RNA test. There is no special protection method to prevent perinatal transmission of HCV. However, pregnant women with a high viral load can infect newborns and the infection can become chronic in babies who develop acute infection (7). The number of anti-human immunodeficiency virus (anti-HIV) positive cases reported each year in Turkey is increasing. It is seen that approximately 0.8% of HIV cases are transmitted from infected mother to baby (8). Although the benefits of the measures to prevent the perinatal transmission of HCV have not been fully determined today (9), it is recommended to screen patients who come for pregnancy follow-up, as the measures to be taken during pregnancy may reduce the risk of transmission for hepatitis B and HIV (10). HCV antibodies (anti-HCV) for HCV, HBsAg for HBV, HIV antibodies (anti-HIV) for HIV are markers screened in the blood.

It is important to know the presence of viruses in early interventions in babies with a healthy follow-up of pregnant women and in deliveries with seropositivity. The aim of this study is to determine the rates of hepatitis B, anti-HCV and anti HIV seropositivity in pregnant women in a province and to evaluate the infections in terms of perinatal outcomes.

Materials and Methods

Eight thousand four hundred and sixty four pregnant women who were delivered in the Gynecology and Obstetrics Clinic of Van Training and Research Hospital between January 1, 2015 and December 31, 2018 were included in the study. HBsAg, anti-HCV and anti-HIV seropositivity rates were examined by ELISA method in pregnant women. Age, abortion, parity, gravida number, birth weight, gestational age, and demographic characteristics were recorded retrospectively by archive registry scanning. In the study, patients who were anti-HIV positive in ELISA results were detected during delivery. With the recommendation of this group of patients to the prenatal infectious diseases clinic, HIV-RNA tests were taken immediately, antiretroviral treatment was initiated, and their deliveries were carried out by cesarean section. Postnatal antiretroviral treatment and follow-up were carried out by the infectious diseases clinic.

Patients with positive HBsAg values were detected during delivery. Emergency deliveries of this patient group were realized and HBV-DNA, HBeAg positivity, treatment, and follow-up were carried out by the infectious diseases clinic in the postpartum period.

Ethics committee approval was obtained for the study from Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee with the decision number of 2019/05 and dated 07-03-2019. Written informed consent was obtained from the patients included in the study and our study was conducted in accordance with the Declaration of Helsinki Principles.

Statistical Analysis

Data were analyzed using (SPSS) 20.0. Student's t-test was used for comparing the means between independent groups, and the chi-square test was used to compare categorical variables. Descriptive statistical methods (number, mean, standard deviation) were used. $P<0.05$ was considered significant.

Results

Eight thousand four hundred and sixty four pregnant women between the specified dates were included in the study. Mean delivery week of the pregnant women participating in the study is 38.5±3.3 weeks. The average birth weight of babies is 3,156.6±547.8 grams. HBsAg seropositivity in pregnant women included in the study was found to be 2.8% (n=55) in 2015, 2.2% (n=52) in 2016, 2.3% (n=47) in 2017 and 2.2% (n=49) in 2018 and the 4-year average was found to be 2.3% (n=203). There was no statistically significant difference between the years in terms of HBsAg positivity ($p>0.96$). Anti-HCV seropositivity in pregnant women included in the study was found to be 0.4% (n=9) in 2015, 0.5% (n=13) in 2016, 0.5% (n=12) in 2017 and 0.6% (n=15) in 2018. The 4-year average was found to be 0.57% (n=49). There

was no statistically significant difference between the years in terms of anti HCV positivity (p>0.63). Anti-HIV seropositivity in pregnant women included in the study was found to be 0.05% (n=1) in 2015, 0.08% (n=2) in 2016, 0.14% (n=3) in 2017 and 0.09% (n=2) in 2018, the average was found to be 0.09% (n=8). There was no statistically significant difference between the years in terms of anti HIV seroprevalence (p>0.74). The distribution of HBsAg, anti-HCV and anti-HIV values and the number of births by years is shown in Table 1 and Figure 1.

According to age groups, HBsAg (n=8,464) seroprevalence was determined as 2.5%, 2.4%, 2.4% and 2.3%, respectively. Anti-HCV seroprevalence (n=8,464) was determined as 0.4%, 0.6%, 0.5%, and 0.5%, respectively, according to age groups.

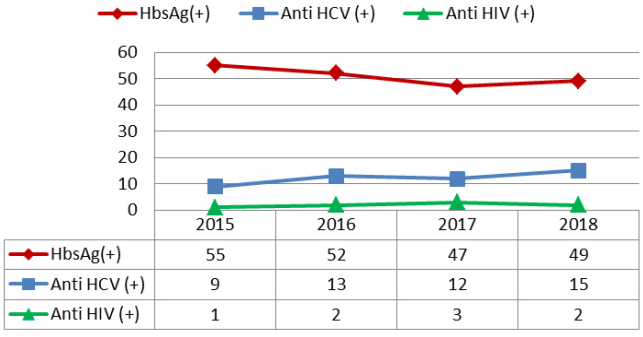

Figure 1. Distribution of HBsAg (+), anti-HCV (+), anti-HIV (+) births by years

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Anti-HIV seroprevalence was found to be 0.07%, 0.07%, 0.07% and 0.15%, respectively, according to age groups. There was no statistically significant difference between age groups and HBsAg, anti-HCV and anti-HIV positive/negativity (p>0.43, p>23, p>0.26, respectively) (Table 2).

There was no statistically significant difference between HBsAg, anti-HCV, anti-HIV positivity/negativity according to some perinatal variables (abortion, parity, gravida, gestational week and birth weight) (p>0.05) (Table 3).

Discussion

When looking at the distribution of HBV infection in the world, where Turkey is in the middle endemisite group, there are three endemic regions: low, medium and high (6). Hepatitis B vaccination was put into the vaccination program by many countries and there was a significant reduction in the disease there. However, in countries without hepatitis B vaccination program, the disease is still seen at high rates. In our country, as in most countries, the frequency of hepatitis B has decreased significantly over the years after the vaccination program was implemented (11). Horizontal and perinatal infection have been reported as the most important infectious pathways of hepatitis B infection. With the addition of low socioeconomic environment and poor hygiene conditions to crowded and public environments such as domestic, nursery, school, prisons, boarding school and kindergarten, the rate of infection increases even more (12).

Chronic HBV infection due to mother-to-child transmission in the perinatal period continues to be an important global health problem. Despite the standard passive-active immunoprophylaxis

Table 1. HBsAg, anti-HCV and anti-HIV values by years

Year	HBsAg (+) n (%)	HBsAg (-) n (%)	p	Anti-HCV (+) n (%)	Anti-HCV (-) n (%)	p	Anti-HIV (+) n (%)	Anti-HIV (-) n (%)	p	Total
2015	55 (2.8)	1864 (97.2)		9 (0.4)	1910 (99.6)		1 (0.05)	1918 (99.95)		1919
2016	52 (2.2)	2308 (97.8)		13 (0.5)	2347 (99.5)		2 (0.08)	2358 (99.92)		2360
2017	47 (2.3)	1983 (97.7)	0.96	1 (0.5)	2018 (99.5)	0.63	3 (0.1)	2027 (99.9)	0.74	2030
2018	49 (2.2)	2106 (97.8)		1 (0.6)	2140 (99.4)		2 (0.09)	2153 (99.91)		2155
Total	203 (2.3)	8261 (97.3)		4 (0.5)	8415 (99.5)		8 (0.09)	8456 (99.91)		8464

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Table 2. Distribution of HBsAg, anti-HCV and anti-HIV by age groups

Age	HBsAg (+) n (%)	HBsAg (-) n (%)	p	Anti-HCV (+) n (%)	Anti-HCV (-) n (%)	p	Anti-HIV (+) n (%)	Anti-HIV (-) n (%)	p	Total
<20	97 (2.4)	3,810 (97.5)	0.43	24 (0.6)	3,891 (99.3)	0.23	3 (0.07)	3,912 (99.93)	0.56	3,915
>20	65 (1.4)	4,331 (98.6)		25 (0.6)	4,412 (99.4)		5 (0.1)	4,432 (99.9)		4,437

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

Table 3. HBsAg, anti-HCV and anti-HIV distribution according to abortion, parity, gravida, gestational week and birth weight

	HBsAg (+) (mean ± SD)	HBsAg (-) (mean ± SD)	p	Anti-HCV (+) (mean ± SD)	Anti-HCV (-) (mean ± SD)	p	Anti-HIV (+) (mean ± SD)	Anti-HIV (-) (mean ± SD)	p
Abortion (n)	1.2±0.3	0.9±0.2	0.67	1.1±0.4	0.9±0.5	0.54	0.8±0.2	0.7±0.1	0.43
Parity (n)	2.0±0.2	1.9±0.7	0.45	2.3±0.6	1.7±0.3	0.34	2.2±0.5	2.0±0.5	0.37
Gravida (n)	2.5±1.4	2.3±1.1	0.43	2.8±0.5	2.6±1.4	0.38	3.3±1.1	2.8±0.7	0.21
Gestational week	39.3±2.5	38.4±3.6	0.21	38.6±3.1	38.4±2.6	0.17	38.4±3.6	37.6±2.3	0.52
Birth weight (gr)	3292.2±337	3284.3±643	0.12	3333.5±323	3300.5±232	0.26	3233.4±323	3404.4±245	0.15

HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, SD: Standard deviation

with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine in newborns, up to 9% of newborns are still infected with HBV. Chronic HBV infection due to transmission from mother to child in the perinatal period is an important global health problem. Standard passive-active immunoprophylaxis with HBIG and HBV vaccine in newborns within 12 hours after birth has proven successful in protecting approximately 90% of newborns from perinatal transmission of HBV (13).

Considering the studies conducted on pregnant women around the world, the prevalence of chronic hepatitis B was found to be 5% on average. Depending on the endemic situation in the region, it can be seen at different rates from 0.6% to high rates exceeding 20% (14,15).

HBsAg rate in pregnant women in studies on hepatitis B prevalence in pregnant women in Turkey was determined to be 4.7%. It was stated that pregnant women should be screened for HBV in order to protect newborns from hepatitis B infection (16). In another study covering the period 2001-2009, they found the hepatitis B carrier rate in pregnant women to be 2.5% (17). In a comprehensive study involving 90351 pregnant women, it was stated as 2.1% HBsAg positivity and it was recommended that hepatitis B examination be performed for every pregnant who comes to follow up (18). In a nationwide study conducted on 20,472 people between 1987-1998, HBsAg and anti-HBs positivity were reported as 4.4% and 23%, respectively. In another nationwide study conducted between 1998 and 2012, 4.3% of the 41,107 people tested were HBsAg-positive (19). In the study conducted with 9,420 pregnant women, HBsAg was found positive in 4.7%, anti-HBs in 38.4%, and anti-HCV in 0.286% of pregnant women (20). In a 20-year evaluation study; 7,605 pregnant women were tested, HBsAg prevalence was 1.5% and anti-HBs positivity was 11.5%, respectively (21). In the study in which 35,295 pregnant women were tested; HBsAg and anti-HBs levels were positive in 425 (1.2%) and 9,583 (27.7%) patients, respectively. In this study, it is stated that from 2013 to 2016, HBV carrier rates decreased from 1.4% to 0.8%, while anti-HBs positivity increased from 25.4% to 30.2% (22).

In our study, HBsAg positivity rates were 2.8% in 2015, 2.2% in 2016, 2.3% in 2017, and 2.2% in 2018. The four year average positivity rate is 2.3%, which is consistent with the literature and supports the fact that we are in the middle endemicity region. Although there are regional differences in these studies, it is seen that the rate of carrier has decreased over the years. The low rate in our study may be related to the increase in social awareness with the spread of hepatitis B vaccine and its inclusion in the routine vaccination program. In addition, the catch-up vaccination initiated after the hepatitis B vaccine was included in the national vaccination program may have also contributed to the decrease in these rates.

Hepatitis B vaccines, which are typically used in three doses, have been included in the routine vaccination program in Turkey since August 1998. While it is administered in 3 (three) doses in the normal administration scheme, vaccination is recommended at 0, 1, 2, and 12. months for people with infection risk. Considering the risk of perinatal transmission, HBIG should be administered in addition to hepatitis B vaccine in the first 24 hours in the postpartum period to newborns from HBV-infected mothers (23).

All babies born from HBsAg positive mothers born in our clinic were consulted by pediatricians. These babies were given HBIG in addition to hepatitis B vaccine. In addition, infected mothers were followed up by infectious diseases physicians.

Since there is no vaccine and antiviral treatment that can reduce the vertical transmission of the infection in pregnant women with anti-HCV positivity, the necessity of routine testing during pregnancy is discussed. However, it has been reported that conditions such as cesarean section and not breastfeeding in elective conditions do not reduce the vertical transmission of HCV infection (9). Considering the studies conducted abroad on anti HCV seropositivity, the seroprevalence in Burkino Faso was determined to be 5.4% and it was stated that this viral agent was mostly transmitted by sexual intercourse (24). In the study conducted on pregnant women in Switzerland, a rate of 0.71% was found (25). There are many studies on anti-HCV positivity in pregnant women in our country. Anti-HCV positivity was detected as 0.6% in the study of Gönen (26) In the study covering 2006-2012, the anti-HCV rate in pregnant women was found to be 0.5% (27). The anti-HCV positivity rate in Turkey has been reported to be in the range of 0-1.5% in the general population and 0-2.04% in pregnant women (28).

In our study, anti-HCV rates in all pregnant women were 0.4% in 2015, 0.5% in 2016, 0.5% in 2017 and 0.6% in 2018. The average four year anti-HCV rate is 0.5%. There was no difference between the years and it is compatible with the literature.

Prevention of HIV transmission from mother to newborn is possible by screening the mother during pregnancy, antiviral treatment and prophylaxis applied to the newborn after birth. Especially pregnant women in the risk group should be screened in HIV-endemic regions (29). Since there is a high risk of transmission

to the baby during delivery in infected mothers with HIV positivity, early diagnosis of HIV and rapid initiation of treatment is of great importance as it may prevent transmission to the baby. It is important to take measures such as starting antiretroviral therapy immediately after diagnosis, planning the delivery method by cesarean section and not breastfeeding the baby in the postpartum period (30) Özlü et al. (27) could not detect a positivity in their study. Madendağ et al. (18) detected a positivity of 0.004 % in their study. In a recent study, all 7,113 pregnant women screened for HIV had negative results (22).

Although there are not enough studies on the subject in our country, it is observed that anti-HIV positivity is low in studies. In the study, the average of four-year anti-HIV positivity was 0.09%, and the rate ranged from 0.05% to 0.14% according to years. The positivity rates are similar to the low case rates detected in our country.

In our study, no significant difference was found between age groups in terms of HBsAg, anti-HCV and anti-HIV seropositivity. This finding indicates that all age groups may be at similar risk for these infections. Similarly, in a study performed on 5,894 patients, no significant difference was found between age groups in terms of HBsAg and anti-HCV seropositivity (31). In the literature, it is stated that the anti-HCV positive patient group is mostly in the advanced age groups (32,33) We think that the reason for the lack of difference between age groups in our study is that the pregnant women in reproductive age who gave birth were in a certain age range.

Considering the studies conducted on HBsAg, anti-HCV and anti-HIV seropositivity in our country, it is seen that studies on the relationship between these infections and pregnancy conditions such as gravida, parity, abortion, birth weight and gestational week are not sufficient. Since all pregnant women in our study were followed-up in our outpatient clinics and their deliveries were carried out in the maternity ward of our clinic, the data were reached safely. In our study, no statistically significant difference was observed between HBsAg, anti-HCV and anti-HIV positivity rates and important perinatal outcomes such as abortion, gravida, parity number, birth weight and gestational week among all pregnant women. In a study conducted in our country, it was reported that there was no significant difference between the HBsAg and anti-HCV groups in terms of abortion, gravida, parity and the number of living children (34).

Study Limitation

The results of the research are valid only for the group in which the research was conducted cannot be generalized.

Conclusion

We think that all pregnant women should be screened for HBsAg, anti-HCV and anti-HIV serology during pregnancy follow-up. Babies born from HBsAg positive mothers should receive HBIG in addition to the postnatal vaccine. Although the transmission risk of HCV is low, we recommend screening pregnant groups in terms of the health status of the society and newborns. In addition, in case of detection of anti HIV positivity, anti HIV testing may be recommended, especially in risky groups, since it is an antiretroviral treatment option. In addition, we think that it would be appropriate to examine HBsAg, anti-HCV and anti-HIV tests at the first examination in pregnant women with low socio-economic status and coming from rural areas. In addition to all these, we believe that it would be beneficial to know the HBsAg, anti-HCV and anti-HIV serologies of the patients in order to protect obstetricians and gynecologists from these viruses.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the study from Van Ministry of Health University Training and Research Hospital Clinical Research and Ethics Committee with the decision number of 2019/05 and dated 07-03-2019.

Informed Consent: Written informed consent was obtained from the patients included in the study and our study was conducted in accordance with the Declaration of Helsinki Principles.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.U., İ.Ç., T.U., Concept: K.U., İ.Ç., T.U., Design: K.U., İ.Ç., T.U., Data Collection or Processing: K.U., İ.Ç., T.U., Analysis or Interpretation: K.U., İ.Ç., T.U., Literature Search: K.U., İ.Ç., T.U., Writing: K.U., İ.Ç., T.U.,

Conflict of Interest: Regarding this study, the authors and/or their family members do not have a scientific and medical committee membership or relationship with their members, consultancy, expertise, working status in any company, shareholding or similar situations that may have a potential conflict of interest.

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