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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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Keywords:

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

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

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

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

Original researches should have the following sections;

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

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

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

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

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

Conclusion: The conclusion of the study should be highlighted.

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

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

Case Reports

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

Review Articles

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

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

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

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

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

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.

Figures, Pictures, Table 's and Graphics:

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

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

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

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

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

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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.

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CONTENTS

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Viral Hepatitis Journal 2022;28(1):1-6

Is Liver Biopsy Necessary in Patients with Chronic Hepatitis B with Normal Alanine Aminotransferase Level?

Alanin Aminotransferaz Düzeyi Normal Olan Kronik Hepatit B'li Hastalarda Karaciğer Biyopsisi Gerekli midir?

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ABSTRACT

Objectives: If not treated early, morbidity and mortality will remain high in hepatitis B virus infection. In this study, it was aimed to analyze the liver biopsy results of patients with chronic hepatitis B with normal alanine aminotransferase (ALT) levels.

Materials and Methods: The study was conducted retrospectively. The patients who were admitted in the infectious diseases and clinical microbiology outpatient clinic, had liver biopsy and received treatment between 01.09.2019 and 01.12.2019, were included.

Results: A total of 169 patients were included in the study. Of the individuals, 95 (56.2%) were female, with a mean age of 42.4±11.15 years. The rates of having an histological activity index (HAI) score of 6/18 and above and a fibrosis stage of 2/6 or more (90%, 100%, respectively) in patients with ALT level above upper limit of normal (ULN) were higher than in patients with ALT level belowULN (63.6% and 79.1%, respectively) (p=0.001 and p=0.002, respectively). When 129 patients with ALT level below ULN were evaluated in subgroup analyses. HAI score was 6 or higher in 59 (58.4%) of the hepatitis B e antigen (HBeAg) negative patients, and fibrosis stage was 2 or higher in 76 (75.2%) patients. In patients with ALT below ULN and HBeAg positivity, the rates of HAI score of 6 and above and fibrosis stage of 2 and above were found to be statistically significantly higher than in HBeAg negative patients.

Conclusion: Liver fibrosis and necroinflammation may develop in patients with normal ALT levels. In making the biopsy decision, ALT level should be considered together with other factors that may affect liver damage.

Keywords: Liver biopsy, normal ALT level, necroinflammation and fibrosis, HBeAg negativity

ÖZ

Amaç: Hepatit B virüsü enfeksiyonu erkenden tedavi edilmediği takdirde yüksek morbidite ve mortaliteye sahip olmaya devam etmektedir. Çalışmada alanin aminotranferaz (ALT) düzeyi normal seyreden kronik hepatit B'li hastaların karaciğer biyopsi sonuçlarının incelenmesi ve kendi klinik deneyimlerimizin paylaşılması amaçlandı.

Gereç ve Yöntemler: Bu retrospektif tanımlayıcı çalışmaya 01.09.2019-01.12.2019 tarihleri arasında enfeksiyon hastalıkları ve klinik mikrobiyoloji polikliniğince takip edilmiş, karaciğer biyopsisi yapılmış olan ve antiviral tedavi alan hastalar alındı.

Bulgular: Toplam 169 hasta çalışmaya dahil edildi. Bireylerin 95'i (%56,2) kadın idi ve ortalama yaş 42,4±11,15 yıldı. ALT değeri normalin üst sınırı (NÜS) ve üzerinde olan hastalarda histolojik aktivite indeksi (HAİ) skorunun 6 ve üzerinde, fibrozis evresinin ise 2 ve üzerinde saptanma oranları (sırasıyla; %90, %100), NÜS'nin altında olan hastalara göre (sırasıyla; %63,6, %79,1) daha yüksek olup fark istatistiksel açıdan anlamlıydı (sırasıyla; p=0,001, p=0,002). Alt grup analizlerinde ALT değeri NÜS'nin altında olan 129 hasta değerlendirildiğinde; hepatit B e antijeni (HBeAg) negatif olan hastaların 59'unda (%58,4) HAİ skoru 6 ve üzerinde, 76'sında da (%75,2) fibrozis evresi 2 ve üzerinde bulundu. ALT değeri NÜS'nin altında ve HBeAg pozitif olan hastalarda, negatif olanlara göre HAİ skoru 6 ve üzerinde olma oranı ve fibrozis evresi 2 ve üzerinde olma oranı istatistiksel açıdan anlamlı olarak daha yüksek bulundu (sırasıyla; p=0,021, p=0,043).

Sonuç: Bu çalışma ile ALT düzeyi normal hastalarda da karaciğerde fibrozis ve nekroenflamasyon gelişebileceği görülmüştür. Biyopsi kararının verilmesinde ALT düzeyi, karaciğer hasarını etkileyebilen diğer faktörlerle birlikte göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Karaciğer biyopsisi, normal ALT düzeyi, nekroinflemasyon ve fibrozis, HBeAg negatifliği

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Introduction

Hepatitis B virus (HBV) infection; it is an important public health problem that progresses to cirrhosis, hepatocellular carcinoma (HCC) and liver failure, has high morbidity and mortality, affects the country's economy and continues to affect globally (1,2).

It is reported that more than 2 billion people worldwide are infected with HBV, approximately 240-257 million individuals progress to chronic HBV infection or chronic hepatitis, and approximately one million people is expected to die annually. HBV is the most common cause of chronic hepatitis and death due to liver failure in Turkey. If HBV-infected individuals are not diagnosed and treated early, they usually present with various complications in the future. In the report published by the World Health Organization in 2020, it is stated that HBV-related deaths prevent infections such as malaria, tuberculosis and human immunodeficiency virus (HIV), which are among the top ten causes of death in recent years (1,2,3,4,5,6).

In chronic hepatitis B patients, it is very important to start treatment before disease-related morbidity and mortality develops (4,5,6). Early treatment contributes to the reduction of social contagion as well as increasing the quality of life of the individual. Countries have their own consensus on initiating treatment and in Turkey, the treatment decision is made according to the liver biopsy results of the patients (4,7). In the evaluation of liver damage, the biopsy decision is applied in line with the recommendations of the international and national guidelines, but there is no clear consensus in the guidelines on this issue. There is no standard for reference ranges of liver enzymes in our country and there may be changes on a laboratory basis (4,7,8). In our study, it was aimed to examine the liver biopsy results of chronic hepatitis B patients with normal alanine aminotransferase (ALT) levels, to evaluate our results using different ALT upper limits of normal determined by our own laboratory and internationally, and to share our own clinical experiences.

Materials and Methods

The study was conducted as a retrospective study. This study was approved by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (approval number: 2019/129, date: 17.07.2019). Patients over the age of 18, who were diagnosed with chronic hepatitis B infection and who were over 18 years of age, who had a liver biopsy and received treatment at the Recep Tayyip Erdoğan University Faculty of Medicine and Training and Research Hospital, Infectious Diseases and Clinical Microbiology Outpatient Clinic between 01.09.2019 and 01.12.2019 were included in the study. Patients with malignancy, pregnancy, metabolic or immunological disease, concomitant viral liver disease, immunosuppressive therapy and chemotherapy, and those with missing data were excluded from the study.

Demographic data and laboratory data of the patients were reviewed retrospectively from patient files and hospital electronic records, modified histological activity index (HAI) scores and fibrosis stage defined by Ishak scoring system (7). ALT values measured at the time of liver biopsy of the patients were recorded. Hepatitis serology was evaluated by hepatitis B surface antigen, anti-HBs, hepatitis B e antigen (HBeAg), anti-HBe "ELISA" method. HBV-DNA levels were studied by polymerase chain reaction. All these values were recorded in the prepared study form. The upper limit of ALT (ULN) was accepted as 55 U/L, which was the upper limit value studied by the microbiology laboratory of our hospital between 01.09.2019 and 01.12.2019. However, in the study of Kwo et al. (8), an evaluation was made according to the actual healthy ALT levels that were stated to be in the population, and the upper limit values for ALT of 25 U/L for women and 33 U/L for men were taken as ULN-2 in our study.

Statistical Analysis

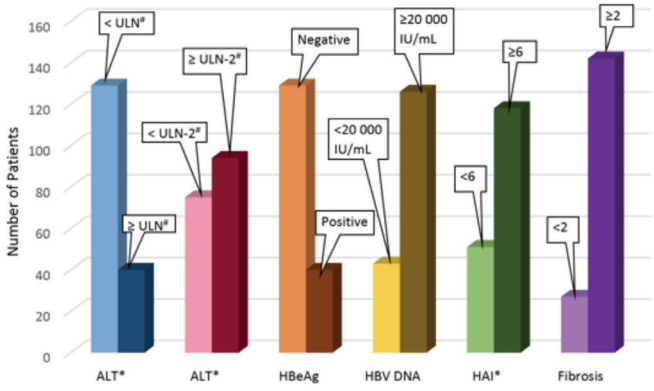
Statistical analysis of the study was performed with the IBM SPSS version 23.0 (Armonk, NY: IBM Corp) program. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive analyzes were given using the mean for normally distributed data and the median for non-normally distributed data. Cross tables were used for statistical evaluation, independent groups t-test was used for variables with normal distribution, and Kruskal-Wallis test was used for those not normally distributed. The cross-tables were compared to see if there was a difference between the groups, using chi-square and Fisher's exact tests when the values observed in the cells did not meet the chi-square test assumptions. P-value below 0.05 were considered as statistically significant.

Results

The data of 241 patients with a diagnosis of chronic hepatitis B who received antiviral therapy were evaluated. Seventy-two of the patients were excluded from the study due to missing data, co-infection with chronic hepatitis C or HIV, a total of 169 patients were included in the study. Ninety-five (56.2%) of the patients were female. Their mean age was 42.4±11.15 (18-73) years. Hundred and three of the individuals (60.9%) were aged 40 years and over. Considering the laboratory values determined when liver biopsy of the patients was performed; the median ALT value was 30 (7-1007) U/L. ALT value was found to be ULN or higher in 40 patients (23.7%), and ULN-2 and higher in 94 patients (55.6%). HBeAg was positive in 129 (76.3%) of the patients. Median HBV-DNA values were found to be 176,063 (2,263-17.3x10^9) IU/mL. The HBV-DNA value of 126 (74.6%) patients was found to be over 20,000 IU/mL (Graphic 1).

Liver biopsy results of the patients presented, the median HAI score was 6 (2-16), and the median fibrosis score was 2 (0-6). HAI score was 6 or higher in 118 patients (69.8%) and fibrosis stage 2 or higher in 142 patients (84%) (Graphic 1).

There was no statistically significant difference in the mean age of the patients between patients with a HAI score of less than 6, patients with a score of 6 and above, and patients with fibrosis stage 2 and patients with a HAI score of 2 and above (p=0.440, p=0.435, respectively) (Table 1). In terms of HAI score and fibrosis stage values; no statistically significant difference was found between patients aged 40 and over and those under (p=0.316, p=0.274), and between women and men (p=0.072, p=0.106, respectively) (Table 2).



Graphic 1. Distribution of patients according to laboratory values and liver histopathology

*ALT: Alanine aminotransferase, HAI: Histological activity index, #: ULN: The upper limit of normal was accepted as 55 U/L, which was taken as the upper limit by our laboratory. ULN-2: Upper limit of normal-2; 25 U/L for women and 33 U/L for men

HAI score was 6 or higher in 35 (87.5%) of 40 patients who were positive for HBeAg at the time of liver biopsy, and 83 (64.3%) of 123 negative patients. However, fibrosis stage 2 and above was found in 38 (95%) of the HBeAg positive patients and 104 (80.6%) of the negative patients. The rates of HBeAg positive patients with a HAI score of 6 and above and a fibrosis stage of 2 and above were found to be statistically significantly higher than in HBeAg negative patients (p=0.005, p=0.030, respectively (Table 2).

The median ALT values of the patients; in patients with HAI score of 6 and above [40 U/L minimum (min)-maximum (max): 11-1007 U/L], compared to patients with less than 6 (21 U/L, min-max: 7-153 U/L), and in patients with fibrosis stage 2 and above (36 U/L, min-max: 7-1,007 U/L), compared to patients with fibrosis stage 2 (20 U/L, min-max: 11-52 U/L) statistically were found to be significantly higher in terms of terms (p=0.000, p=0.000, respectively) (Table 1). The rates of HAI score of 6 and above and fibrosis stage of 2 and above in patients with ALT value of ULN and above (90%, 100%, respectively), compared to patients with ALT below ULN (63.6% and 79.1%, respectively) were statistically significant. were found to be significantly higher (p=0.001, p=0.002, respectively). The rates of having an HAI score of 6 and above and fibrosis stage of 2 and above were found to be statistically significantly higher in patients with ALT of ULN-2 and above, compared to patients with a lower ALT (p=0.000, p=0.001, respectively) (Table 2).

Median HBV-DNA values; in patients with a HAI score of 6 and above (507,408.5 IU/mL), compared to patients with a HAI score of less than 6 (12,170 IU/mL), and in patients with a fibrosis score of 2 or above (335,020.5 IU/mL), compared to patients with a HAI score of less than 6 (11,936 IU) /mL) was found to be statistically significantly higher (p<0.001, p<0.001, respectively) (Table 1). In patients with HBV-DNA level of 20,000 IU/mL and above, the rates of detection of HAI score of 6 and above, and fibrosis stage of 2 and above (79.4%, 89.7%, respectively); it was found to be statistically significantly more common than patients with <20,000 IU/mL (41.9% and 67.4%, respectively) (p<0.001, p=0.001, respectively) (Table 2).

When 129 patients with ALT values below ULN were evaluated in subgroup analyses; HAI score was 6 or higher in 59 (58.4%) HBeAg negative patients, and fibrosis stage 2 or higher in 76 (75.2%) patients. HAI score was 6 and above in 23 (82.1%) of HBeAg positive patients, and fibrosis stage 2 and above in 26 (92.6%) patients. In patients with ALT below ULN and positive for HBeAg, the rate of HAI score of 6 and above and fibrosis stage 2 and above were found to be statistically significantly higher than in HBeAg negative patients (p=0.021, p=0.043, respectively). When patients with an ALT value below ULN-2 were evaluated, no statistically significant difference was found between HBeAg negative and positive patients in terms of HAI score of 6 and above and fibrosis stage 2 and above (p=0.069, p=0.102, respectively), (Table 3).

In patients with ALT below ULN, 18 (42.9%) patients with HBV-DNA levels below 20,000 IU/mL had HAI score of 6 and above, and 28 (66.7%) had fibrosis stage 2 and above. Of the patients with HBV-DNA level of 20,000 IU/mL and above, 64 (73.6%) had a HAI score of 6 and above, and fibrosis stage 2 and above in 74 (85.1%). In patients with ALT below ULN and HBV-DNA level of 20,000 IU/mL and above, the rate of HAI score of 6 and above and fibrosis stage 2 and above were found to be statistically significantly higher than those with a lower ALT level (p=0.001 and p= 0.016, respectively). When patients with ALT values below ULN-2 are evaluated, the rate of HAI score of 6 and above in patients with HBV-DNA level of 20,000 IU/mL and above (73.7%) compared to the rate of patients with HBV-DNA level below (37.8%) was found to be statistically significantly higher (p=0.002). However, no statistically significant difference was found between patients

Table 1. Distribution of patients' age, alanine aminotransferase and HBV-DNA values according to liver histopathology results

	Age (years) [mean ± standard deviation]#	p	ALT* (U/L) [median (min-max)]#	p	HBV-DNA (IU/mL) [median (min-max)]#	p
HAI* score						
<6 (n=51)	43.4±11.02	0.440	21 (7-153)	<0.001	12,170 (2,263-13,076x10^9)	<0.001
6 (n=118)	41.9±11.22		40 (11-1007)		507,408.5 (2,737-17,3x10^9)	
Fibrosis stage						
<2 (n=27)	43.9±12.12	0.435	20 (11-52)	<0.001	11,936 (2,263-2,299x10^9)	<0.001
≥2 (n=142)	42.1±10.97		36 (7-1007)		335,020.5 (2,737-17,3x10^9)	

*ALT: Alanine aminotransferase, HAI: Histological activity index, HBV: Hepatitis B virus, #: The mean ± standard deviation values were given for the data conforming to the normal distribution, and the median (minimum-maximum) values were given for the data that did not

with HBV-DNA level of 20,000 IU/mL and above and those with below in terms of the rate of fibrosis stage 2 and above (p=0.123) (Table 3).

Discussion

HBV infection is a global public health problem and has attracted attention with its increasing morbidity and mortality rates in recent years. There is no clear consensus on which patient group should be biopsied for initiation of treatment in HBV-infected individuals, and there is no common recommendation in the guidelines regarding biopsy, especially in patients with negative HBeAg and normal ALT levels (2,3,4,5). Countries have experience in line with their own guides. As a result of our research, which is one of the first studies conducted in our country on this subject, significant fibrosis and necroinflammation in the liver were found in patients with high ALT levels as well as patients with normal ALT levels. It seems ALT alone is not sufficient and should be evaluated together

Table 2. Distribution of liver histopathology results of the patients

	HAI* score (n, %)		p	Fibrosis stage (n, %)		p
	<6	≥6		<2	2	
Age (years)						
<40	17 (25.8)	49 (74.2)	0.316	8 (12.1)	58 (87.9)	0.274
≥40	34 (33.0)	69 (67.0)		19 (18.4)	84 (81.6)	
Gender						
Female	34 (35.8)	61 (64.2)	0.072	19 (20.0)	76 (80.0)	0.106
Male	17 (23.0)	57 (77.0)		8 (10.8)	66 (89.2)	
HBeAg						
Negative	46 (35.7)	83 (64.3)	0.005	25 (19.4)	104 (80.6)	0.030
Positive	5 (12.5)	35 (87.5)		2 (5.0)	38 (95.0)	
ALT*						
<ULN#	47 (36.4)	82 (63.6)	0.001	27 (20.9)	102 (79.1)	0.002
≥ULN#	4 (10.0)	36 (90.0)		0 (0)	40 (100)	
AST						
<ULN-2#	33 (44)	42 (56)	<0.001	20 (26.7)	55 (73.3)	0.001
≥ULN-2#	18 (19.1)	76 (80.9)		7 (7.4)	87 (92.6)	
HBV-DNA (IU/mL)						
<20,000	25 (58.1)	18 (41.9)	<0.001	14 (32.6)	29 (67.4)	0.001
≥20,000	26 (20.6)	100 (79.4)		13 (10.3)	113 (89.7)	

*ALT: Alanine aminotransferase, HAI: Histological activity index, HBV: Hepatitis B virus, #ULN: The upper limit of normal was accepted as 55 U/L, which was taken as the upper limit of normal by our laboratory. ULN-2: Upper limit of normal-2; 25 U/L for women and 33 U/L for men

Table 3. Distribution of liver histopathology results of patients with ALT levels below the upper limit of normal

	HAI* score (n, %)		p	Fibrosis stage (n, %)		p
	<6	≥6		<2	≥2	
ALT < ULN#*						
HBeAg						
Negative	42 (41.6)	59 (58.4)	0.021	25 (24.8)	76 (75.2)	0.043
Positive	5 (17.9)	23 (82.1)		2 (7.1)	26 (92.9)	
HBV-DNA (IU/mL)						
<20,000	24 (57.1)	18 (42.9)	0.001	14 (33.3)	28 (66.7)	0.016
≥20,000	23 (26.4)	64 (73.6)		13 (14.9)	74 (85.1)	
ALT <ULN -2#*						
HBeAg						
Negative	32 (48.5)	34 (51.5)	0.069	20 (30.3)	46 (69.7)	0.102
Positive	1 (11.1)	8 (88.9)		0 (0)	9 (100)	
HBV-DNA (IU/mL)						
<20,000	23 (62.2)	14 (37.8)	0.002	13 (35.1)	24 (64.9)	0.123
≥20,000	10 (26.3)	28 (73.7)		7 (18.4)	31 (81.6)	

*ALT: Alanine aminotransferase, HAI: Histological activity index, HBV: Hepatitis B virus, #ULN: The upper limit of normal was accepted as 55 U/L, which was taken as the upper limit by our laboratory. ULN-2: Upper limit of normal-2; 25 U/L for women and 33 U/L for men

with other factors that may affect liver damage when deciding on liver biopsy to initiate treatment.

Considering the studies in the literature examining the relationship between ALT level and liver histopathology; in the study of Lai et al. (9), 37% of the patients whose ALT levels were consistently normal were found to have significant fibrosis or inflammation (10). In the study of Park et al. (11), significant fibrosis was reported in 61.9% of patients whose ALT level was 2 times or less than ULN. In our study, although the ALT level was below ULN or ULN-2, the percentage of patients with HAI score of 6 and above (63.6% and 56%, respectively) and the percentage of patients with fibrosis stage 2 and above (79.1% and 73.3%, respectively) were detected high. In patients with ALT levels below ULN or UL-2, the rates of high HAI score or fibrosis stage were generally higher than mentioned in the literature. It has been mentioned in studies that ALT may be insufficient to show liver damage, may be affected by various factors such as herbal medicine use in the course of the disease, and may be seen as lower than its true value and may be misleading. In addition, it has been reported that fibrosis and necroinflammation in the liver are affected by many factors such as age, gender, serum HBV-DNA level (11,12,13,14,15,16,17). In addition, factors such as family history, age at onset of the disease, smoking-alcohol use may also cause liver damage. In our study, the detection of significant fibrosis and necroinflammation in the liver in patients with normal ALT levels compared to previous studies may be related to these additional factors affecting liver damage.

It has been observed that there are different recommendations in the guidelines regarding liver biopsy indications in patients with HBeAg negative and ALT levels within normal limits. APASL 2016 guideline recommended liver biopsy to determine fibrosis status if patients are over 35 years old. However, biopsy is not recommended for these patients in the current AASLD and EASL guidelines (3,4,5,6). In the literature, different results have been found in studies on this subject. In the study of Liao et al. (12), the rates of detecting significant fibrosis in the liver in patients with normal ALT levels were reported as 49.4% in HBeAg positive patients and 30.9% in HBeAg negative patients. In our study, the HAI score was 6 or higher in 83 (64.3%) of 129 patients who were HBeAg negative. In 104 (80.6%) fibrosis stage 2 and above were detected. However, in our study, it was found that although HBeAg was negative in patients with normal ALT levels, significant necroinflammation (58.4% in those below ULN, 51.5% in those below ULN-2) and fibrosis (75.5% for those below ULN, 69.7% for those below UL-2) could be seen at high rates. In our study, the percentage of HBeAg-negative patients with elevated HAI score or fibrosis stage was found to be higher than in the literature. This situation may be related to epidemiological factors. In a systematic review, it was reported that histologically significant liver damage is rare in patients with HBV-DNA level below 20,000 IU/mL, HBeAg negative, and ALT level normal, and that liver biopsy is not required and patients should be followed up (13). In the study of Abdo et al. (14), the rate of detection of necroinflammation 2 and above was 10.2%, and the rate of detection of fibrosis stage 2 and above was 13.6% in patients whose HBV-DNA level was below 20,000 IU/mL and ALT level was normal. In our study, in patients with ALT levels within normal limits and HBV-DNA levels below 20,000 IU/mL, significant necroinflammation (42.9% in patients below ULN, 37.8% in patients below ULN-2) and fibrosis (66.7% of patients with ULN below and 64.9% of those with ULN-2) were observed. In our study, in patients with normal ALT levels, significant necroinflammation and fibrosis were detected at higher rates compared to the literature, although HBeAg negative or HBV-DNA was below 20,000 IU/mL. In these patients, there may be regional differences and factors such as age of the disease, presence of hepatitis in the family, alcohol-smoking, drug use, which may affect liver damage but not evaluated in our study.

Initiation of treatment without delay in hepatitis B infection; is very important in terms of preventing the progression of the disease, increasing the life span and quality, and reducing the development of extrahepatic complications, cirrhosis and HCC (18,19,20). It has been reported that antiviral treatment inhibits HBV replication, reduces necroinflammatory activity, limits the progression of fibrosis, and reduces the risk of HCC. It is stated that decompensated liver cirrhosis and HCC develop in 25-40% of chronic hepatitis B patients who do not receive appropriate treatment, and more than 1 million of these patients die each year. Today, it has been stated that the most effective method to prevent the clinical progression of HBV infection is treating patients with antiviral therapy (4,5,6,7,14). Although it differs according to the countries, it has been observed that there are some obligations before starting the treatment. In Turkey, liver biopsy is required to initiate treatment. Antiviral treatment could be started in patients with HAI score of 6 and above or fibrosis stage 2 and above (7). In addition, it has been determined that there are differences of opinion and difficulties in the decision of biopsy in the literature and the real world. While some clinicians argue that patients with normal liver enzymes should be followed without biopsy, others seem to believe that they should be evaluated for treatment by performing a biopsy. It is thought that sharing the results of studies on this subject may contribute to the formation of a common consensus.

Study Limitations

These outputs will be shared with VHSD and TKAD and can be used as references in a possible national guideline update. Although it is known that various factors such as having a family history of chronic hepatitis or cirrhosis, duration of the disease, alcohol-cigarette use, etc. may have an effect in determining liver damage, the fact that these factors were not evaluated due to the retrospective nature of our study was considered as an important limitation of our study. In addition, another limitation of our study is that the ULN value of ALT of our hospital at the time of the study were 55 for both men and women. However, our data were also evaluated according to the actual healthy ALT levels that should be present in the population as stated in the study of Kwo et al. (8). The ALT values recommended for our country in the study of Degertekin et al. (21) are quite close to the values in the study of Kwo et al. (8).

Conclusion

In our study, it was found that patients with ALT levels within normal limits could have significant fibrosis or necroinflammation in the liver, even though they were HBeAg negative or HBV-DNA level

was below 20,000 IU/mL. It has been observed that only laboratory values can be misleading in the decision to perform liver biopsy and start treatment. In this context, ALT elevation alone should not be taken as a reference in making the biopsy decision for the initiation of treatment. It should be considered that patients should be evaluated as a whole with additional factors that may affect liver damage. However, it is thought that a standardization should be made in the evaluation of the ALT normal range in Turkey and further studies are needed on this subject. Considering reference values separately for men and women and using the common reference values can contribute more to data of our country.

Ethics

Ethics Committee Approval: This study was approved by the Recep Tayyip Erdoğan University Non-Interventional Clinical Research Ethics Committee (approval number: 2019/129, date: 17.07.2019).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.E.Y., İ.B., T.I., M.B., U.K., A.E., Concept: İ.E.Y., İ.B., T.I., M.B., U.K., A.E., Data Collection or Processing: İ.E.Y., T.I., Analysis or Interpretation: İ.E.Y., T.I., Literature Search: İ.E.Y., T.I., Writing: İ.E.Y., T.I.

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Research Article

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The Effect of Dietary Supplement Use on Quality of Life and Depression in Patients with Chronic Liver Disease: A Cross-Sectional Study

Kronik Karaciğer Hastalarında Diyet Desteği Kullanımının Yaşam Kalitesi ve Depresyon Üzerindeki Etkisi: Kesitsel Bir Çalışma

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ABSTRACT

Objectives: Individuals with chronic liver disease (CLD) often use dietary supplements (DS) to cope with conditions that negatively affect quality of life (QoL), such as depression and fatigue. This study aims to determine the effect of DS use on QoL and depression in patients with CLD.

Materials and Methods: The population of this descriptive study consisted of all patients (n=330) diagnosed with CLD who admitted to the gastroenterology outpatient clinic between April 1, and May 30, 2018, and patients aged 18 years or older, without cognitive problems and who agreed to participate in the study. Data were collected using Patient Information Form (17 item), which includes socio-demographic and DS usage characteristics, "Chronic Liver Disease Quality of Life Inventory 2.0" (LDSI 2.0) and Beck Depression Scale (BDI).

Results: 48.4% of patients have used DS in the past year. LDSI 2.0 was found to be statistically significant in patients using DS compared to those who did not use a total score. In the patients with better income (p=0.02), who did not drink alcohol (p=0.01), patients without additional chronic illness (p=0.001) and those with 6-10 years of illness (p=0.02) preferred DS more. There was no statistically significant difference between the use of DS and BDI scores (p>0.05). A statistically significant, positive, strong relationship between LDSI 2.0 and BDI scores was also found (r=0.536; p<0.0001**).

Conclusion: The QoL of those who did not use DS was low. Considering that almost half of the patients with CLD use DS, doctors and nurses should question the DS used by patients when taking anamnesis. Because DS can interact with the drugs used, health professionals should improve their knowledge of the subject with evidence-based information and guide patients properly.

ÖZ

Amaç: Kronik karaciğer hastaları (KKH) diyet takviyelerini (DD) en çok depresyon ve yorgunluk gibi yaşam kalitesini (YK) etkileyen durumlarla baş edebilmek için kullanmaktadırlar. Bu çalışmanın amacı KKH'de DD kullanımının YK ve depresyon üzerine etkisini belirlemektir.

Gereç ve Yöntemler: Araştırmanın örneklemini 01 Nisan-30 Mayıs 2018 tarihleri arasında gastroenteroloji polikliniğine başvuran KKH tanısı almış, 18 yaş ve üstü hastalar (n=330) oluşturmuştur. Veriler, sosyodemografik ve DD kullanım özelliklerini içeren Hasta Tanıtım Formu (17 soru), "Kronik Karaciğer Hastalığı Yaşam Kalitesi Ölçeği 2.0 (LDSI 2.0)" ve Beck Depresyon Ölçeği (BDÖ) ile toplanmıştır.

Bulgular: Yaş ortalaması 48,8±7,1 olan hastaların, %48,4'ü son bir yıldır DD kullanmaktadır. LDSI 2.0 ölçeği toplam puanının DD kullanan hastalarda, kullanmayanlara göre anlamlı düzeyde düşük olduğu, YK'nin anlamlı düzeyde yüksek olduğu (p=0,04) bulunmuştur. Maddi durumu iyi olanların (p=0,02), alkol kullanmayanların (p=0,01), ek bir kronik hastalığa sahip olanların (p=0,001) ve hastalık süresi 6-10 yıl olanların (p=0,02) istatistiksel olarak anlamlı düzeyde daha fazla DD tercih ettiği bulunmuştur. DD kullanan ve kullanmayanlar hastaların, BDÖ puanları arasında istatistiksel olarak anlamlı fark bulunmamıştır (p>0,05). LDSI 2.0 ile BDÖ ölçeği arasında istatistiksel olarak anlamlı, pozitif yönde güçlü bir ilişki saptanmıştır (r=0,536; p<0,0001**).

Sonuç: KKH olan bireylerin yaklaşık yarısı DD kullanmaktadır. DD kullanmayanların YK'si daha düşüktür. Bu nedenle hastaların tıbbi öyküsü alınırken, kullandıkları DD sorgulanmalıdır. Bilinçsiz kullanımı ve hepatotoksisiteyi önlemek için etkinliği kanıtlanmış DD, geleneksel tedavilerle entegre edilebilir.

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Anahtar Kelimeler: Kronik karaciğer hastalığı, diyet desteği, yaşam kalitesi, depresyon

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Introduction

Although great advances in the management of liver diseases have been made in the last three decades, approximately 29 million people in European countries still suffer from chronic liver diseases (CLD) (1). According to the National Health and Nutrition Examination Surveys, the prevalence of CLD in the USA has become 14.78% between 2005 and 2008 while it was 11.7% between 1994 and 1998 (2). Every year, 170,000 people die in Europe because of liver cirrhosis (1). It is usually very hard for patients to tolerate the medical treatments used for the underlying etiologies of CLD, such as antiviral medications. In certain cases, the limited effectiveness of the medical treatments has driven individuals with CLD to seek complementary and alternative medicine (CAM) methods (3).

Even though these methods have been used since the dawn of humankind, their prevalence has increased after the 1990's (4). According to the health statistics report published in 2015 by the Center of Diseases Protection and Control, the rate of using any one CAM method among adults in the USA of age 18 and above in the last 12 months has been reported to be 33.2% (5). Individuals with CLD have been reported to use CAM methods to treat their disease and cope with their symptoms in differing rates 27.3%, 39%, 46% preferring dietary supplements (DS) most (3,6,7,8). CAM methods include natural products (such as herbal products, vitamins and minerals, and probiotics) and mind and body practices (such as yoga, chiropractic and osteopathic manipulation, meditation, acupuncture, relaxation techniques and breathing techniques). Natural products are widely marketed, readily available to consumers, and often sold as "DS". However, DS's are among the most widely used CAM methods in CLD (6,7,8).

Individuals with CLD, beside fighting the disease, have to cope with the psychological, economic, and social problems caused by the disease. Symptoms seen in CLD (acid, jaundice, insufficient nutrition, fatigue, itching, pain, hopelessness, loss of workforce, depression etc.) negatively affect the quality of life (QoL) of patients. As the severity of the symptoms increase, the patient becomes unable to perform daily life activities (DLA) alone and dependent on family members or professional care, and this can bring along depressive mood changes (9,10). Therefore, patients with CHD use DS to cope with both physical and mental symptoms and improve their QoL. Nevertheless, physicians must be aware of DS use in patients with CLD to determine the most widely used techniques and the potential hepatotoxicity of various herbal techniques. No studies examining the effect of DS use in individuals with CLD on QoL and depression could be found in Turkey. Therefore, this study was performed in order to examine the effect of DS use, which is performed widely in CLD, on QoL and depression.

Materials and Methods

Population and Sample of the Study

This descriptive and cross-sectional study was performed with patients presenting at the gastroenterology polyclinic of a university hospital who were diagnosed with CLD. An average of 8 patients with CLD present at a University Health and Application Center Gastroenterology Polyclinic daily. The population of this study consisted of all of the patients diagnosed with CLD who presented at the gastroenterology polyclinic between the dates of April 1st 2018 and May 30th 2018 (n=330), while the sample consisted of (n=256) patients who were 18 years of age or above, diagnosed with CLD, had without any communication problems, and willing to participate in the study.

The study was approved by the Zonguldak Bülent Ecevit University Clinical Research Board of Ethics (approval number: 2018-93-28/03, date: 28/03/2018). We ran the study according to the Helsinki Declaration (World Medical Association Declaration of Helsinki Ethical Principles For Medical Research Involving Human Subjects). Each patient was informed about the study and written consent was taken from the patients.

Data Collection

Data were collected using Patient Information Form (17 item), which includes socio-demographic and DS usage characteristics, "Chronic Liver Disease Quality of Life Inventory 2.0 (LDSI 2.0)" and Beck Depression Scale. The LDSI 2.0 is a disease specific scale developed by van der Plas et al. (11) in 2003 to measure the QoL of individuals diagnosed with CLD and its effects on DLA. The Turkish validity and reliability study of the scale was performed by Eraydın et al. (9). This scale measures different aspects of health related QoL such as symptom severity and the effect of symptoms on DLA. The scale consists of 2 sections and a total of 24 items. The first section consists of 18 items and the second section consists of 6 items. In section 1, where symptom related status is evaluated, 9 items were separated into two questions "a" and "b". While the nine questions titled "a" measure the severities of itching, joint pain, pain in the right upper abdomen, sleepiness during the day, worry about family situation, decreased appetite, depression, fear of complications and jaundice; the questions titled "b" measure the hindrance caused by these symptoms to DLA.

The second section of the scale, consisting of 6 extra items added by the Nederlandse Leverpatiënten Vereniging (NLV) (Dutch liver patient association NLV as important aspects of health-related QoL of chronic liver patients based on frequent contact with other liver patients and their own experience as

chronic liver patients, evaluates memory problems due to liver disease, change of personality due to liver disease, hindrance in financial affairs due to liver disease, involuntary change in use of time, decreased sexual interest and decreased sexual activity. All items in the scale concern the last week, and the scale has a 5-way Likert type scoring system between "0" (not at all) and "4" (to a high extent). Higher scores from the scale indicate worse QoL. In our study the Cronbach alpha value of the LDSI 2.0 was found to be 0.84.

The BDI was developed by Beck et al. (12) and tested for validity and reliability in our country by Hisli (13). The BDI is a multiple choice 21 item scale used to determine the presence and severity of depression. The highest score that can be attained from the scale is 63. Higher total scores indicate higher depression severity. In our study, the Cronbach alpha value of the BDI was found to be 0.81. Data was evaluated in the SPSS 16.0 program using percentages, the t-test, chi-squared, ANOVA, and the Pearson correlation test.

Statistical Analysis

Data was evaluated using the SPSS 11.5 program and after the skewness and kurtosis values exhibited the conditions of normal distribution, data was evaluated using percentages, mean values, standard deviation, the t-test, ANOVA, regression analysis, and the Pearson correlation test.

Results

The mean age of the liver patients was 48.8±7.1, almost half of them were female (43.4%), and most were married (72.3%), housewives (27.0%), retired (25.0%), elementary school graduates (34.8%), and had a moderate level of income (61.3%), poor (9.8%) and good (28.9%). The mean diagnostic duration of the patients was 4.5±2.3 years. Most were diagnosed with liver steatosis (35.9%), and cirrhosis [22.3%, and hepatitis B (18.8%), and hepatitis C (9.4%), and liver cancer (12.1%), and other (1.6%)].

Almost half (43.4%) had an additional chronic illness. Most used tobacco (64.5%) and alcohol (52.5%). A majority of the patients (76.6%) were under treatment, and attended regular checkups (72.3%). 48.4% of the patients with CLD used DS for the last year (Table 1).

The relationship between the DS use of individuals with CLD and their socio-demographic and relevant medical characteristics was given in Table 2. Accordingly, patients with better economic status (p=0.02), patients who did not use alcohol (p=0.01), patients with no additional chronic illness (p=0.001), and those with CLD for 6-10 years patients (p=0.02) were found to prefer DS more. It was found that among socio-demographic characteristics and the medical characteristics questioned in our study, income level, alcohol use status, disease duration, and the presence of an additional chronic illness affected DS use. In the multiple regression analysis performed, additional chronic illness and alcohol use status were found to have a predictive value of 0.6% (R^2=0.061, p=0.003) (Table 3).

The DS used by the individuals with CLD were given in Table 4. Accordingly, the patients used nigella sativa (31.2%), green tea (29.3%), garlic (25.8%), cabbage (24.2%), willow leaves (21.5%), ginger (19.1%), apple vinegar (15.6%), artichoke (13.3%),

Table 1. The socio-demographic characteristics of the individuals with CLD as well as certain medical characteristics (n=256)

Variables	n	%
Age (years) mean ± SD (range: 20-89)	**48.8±7.1**	
Gender		
Female	111	43.4
Male	145	56.6
Marital status		
Single	185	72.3
Married	71	27.7
Education		
Illiterate	16	6.2
Elementary	89	34.8
High school	84	32.8
University	67	26.2
Level of income		
Poor	25	9.8
Moderate	157	61.3
Good	74	28.9
Occupation		
Housewife	69	27.0
Laborer	37	14.5
State employed	47	18.4
Retired	64	25.0
Independent business	39	15.1
Duration of disease (year ± SD)	**4.5±2.3 years (range: 0-20)**	
1-5 years	191	74.6
6-10 years	50	19.5
11-15	12	4.7
16 years and above	3	1.2
Type of liver disease		
Cirrhosis	57	22.3
Hepatitis B	48	18.8
Hepatitis C	24	9.4
Liver cancer	31	12.1
Liver steatosis	92	35.9
Other	4	1.6
Presence of other chronic disease		
Yes	111	43.4
No	145	56.6
Smoking status		
Yes	165	64.5
No	91	35.5
Alcohol use status		
Yes	134	52.3
No	122	47.7
Social drinker	51	38.0

Table 1. Continued

Variables	n	%
Alcohol use status		
A few times a month	35	26.0
A few times a week	28	21.0
Almost every day	20	15.0
Under treatment		
Yes	196	76.6
No	60	23.4
Attendance to regular check ups		
Yes	185	72.3
No	71	27.7
Dietary supplement use in the last year		
Yes	124	48.4
No	132	51.6

CLD: Chronic liver disease, SD: Standard devition

Table 2. The factors related to the DS use of liver patients according to socio-demographic characteristics as well as certain medical characteristics (n=256)

Variables	Dietary supplement not used (n=132)	Dietary supplement used (n=124)	p
Age (years)			
20-39	30 (44.8)	38 (55.2)	0.18
40 and above	102 (54.3)	86 (45.7)	
Gender			
Female	54 (48.6)	58 (51.4)	0.38
Male	78 (54.2)	66 (45.8)	
Marital status			
Single	34 (48.6)	36 (51.4)	0.53
Married	98 (53.0)	88 (47.0)	
Education			
Illiterate	7 (43.8)	9 (56.2)	0.28
Elementary	52 (58.4)	37 (41.6)	
High school	37 (44.6)	47 (55.4)	
University	36 (53.7)	31 (46.3)	
Level of income			
Good	8 (32.0)	17 (68.0)	0.02Ŧ*
Moderate	91 (57.7)	67 (42.3)	
Poor	34 (45.9)	40 (54.1)	
Occupation			
Housewife	36 (52.2)	33 (47.8)	0.27
Laborer	21 (56.8)	16 (43.2)	
State employed	28 (60.9)	18 (39.1)	
Retired	26 (40.6)	38 (59.4)	
Independent business	21 (53.8)	19 (46.2)	

Table 2. Continued

Variables	Dietary supplement not used (n=132)	Dietary supplement used (n=124)	p
Duration of disease (year ± SD)			
1-5 years	104 (54.7)	86 (45.3)	0.04Ŧ*
6-10 years	19 (38.0)	32 (62.0)	
11-15 years	6 (50)	6 (50.0)	
16 years and above	3 (100)	0 (0.0)	
Presence of other chronic disease			
Yes	44 (39.6)	67 (60.4)	0.001Ŧ**
No	88 (60.7)	57 (39.3)	
Smoking status			
Yes	88 (53.3)	77 (46.7)	0.44
No	44 (48.4)	47 (51.6)	
Alcohol use status			
Yes	72 (59.0)	50 (41.0)	0.01Ŧ*
No	60 (44.8)	74 (55.2)	
Under treatment			
Yes	97 (49.2)	101 (50.8)	0.13
No	35 (60.3)	23 (39.7)	
Attendance to regular checkups			
Yes	91 (49.2)	94 (50.8)	0.22
No	41 (57.7)	30 (42.3)	

*P<0.05, **p<0.001, Ŧchi-square test. DS: Dietary supplements, SD: Standard deviation

Table 3. The examination of dietary supplement use according to socio-demographic and certain medical characteristics through regression analysis

Dietary supplement use				
	B	**Beta**	**t**	**p**
Constant	1.379	-	6.878	0.000
Disease duration	0.000	-0.006	-0.085	0.933
Presence of other chronic disease	0.199	0.198	2.993	**0.003**
Alcohol use	-0.127	-0.127	-2.055	**0.041**
Income	0.011	0.013	0.212	0.832

R: Regression co-efficient. R=0.248, R^2=0.061, F=4.081, p=0.003

turmeric (12.1%), vitamin E (12.1%), milk thistle (11.7%), and lavender (10.5%) most.

The relationship of DS use to depression and QoL in individuals with CLD was given in Table 5. The mean LDSI 2.0 symptom severity (p=0.04) and effect on DLA scores of the patients who used DS were found to be lower, and thus QoL among those patients was found to be higher on a statistically significant level (p=0.04). The mean scores from the extra NLV items in section 2 were also found to be lower in those who used DS, and thus QoL among those patients was found to be higher on a statistically significant level (p=0.04). The LDSI 2.0 QoL

scale total scores of the CLD patients who used DS were also found to be lower, showing that QoL among those patients was higher than those who did not use DS on a statistically significant level (p=0.04).

The BDI mean score of the patients who used DS was 20.11±6.03, indicating a moderate level of depressive mood. There was no statistically significant difference between the use of DS and BDI scores (p>0.05). A statistically significant, positive, strong relationship between LDSI 2.0 and BDI scores was also found (r=0.536; p<0.0001**).

Table 4. The dietary supplements used by the individuals with CLD (n=124)

Dietary supplements used*	n	%
Nigella	80	31.2
Green tea	75	29.3
Garlic	66	25.8
Cabbage	62	24.2
Willow leaves	55	21.5
Ginger	49	19.1
Apple vinegar	40	15.6
Artichoke	34	13.3
Turmeric	31	12.1
Vitamin E	31	12.1
Milk thistle	30	11.7
Lavender	27	10.5
Dandelion	27	10.5
Celery	27	10.5
Omega 3-6-9	24	9.4
Licorice	17	6.6
Ginseng	12	4.7
Asia seeds	5	2.0

*More than one option was selected. CLD: Chronic liver disease

Discussion

Although studies on CAM use in individuals with CLD have been found in the literature (3,7,8,14) no studies directly examining DS use or exhibiting the relationship between DS use and QoL and depression could be found. For this reason, our findings could guide future studies in this aspect. In this study, we found that approximately half of the patients (48.4%) used DS within the last year. Patients with better economic status, patients who did not use alcohol, patients with no additional chronic illness, and those with CLD for 6-10 years patients, were found to prefer DS more on a statistically significant level. In the regression analysis performed, the presence of an additional chronic disease and alcohol use status were found to be determining factors for DS use. In a study by Richmond et al. (8), patients with chronic hepatitis C were found to use multivitamins (56%) and herbal products (25%) on rates similar to ours. In the same study, patients with higher income levels and additional chronic diseases were found to use CAM methods more in a similar manner to our study (8). In a study conducted by Ferrucci et al. (3) with CLD patients, vitamins (39.6%) and herbal products (16.2%) were found to be used most widely, and in a manner parallel to our study, patients with higher income levels were found to use CAM methods more.

In this study, DS use was found not to be affected by gender Ferrucci et al. (3) and education level (7,8) in a manner contrary to the other three studies. This finding may be caused by sample, regional differences, or our study directly questioning DS use. We also found that patients who did not use alcohol consumed significantly more DS. Patients who did not use alcohol may

Table 5. The relationship of DS use to depression and QoL in individuals with CLD (n=256)

Scales	Dietary supplement not used (n=132)	Dietary supplement used (n=124)	h; χ^2; p
Symptom severity mean score (mean ± SD)	15.28±6.43	13.46±6.23	**t: -1.917; 0.04^{h*}**
Symptom effect on DLA mean score (mean ± SD)	12.35±6.20	10.42±6.79	**t: -1.926; 0.04^{h*}**
Extra NLV (additional items) (mean ± SD)	7.17±3.50	5.88±4.39	**t: -1.886; 0.04^{h*}**
LSDI 2.0 mean (mean ± SD)	34.81±8.9	29.59±6.72	**t: -2.045; 0.04^{h*}**
Mean BDI score (mean ± SD)	19.84±7.15	20.11±6.03	t=0.181; 0.85^{h}
BDI			
Depression no (0-9 points)	25 (46.3)	31 (53.7)	χ^2:1.811; 0.61^{ŦF}
Mild (10-16 points)	27 (57.4)	20 (42.6)	
Moderate (17-29 points)	54 (55.1)	46 (44.9)	
Severe (30-63 points)	26 (49.1)	27 (50.9)	
LDSI 2.0 (BDI)	r=0.536; p<0.0001**		

r: Correlation coefficient. *p<0.05, **p<0.001, ŦFchi-square test, h: t-test, DS: Dietary supplements, QoL: Quality of life, CLD: Chronic liver disease, SD: Standard deviation, DLA: Daily life activities, NLV: Nederlandse Leverpatiënten Vereniging, LSDI: The Liver Disease Symptom Index, BDI: Beck Depression Scale

have given their disease more importance, wanted more control and responsibility over their own treatment, and thus sought DS (15,16). Since no studies in the literature could be found on alcohol use status and DS preferences, this result needs to be supported by further studies. In this study, those with CLD for 6-10 years were found to use DS more. No studies in the literature examining he relationship between DS use and disease duration among the studies related to CAM method and DS use in CLD could be found. In studies performed with different disease groups, disease duration was found to be affected by CAM use in patients with rheumatoid arthritis (17) while no such relationship could be found in patients with inflammatory bowel disease (18). In our study, it was found that those with disease durations of 6 to 10 years used more DS compared to the first 5 years. The reason behind this may be patients using medical drug treatments such as retroviral treatments for the first 5 years, being questionably satisfied with their treatment, and preferring DS later on. Similarly, the patients may have feared the hepatotoxic effects of DS for the first five years and not used them. Those with disease durations of 6 years and above, on the other hand, may have sought DS thinking they had no other choice. In studies performed on CAM use with different sample groups, the patients have been reported to use those methods mostly because of being unsatisfied with their treatments and having no other choice (15,16,19). Almost half of the individuals with CLD were found to use DS. The most commonly used DS were respectively nigella, green tea, garlic, cabbage, willow leaves, ginger, apple vinegar, artichoke, turmeric, vitamin E, milk thistle and lavender. In the studies by Richmond et al. (8), Coughlan et al. (14), and White et al. (7), the herbal product most widely used by patients with hepatitis C was milk thistle. Although the patients consumed milk thistle with a similar rate in our study, they used other DS even more. In the study by White et al. (7), patients were found to consume dandelion, licorice, and garlic in rates similar to our results (7,14).

In individuals with CLD, beside symptoms such as acid, pain, jaundice, fatigue, and itching, complications related to the disease such as peritonitis, varicosity, and encephalopathy and psychological issues such as anxiety and depression all affect QoL negatively (9,20). In this study, the LDSI 2.0 QoL scale total scores of the CLD patients who used DS were found to be lower, showing that QoL among those patients was higher than those who did not use DS on a statistically significant level. In the study by White et al. (7), CAM methods were reported to be used by patients with hepatitis C mostly to decrease fatigue, strengthen the immune system, and to improve gastrointestinal function. The patients reported no side effects, and the researchers found that the presence of the headache symptom was the determining factor in herbal product use (7). In the literature, only two studies evaluating the relationship between DS use in CLD and QoL could be found (8,14). In the study conducted by Richmond et al. (8) with patients with chronic hepatitis C, no significant difference in the QoL levels of those who did and did not use CAM methods could be found. These findings contradict our study. This difference may be caused by our use of a CLD specific QoL scale or our questioning of solely DS. In the study by Coughlan et al. (14) patients with worse QoL levels were found to resort to CAM applications more. In our study, the, the symptom severity score and the effect of symptoms on DLA were higher in those who did not use DS and their QoL levels were lower. Patients with CLD also used DS to cope with their symptoms.

Individuals with CLD are under greater risk of depression because of disrupted QoL and disease related complications (10,21). In our study, although the patients who used DS had moderate depressive mood levels, no significant difference between those who did and did not use DS could be found. However, the positive strong relationship we found between the LDSI 2.0 and the BDI support the studies by Fábregas et al. (21) and Dan et al. (22).

Study Limitations

The results are based on cross-sectional data, therefore the conclusion of a causal relationship between variables cannot be derived. Therefore, longitudinally research is needed to reveal the relationship between variables in the future.

Conclusion

Approximately half of the patients with CLD were found to use DS in this study, with those with higher income levels, those who did not use alcohol, those with CLD for 6-10 years, and those with an additional chronic illness preferring DS more. The most commonly used DS were found to be respectively nigella (31.2%), green tea (29.3%), garlic (25.8%), cabbage (24.2%), willow leaves (21.5%), ginger (19.1%), apple vinegar (15.6%), artichoke (13.3%), turmeric (12.1%), vitamin E (12.1%), milk thistle (11.7%), and lavender (10.5%). Additionally, those who did not use DS were found to have lower QoL levels, and DS use was found not to be affected by depression status.

As it can be seen, the number of studies exhibiting the relationship between DS use and QoL and depression is insufficient. For this reason, randomized controlled studies with large samples are required to examine the relationship between DS use, QoL, and depression. Additionally, when it is considered that almost half of the CLD patients used DS, in order to prevent drug interactions and hepatotoxicity, the DS used by patients should be questioned while taking anamnesis and the QoL levels of patients should be evaluated using disease specific scales. Thus, health personnel are expected to follow scientific studies on the subject with high levels of evidence, utilize the results of those studies, and guide the healthy/ill individual correctly.

Ethics

Ethics Committee Approval: The study was approved by the Zonguldak Bülent Ecevit University Clinical Research Board of Ethics (approval number: 2018-93-28/03, date: 28/03/2018).

Informed Consent: Each patient was informed about the study and written consent was taken from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Research Article

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A Study of the Hepatitis B Frequency and Its Possible Adverse Outcomes on Pregnancy at a University Hospital

Bir Üniversite Hastanesinde Gebe Hastalarda Hepatit B Sıklığı ve Gebelik Üzerine Etkilerinin Araştırılması

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ABSTRACT

Objectives: Hepatitis B virus (HBV) is a major global public health problem. Maternal-fetal transmission of viral hepatitis may contribute to pregnancy-related complications. This study aimed to evaluate the frequency of HBV and its possible adverse pregnancy outcomes.

Materials and Methods: The study group consisted of patients followed up in the obstetrics service. Pregnancy-related discharge codes were queried approximately 2017-2019. Hepatitis B surface antigen (HBsAg) levels in serum samples were studied by chemiluminescence enzyme immunoassay method (Architect, Abbott Laboratories, USA). The HBsAg-positive group and HBsAg-negative group data were analyzed using SPSS version 22 (SPSS Inc.; Chicago, IL, USA).

Results: HBsAg was positive in 255 (2.1%) patients. Two groups compared in terms of age and there was no significant difference (p=0.45). Two groups compared in terms of pregnancy outcomes and there was no significant difference (p=0.1).

Conclusion: The study group consisted of patients with pregnancy complications and HBsAg positivity was found to be 2.1%. A lower rate was found compared to other regions. Studies to be conducted in different endemic regions of Hepatitis B in our country will illuminate the effect of hepatitis B on pregnancy better.

Keywords: Hepatitis B, pregnancy complications, HBsAg seropositivity

ÖZ

Amaç: Hepatit B virüsü (HBV) global halk sağlığı sorunları arasında yer alır. Gebelikte viral hepatitlerin anneden bebeğe transplesantal geçişi çeşitli komplikasyonlara neden olabilir. Çalışmamızda gebe hasta grubunda HBV sıklığının belirlenmesi ve gebelik üzerine olan olası etkilerinin araştırılması amaçlandı.

Gereç ve Yöntemler: Çalışma grubu kadın hastalıkları ve doğum kliniğine başvuran hastalardan oluşmaktadır. 2017-2019 yılları arasında takip edilen hastaların gebelik ilişkili komplikasyonları incelendi. Hepatit B yüzey antijen (HBsAg) düzeyi kemiluminesans enzim immünassay yöntemiyle (Architect, Abbott Laboratories, USA) belirlendi. HBsAg pozitif hasta ve HBsAg negatif hasta verilerini karşılaştırmak için SPSS versiyon 22 (SPSS Inc.; Chicago, IL, USA) kullanıldı.

Bulgular: HBsAg pozitifliği 255 (%2,1) hastada saptandı. İki grubun yaş ortalaması karşılaştırıldı, anlamlı fark saptanmadı (p=0,45). İki grup gebelik komplikasyonları yönünden karşılaştırıldı, anlamlı fark saptanmadı (p=0,1).

Sonuç: Çalışmamızdaki hasta popülasyonu gebelik ilişkili komplikasyonlar nedeniyle kadın hastalıkları ve doğum kliniğine başvuran hastalardan oluşmaktaydı ve HBsAg pozitifliği %2,1 bulundu. Diğer bölgelerden bildirilen çalışmalara göre daha düşük bir oran saptandı. Ülkemizde farklı endemik bölgelerde yapılacak çalışmalarla hepatit B'nin gebelik üzerine etkisi daha iyi aydınlatılacaktır.

Anahtar Kelimeler: Hepatit B, gebelik komplikasyonları, HBsAg seropozitifliği

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Intoduction

Hepatitis B virus (HBV) is major global public health problem worldwide that lead to chronic hepatitis, cirrhosis and hepatocellular carcinoma (1). More than 2 billion people live with HBV and 248 million of these are chronically infected (2). Turkey is on the whole considered to have a intermediate HBV endemicity. Between the years 2008-2011 comprehensive study was done by Liver Research Association of Turkey. Seropositivity rate for hepatitis B surface antigen (HBsAg) determined 4% (3).

There are three possible HBV transmission ways from infected mother to infant: First transplacental transmission, the second is perinatal transmission during childbirth, the third is postnatal tranmission during care and breastfeeding (4). To prevent transmission, HBV screening is part of routine prenatal care in Turkey. Hepatitis B immunoglobulin prophylaxis is given to infant born to mothers with HBsAg positive (5). HBsAg screening is recommended for all pregnant woman in local guideline (6).

In addition, maternal-fetal transmission of viral hepatitis may contribute to pregnancy-related complications such as gestational diabetes mellitus (GDM), preterm birth (PTB), intrauterine growth restriction, pre-eclampsia, antepartum haemorrhage (7). The aim of this study was to evaluate the frequency of HBV and its possible adverse pregnancy outcomes.

Materials and Methods

This retrospective study was conducted at a Necmettin Erbakan University Hospital Ethics Committee (approval number: 2021-126; date: 19.02.2021). The present study did not require informed consent owing to its retrospective nature. The study population comprised pregnant women who attended the Meram Faculty of Medicine, Gynecology and Obstetrics Inpatient Clinic. Pregnancy-related disharge codes was queried between 2017-2019. HBsAg status of the patients examined. HBsAg positive patients identified. The medical records of the patients involved in the study were reviewed by gynecologist. Inclusion criteria consisted of absense of medical or surgical disease such as liver disease, pre-GDM and hypertension. HBsAg status was routinely screened. HBsAg levels in serum samples were tested by the chemiluminescence enzyme immunoassay method (Architect, Abbott Laboratories, USA). The HBsAg positive patients constituted case group. They were divided into four groups according to pregnancy complications. Abortion, pre-eclampsia, PTB/premature of membranes, abortion imminens, postpartum hemorrhage and GDM were included in the obstetric complication group; intrauterin growth restriction, fetal anomaly and macrosomia were inclueded in fetal complication group, oligohidramnios, hyperemesis gravidarum, polyhydramnios and ectopic pregnancy were inclueded in other, the last group consisted of normal patients with no complications or clinical findings. HBsAg negative patients who applied in the same period and had similar demographic characteristics with case group constituted control group.

Statistical Analysis

To compare HBsAg-negative patient (control group) data and HBsAg-positive patient (case group) data were analyzed using SPSS version 22 (SPSS Inc.; Chicago, IL, USA). Categorical variables were compared using the χ^2 test. Continuous variables were expressed as means ± standard deviation and compared using the t-test. $P<0.05$ was considered to be statistically significant.

Results

In total, 11,941 pregnant patients data reviewed. HBsAg positivity was detected in 255 (2,1%) patients. Among these 115 women were excluded from the study because of medical complications or incomplete records. The case group included 140 patients (Figure 1). The control group included 287 patients. Two groups compared in terms of age and there was no significant difference (p=0.45). Two groups compared in terms of pregnancy outcomes and there was no significant difference (p=0.1). Obstetric complication constituted a significant part of pregnancy outcomes (42.1%) in the case group. In the control group, the majority of the patients (40.8%) were normal patients (Table 1).

Discussion

It is recommended to screen routinely pregnant patients for HBV infection by various international guidelines (8,9,10). Perinatal transmission from mother to infant is the most important cause of HBV infection, especially in regions with high prevalence, with a risk of chronicity over 90% (11). Since our country is located in the middle endemic region in terms of HBV infection, HBsAg screening is recommended in the antenatal care guidelines prepared by the Ministry of Health. Hepatitis B vaccine administration for all newborns started in 1998 and was included in the routine vaccination calendar in Turkey.

Although HBsAg seropositivity rates vary from region to region in our country, the average HBsAg positivity was found to be 4.4% (12). When the studies reported from different provinces are examined; similar rates were reported as 4.8% in Şanlıurfa (13), 5.7% in Rize (14), 4.7% in İstanbul (15) and 3.47% in Kırıkkale (16). Also, Çınar Tanrıverdi et al. (17) from Erzurum found the HBsAg positivity in their study was 1.2%, which is lower than other studies, while Kaleli et al. (18) from Denizli found a high rate of 7.6%. The population of our study consisted of patients who were followed up with a pregnancy-related diagnosis in the

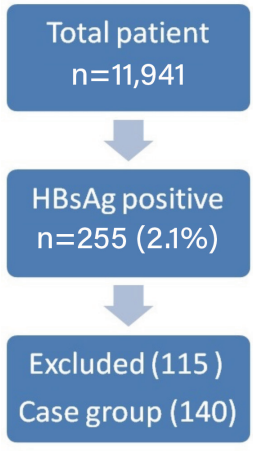

Figure 1. Setting case group
HBsAg: Hepatitis B surface antigen

obstetrics and gynecology service and HBsAg positivity was found to be 2.1%. The study of Tüzüner et al. (19) from our university reported this rate as 2.81% in blood donors between 2013 and 2016.

HBV infection does not affect fertility unless there is advanced liver disease. However, it has not been clearly revealed how chronic hepatitis B infection affects pregnancy and the fetus. There are studies (20,21) suggesting that it increases the risk of GDM, abortion imminens, PTB, antepartum and pospartum hemorrhage, as well as studies suggesting the opposite (22). In a large cohort study conducted by Bajema et al. (23) in the United States of America in a low endemic region, they did not find a statistically significant relationship between hepatitis B infection and adverse pregnancy outcomes. Similarly in our study, when the case group and the control group were compared, no significant difference was found in terms of pregnancy outcomes.

In a cohort study conducted by Liu et al. (24) from China, it has been shown that the risk of PTB (odds ratio: 1.18) increases at a very low rate in HBsAg positive pregnant women. In the study conducted by Sirilert et al. (25) in Thailand the rate of premature birth was found to be statistically significantly higher in HBsAg and hepatitis B e antigen-positive patients. It was suggested that HBV-DNA triggers placental inflammation in relation to the amount of viral load, leading to premature birth (25). In our study, the abortion rate was 15.7% in the case group and 8.7% in the control group. While the rate of cases with the threat of PTB or premature rupture of membranes was 11.1% in the control group, this rate was 7.8% in the case group. Since our hospital is a tertiary unit, most of the patients consist of complicated patients. Therefore, the rate of patients diagnosed with PTB or premature rupture of membranes is high in the control group. In our study, no significant difference was found between the case group and the control group in terms of pregnancy outcomes.

In a study conducted in the USA, it was emphasized that depending on the conditions such as the chronicity of the infection, the degree of damage to the liver, comorbid conditions and access to health care, whether or not women are infected with HBV may change. It has been suggested that the findings revealed in the highly endemic region may not be valid for a country such as America where HBV infection is much less common (26). This may be due to the fact that our region is a low endemic region for hepatitis B. Studies to be conducted in different endemic regions of hepatitis B in our country will illuminate the effect of hepatitis B on pregnancy better.

Table 1. Characteristics of the patients

	HBsAg positive (n=140)	HBsAg negative (n=287)	p-value
Maternal age	31.2±5.9	30.8±6.07	0.45
Older pregnant woman (≥35 y)	43	88	0.9
Pregnancy outcomes	-	-	0.1
Obstetric complications	59 (42.1%)	114 (39.7%)	-
Abortion	22 (15.7%)	25 (8.7%)	-
Pre-eclampsia	11 (7.8%)	11 (3.8%)	-
Preterm birth/premature rupture of membranes	11 (7.8%)	32 (11.1%)	-
Abortion imminens	6 (4.3%)	11 (7.3%)	-
Postpartum hemorrhage	7 (5%)	5 (1.7%)	-
Gestational diabetes mellitus	2 (1.4%)	20 (7%)	-
Fetal complications	15 (10.7%)	21 (7.3 %)	-
IUGR	7 (5%)	7 (2.4%)	-
Fetal anomaly	6 (4.3%)	11 (3.8%)	-
Macrosomia	2 (1.4%)	3 (1%)	-
Other	24 (17.1%)	35 (12.2 %)	-
Oligohydramnios	17 (12.1%)	27 (9.4%)	-
Hyperemesis gravidarum	4 (2.9%)	2 (0.7%)	-
Polyhydramnios	2 (1.4%)	6 (2.1%)	-
Ectopic pregnancy	1 (0.7%)	0 (0%)	-
Normal	42 (30%)	117 (40.8%)	-

HBsAg: Hepatitis B surface antigen, IUGR: Intrauterine growth restriction

Study Limitations

Retrospective nature of the present study and the inability to eliminate sub-standard prenatal care conditions that might have affected pregnancy outcomes were limitations.

Conclusion

In this study, no significant difference was found between the case group and the control group in terms of pregnancy outcomes. HBsAg positivity was found 2.1% in our study group. This rate is lower than other studies. Studies to be carried out in the high endemic region will better illuminate the effect of hepatitis B on pregnancy.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee Necmettin Erbakan University Meram Faculty of Medicine (approval number: 2021-126; date: 19.02.2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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Research Article

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An Evaluation of Chronic Hepatitis C Patients' Responses to Direct-Acting Antivirals According to Transient Elastography and Serum Biomarkers

Kronik Hepatit C Hastalarının Direkt Etkili Antivirallere Yanıtlarının Transient Elastografi ve Serum Biyomarkerleri Eşliğinde Değerlendirilmesi

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ABSTRACT

Objectives: In this study, it was evaluated the changes in liver stiffness measurements measured by AST to Platelet Ratio index (APRI), Fibrosis 4 index (FIB-4), Age Platelet index (API), AST-ALT ratio (AAR) and transient elastography (TE) among the non-invasive fibrosis scores in chronic hepatitis C (CHC) patients treated with direct-acting agents (DAA) and the effect of treatment.

Materials and Methods: Ombitasvir-paritaprevir-ritonavir-dasabuvir ± ribavirin (RBV) or sofosbuvir ± ledipasvir (SOF ± LDV) ± RBV was given to the patients. Fibrosis scores were calculated with the biochemical data of the patients before the treatment, at the 4th week of the treatment, at the end of treatment and at the sustained virological response 12 (SVR12). Liver stiffness measurements were recorded before treatment with TE and in SVR12. Post-treatment SVR12 responses were evaluated.

Results: SVR12 was achieved in 97.9% of 95 patients included in the study. Significant regression was found in APRI and FIB-4 scores, which are among the 4 serum fibrosis markers calculated in all patients (p<0.001, p<0.001). Liver stiffness was measured using TE in 75 patients. It was determined that the liver stiffness measurement (9.3±6.5 kPa) in SVR12 significantly decreased compared to the baseline (11.6±7.8 kPa) (p<0.001).

Conclusion: DAA provides improvement in fibrosis scores and persistent viral response in patients. In our study, in which fibrosis was evaluated non-invasive methods, it was observed that there was a significant improvement in liver fibrosis with APRI, FIB-4 and TE measurements.

Keywords: Hepatitis C, direct-acting antivirals, liver fibrosis, transient elastography, APRI, FIB-4

ÖZ

Amaç: Bu çalışmada direkt etkili ajanlarla (DEA) tedavi edilen kronik hepatit C hastalarında non-invaziv fibrozis skorlarından AST to Platelet Ratio index (APRİ), Fibrosis 4 indeks (FIB-4), Age Platelet index (APİ), AST-ALT ratio (AAR) ve transient elastografi (TE) ile ölçülen karaciğer sertlik ölçümlerindeki değişiklikleri ve tedavinin etkisini değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler: Hastalara ombitasvir-paritaprevir-ritonavir-dasabuvir ± ribavirin (RBV) veya sofosbuvir ± ledipasvir (SOF ± LDV) ± RBV verildi. Hastaların tedavi öncesinde, tedavinin 4. haftasında, tedavi sonunda ve kalıcı virolojk yanıt 12'de (KVY12) bakılan biyokimyasal verileri ile fibrozis skorları hesaplandı. TE ile tedavi öncesi ve KVY12'de karaciğer sertlik ölçümleri kaydedildi. Tedavi sonrası KVY12 yanıtları değerlendirildi.

Bulgular: Çalışmaya alınan 95 hastanın %97,9'unda KVY12 elde edildi. Hastaların tamamında hesaplanan 4 serum fibrozis belirteçlerinden APRİ ve FIB-4 skorunda anlamlı gerileme, saptandı (p<0,001, p<0,001). Yetmiş beş hastada TE ile karaciğer sertliği ölçümü yapıldı. KVY12'deki karaciğer sertlik ölçümünün (9,3±6,5 kPa), başlangıca göre (11,6±7,8 kPa) belirgin oranda gerilediği belirlendi (p<0,001).

Sonuç: DEA, hastalarda kalıcı viral yanıtın yanı sıra fibrozis skorlarında iyileşme de sağlamaktadır. Fibrozisin non-invaziv yöntemlerle değerlendirildiği çalışmamızda APRİ, FIB-4 ve TE ölçümleri ile karaciğer fibrozisinde belirgin iyileşme olduğu görülmüştür.

Anahtar Kelimeler: Hepatit C, direkt etkili antiviraller, karaciğer fibrozisi, transient elastografi, APRİ, FIB-4

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Introduction

Hepatitis C virus (HCV) infection is one of the most important causes of chronic liver diseases worldwide. HCV is a slowly progressive disease, characterized by progressive and persistent hepatic inflammation. Cirrhosis develops within 20 years in 20-30% of chronic hepatitis C (CHC) patients, and 1-4% of patients developing cirrhosis progress to hepatocellular carcinoma (HCC) every year (1).

The main objective of treatment in CHC is to achieve sustained virological response (SVR) and cure. Cure permits eradication of the infection. Due to the success of treatment with direct-acting agents (DAA), all patients with CHC are potential candidates for antiviral therapy. Early treatment is very important in terms of preventing potential complications of CHC. The treatment decision in CHC patients is generally based on serum HCV-RNA, genotype, alanine aminotransferase (ALT) levels, and the degree of necroinflammation at liver biopsy and the stage of liver fibrosis (2,3). Biopsy, regarded as the gold standard in the evaluation of fibrosis in liver diseases, entails a number of difficulties, including being invasive, the risk of being unable to obtain sufficient sample, the possibility of different histopathological features occurring in different regions, variations in interpretation among pathologists, and low acceptance rates among patients. This has led to the development of non-biopsy, non-invasive methods in the evaluation of fibrosis (4). The current guidelines describe a combination of direct biochemical markers [AST to Platelet Ratio index (APRI), Fibrosis 4 index (FIB-4), AST-ALT ratio (AAR), Age Platelet index; (API) etc.] and transient elastografi (TE) as the most effective approach in assessing the severity of chronic liver disease and fibrosis (2,5).

Recent studies have reported that fibrosis can regress, although these have particularly involved patients receiving interferon (IFN) therapy (6). The number of studies examining changes occurring in non-invasive fibrosis values and liver stiffness measurements in patients treated with DAA is limited. The purpose of the present study was therefore to investigate responses to treatment in patients receiving DAA therapy, and also the effect of treatment on fibrosis, using non-invasive fibrosis scores and TE.

Materials and Methods

Approval for this study was granted by the Karadeniz Technical University Scientific Research Ethical Committee, Turkey (approval number: 2019/042). The research was performed retrospectively among patients under follow-up with diagnoses of CHC and receiving DAA. Patients completing DAA therapy and attending regular follow-ups for at least 12 weeks were included in the study. Patients' demographic characteristics, viral loads, HCV genotypes, stage of disease and DAA used in treatment were recorded.

HCV-RNA, aspartate aminotransferase (AST), ALT, alpha fetoprotein (AFP), alkaline phosphatase (ALP), gamma-glutamil transferase (GGT), total bilirubin, albumin, protein, blood urea nitrogen, creatinine, international normalized ratio (INR), prothrombin time, hemoglobin (HB), white blood cell (WBC), and platelet (PLT) levels were assessed at the beginning of treatment, four weeks after commencing treatment, at the end of treatment (EOT), and 12 weeks after the EOT. Responses were evaluated based on the levels of these parameters during follow-up.

Fibrosis scores (APRI, FIB-4, AAR and API) were calculated from routinely requested biochemical tests before treatment, four weeks after commencing treatment, at the EOT, and 12 weeks after the EOT (7,8). The courses of the changes in these were recorded and evaluated at the four different time points. In addition, degrees of fibrosis in TE liver stiffness measurement results were recorded before and 12 weeks after the EOT. F_{0-1}<7.1 kPa was regarded as no/mild fibrosis, F_2=7.1-9.4 kPa as moderate fibrosis, F_3=9.5-12.4 kPa as severe fibrosis, and F_4≥12.5 kPa as cirrhosis.

Undetectable HCV-RNA measured using the quantitative polymerase chain reaction (PCR) test on the 12th week after completion of treatment was regarded as SVR (2). HCV-RNA was determined with real-ime PCR, using HCV Quantitative test version 2.0 (Roche Molecular Systems, USA) on a COBAS TaqMan platform.

Statistical Analysis

Statistical analysis was performed on IBM SPSS version 23.0 software. Descriptive statistics were expressed as mean, standard deviation, minimum, and maximum values for numerical variables. The chi-square test was applied in the comparison of qualitative data. Normality of distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Since the data were not normally distributed, the Friedman test was applied to compare measurement variables between two dependent groups, while the Wilcoxon test was used to compare more than two dependent groups. The post-hoc Bonferroni test was applied to identify the source of any significant difference emerging between the groups. Since the data were not normally distributed, Spearman's correlation analysis was applied in the evaluation of relationships between liver stiffness values obtained using TE and other biochemical values and fibrosis scores. Statistical alpha significance was set at $p<0.05$.

Results

Ninety-five patients receiving DAA with a diagnosis of CHC at the Karadeniz Technical University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Turkey, were included in the study. Forty-seven (49.5%) patients were men and 48 (50.5%) women, with a mean age of 62.6±10.5 years. The most common genotype was genotype 1 at 96.8% (n=92), followed by genotype 3 at 2.1% (n=2), and genotype 4 at 1.1% (n=1). In addition, 91.3% of the genotype I patients were genotype 1b. Analysis showed that 47.4% (n=45) of the patients were treatment-naïve and 52.6% (n=50) were treatment-experienced, while 80% (n=76) were non-cirrhotic and 20% (n=19) were cirrhotic. Decompensated cirrhosis was present in one cirrhotic patient (Table 1).

A ombitasvir-paritaprevir-ritonavir-dasabuvir (PrOD) regimen was applied to 57.9% (n=55) of patients, and an sofosbuvir (SOF) regimen to 42.1% (n=40). While 56.8% (n=54) of patients were started on PrOD, 1.1% (n=1) were started on PrOD + ribavirin (RBV), 25.3% (n=24) on SOF/ledipasvir (LDV), 14.7% (n=14) on SOF/LDV + RBV, and 2.1% (n=2) on SOF + RBV. In terms of

responses to treatment, SVR was achieved in 97.9% (n=93) of all patients. HCV-RNA elevation was again observed 12 weeks after completion of treatment in two patients, despite response having been achieved. Serum HCV-RNA, ALT, AST, AFP, ALP, GGT, total bilirubin, protein, albumin, WBC, PLT, and INR values investigated before treatment, at the 4th week of treatment, at the EOT, and SVR12 are shown in Table 2. Changes observed with treatment were statistically significant.

The courses during treatment of the APRI, FIB-4, AAR, and API scores calculated before commencement of treatment are shown in Table 3. APRI, FIB-4, and API decreased on the 4th week of treatment and at the EOT, while an increase was observed in AAR. The decrease in APRI persisted in SVR12 after treatment, while an increase was observed in FIB-4, AAR and API at SVR12 compared to at the EOT. The changes in the APRI, FIB-4 and AAR fibrosis scores were statistically significant (p<0.001, p<0.001, p<0.001).

Post-hoc Bonferroni analysis was applied in order to determine the timing of statistically significant differences in fibrosis scores. Accordingly, the decreases between pretreatment APRI and FIB-4 scores and those on the other weeks were found to be statistically significant. The increases in AAR scores on the other weeks compared to pretreatment values were also statistically significant (Table 4).

TE was used to measure liver stiffness before treatment and at SVR12 in 75 patients. Mean liver stiffness values were 11.6±7.8 kPa and 9.3±6.5 kPa, respectively, and the decrease at SVR12 was statistically significant (p<0.001) (Figure 1).

F_{0-1} fibrosis was determined in 34.7% (n=26) before treatment, F_2 in 17.3% (n=13), F_3 in 13.3% (n=10), and F_4 in 34.7% (n=26). 50% (n=13) of the pretreatment 26 F_4 patients remained at F_4, while 19.2% (n=5) improved to F_3, 11.5% (n=3) to F_2, and 19.2% (n=5) to F_{0-1}. 20% (n=2) of the 10 pretreatment F_3 increased to F_4, 10% (n=1) remained at F_3, 50% (n=5) improved to F_2, and 20% (n=2) improved to F_{0-1}. In addition, 92.3% (n=12) of the 13 pretreatment F_2 patients improved to F_{0-1}, and 7.7% (n=1) increased to F_3. Moreover, 34.7% (n=26) of patients were F_{0-1} before treatment and 76.9% (n=20) remained as F_{0-1}, while 15.4% (n=4) progressed to F_2, and 7.7% (n=2) to F_3. In addition, the 34.7% (n=26) of patients who were F_{0-1} before treatment increased to 52% (n=39) at SVR12, while the incidence of F_3 decreased from 13.3% (n=10) to 12%, F_2 from 17.3% (n=13) to 16% (n=12), and F_4 from 34.7% (n=26) to 20% (n=15) (Figure 2).

The relationships between liver stiffness measurements obtained with TE and biochemical parameters and non-invasive fibrosis scores were also investigated. Negative correlation was determined between liver stiffness values and AAR and PLT

Table 1. Demographic characteristics of the patients

Characteristics	**n (%)**
Mean age ± standard deviation	62.6±10.5
Gender	
Women	48 (50.5%)
Men	47 (49.5%)
HCV genotype	
Genotype 1*	92 (96.8%)
Genotype 3	2 (2.1%)
Genotype 4	1 (1.1%)
Treatment-naive	45 (47.4%)
Treatment-experienced	50 (52.6%)
Non-cirrhotic	76 (80%)
Cirrhotic	19 (20%)

*Genotype 1: 1b, 1a and non-subtyped, HCV: Hepatitis C virus

Table 2. Laboratory values of the patients before treatment, at the 4th week of treatment, at the EOT and SVR12

Laboratory	**Before treatment [mean ± SD (min.-max.)]**	**4th week [mean ± SD (min.-max.)]**	**EOT [mean ± SD (min.-max.)]**	**SVR12 [mean ± SD (min.-max.)]**	**p**
HCV-RNA	1,725,952,6±6,534,968,8 (336-60,050,000)	9.9±45.9 (0-413)	0	340,105,3±2,945,926,3 (0-28.500,000)	**<0.001**
ALT	67.7±64.7 (10-377)	22.6±20.7 (3-124)	18.5±14.8 (3-77)	17.6±15.3 (4-132)	**<0.001**
AST	67.5±57.5 (13-363)	28.8±16.3 (7-113)	26.4±13.8 (6-93)	25.6±11.2 (7-80)	**<0.001**
AFP	11.5±22.7 (1.2-149.2)	7.3±13.6 (0.9-121.9)	5.4±12.1 (0.7-116.4)	4.8±8.5 (0.8-78.1)	**<0.001**
ALP	94.3±38.7 (41-227)	93.5±37.1 (44-254)	99.0±38.5 (44-254)	90.0±38.7 (32-282)	**0.005**
GGT	73.5±76.3 (10-524)	37.2±29.0 (10-236)	27.2±19.9 (8-161)	26.2±15.9 (9-136)	**<0.001**
Total bilirubin	0.9±0.5 (0.1-3.1)	1.0±0.5 (0.2-2.9)	0.9±0.5 (0.3-3.6)	0.9±0.4 (0.3-2.5)	**0.001**
Protein	7.5±0.7 (2.5-8.6)	7.5±0.4 (6.1-8.4)	7.5±0.6 (4.2-8.5)	7.6±0.6 (4-9)	**0.027**
Albumin	4.0±0.4 (2.8-4.8)	4.0±0.4 (2.9-4.7)	4.2±0.5 (2.9-7.4)	4.3±0.4 (3.0-6.2)	**<0.001**
INR	1.0±0.2 (1-2)	1.1±0.2 (0.9-1.5)	1.1±0.2 (0.8-2.2)	1.1±0.2 (1-2)	**0.015**
WBC	6,559,2±2,491,5 (2,590-15,800)	6,917,0±2,298,2 (2,500-16,890)	6.714.3±2.116.7 (2,300-13,800)	6.619.5±2.042.8 (2,900-12,830)	0.160
PLT	196,736,8±77,971,5 (57,000-432,000)	202,389,5±74,709,1 (58,000-366,000)	205,494,7±75,127,7 (57,000-465,000)	202,410.5±74,632,5 (63,000-495,000)	0.192

EOT: End of treatment, SVR12: Sustained virologic response 12, SD: Standard deviation, min.: Minimum, max.: Maximum, HCV: Hepatitis C virus, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AFP: Alpha fetoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamil transferase, INR: International normalized ratio, WBC: White blood cell, PLT: Platelet

values, while positive correlation was determined with APRI, ALT, AST, AFP, total bilirubin, ALP, GGT, and INR (Table 5).

Discussion

HCV is one of the main causes of chronic liver disease worldwide (1). Liver damage in patients can range from minimal histological changes to advanced fibrosis. If the infection is not treated, it can result in cirrhosis, HCC, and death.

The objective in the treatment of CHC is cure. Current DAA therapies exhibit high effectiveness, a high-barrier viral resistance effect, and a low side-effect profile (9). Several clinical studies have shown that SVR exceeding 90% has been achieved in patients treated with DAA (10,11).

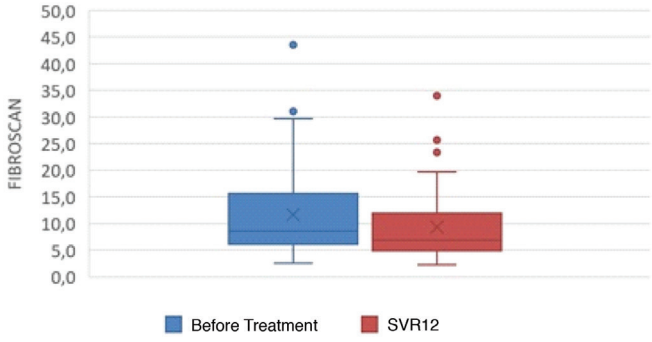

Figure 1. Changes in fibroscan values with treatment

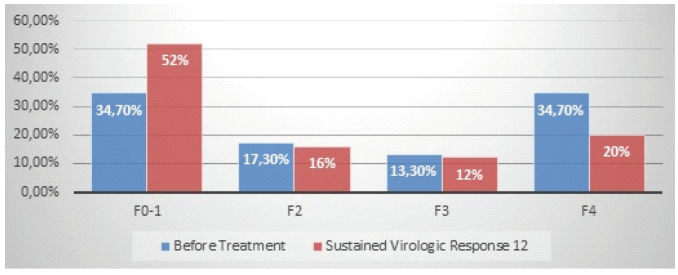

Figure 2. Fibrosis stage before treatment and at SVR12 according to fibroscan value

Before treatment, the degree of necrosis and inflammation in the liver must be graded, fibrosis must be scored, other hepatic pathologies must be excluded, and the treatment options and duration must be determined (12). Several serological and biochemical marker methods have been developed for the non-invasive evaluation of liver fibrosis (4,13). APRI and FIB-4, indirect biochemical markers frequently employed among the non-invasive methods are accepted by current guidelines for the determination of the degree of fibrosis (2). One study investigating the specificity and sensitivity of serum biomarkers and liver stiffness in determining fibrosis in patients diagnosed with CHC compared the effectiveness of biopsy APRI, FIB-4 and TE in 81 patients, and reported that all three were effective in determining liver fibrosis (14). Köksal et al. (15) showed that the non-invasive markers APRI, FIB-4, API and the Forns index exhibited good performances in determining liver fibrosis, and that that the use of at least two tests together would further enhance their diagnostic value.

Another study evaluating changes in liver fibrosis using TE, APRI and FIB-4 in CHC patients treated with DAA achieved an SVR12 rate of 92.7%. Significant decreases in TE, APRI and FIB-4 were observed in all patients 12 weeks after treatment, and particularly in those with more advanced fibrosis (p<0.001) (16).

Comparison of pre-treatment measurements and those at the 4th week of treatment, at the EOT, and at SVR12 revealed a significant decreased in pretreatment APRI scores and those at the other weeks (p<0.001), and that this decrease persisted after the 4th week of treatment. The significant decrease in APRI scores, calculated using AST and PLT values, particularly in the first four weeks, may be associated with a rapid decrease in AST values. A significant decrease was observed between pretreatment FIB-4 scores and the other weeks (p<0.001), although an insignificant increase was determined between the EOT and SVR12 (p=1.000). The significant increase between pretreatment AAR scores and

Table 3. Fibrosis scores before treatment, at the 4th week, at the EOT and SVR12

Fibrosis scores	Before treatment (mean ± SD)	4th week (mean ± SD)	EOT (mean ± SD)	SVR12 (mean ± SD)	p
APRI	1.4±1.9	0.5±0.5	0.5±0.4	0.4±0.3	**<0.001**
FIB-4	3.4±3.0	2.5±1.9	2.3±1.5	2.4±1.5	**<0.001**
AAR	1.1±0.6	1.6±0.7	1.7±0.7	1.8±0.7	**<0.001**
API	5.8±2.2	5.7±2.2	5.6±2.1	5.8±2.1	0.229

EOT: End of treatment, SVR12: Sustained virologic response 12, SD: Standard deviation, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis 4 Index, AAR: AST-ALT ratio, API: Age Platelet Index,

Table 4. The results of posthoc bonferroni analysis performed for the patients' fibrosis scores before treatment, at the 4th week of treatment, at the EOT and SVR12

Fibrosis scores	Posthoc Bonferroni analysis					
	BT-4th week	BT-EOT	BT-SVR12	4th week-EOT	4th week-SVR12	EOT-SVR12
APRI	**<0.001**	**<0.001**	**<0.001**	0.694	1.000	1.000
FIB-4	**<0.001**	**<0.001**	**<0.001**	1.000	1.000	1.000
AAR	**<0.001**	**<0.001**	**<0.001**	0.864	1.000	1.000

EOT: End of treatment, SVR12: Sustained virologic response 12, BT: Before treatment, APRI: AST to Platelet Ratio Index, FIB-4: Fibrosis 4 Index, AAR: AST-ALT ratio

the other weeks (p<0.001) was evaluated as incompatible with APRI and FIB-4 scores. No significant change was observed in API scores between any time points (p=0.229).

The number of studies evaluating early changes in fibrosis scores with DAA therapies is limited. Hsu et al. (17) evaluated the rapid decrease in non-invasive fibrosis scores in patients diagnosed with CHC receiving DAA therapy. APRI and FIB-4 scores were calculated on the second and 4th weeks of treatment, at the EOT, and at SVR12. Scores decreased rapidly and statistically significantly from the second week until SVR12. Since healing in fibrosis is a long-term process, the authors attributed the early decrease in non-invasive scores at the second week of treatment to the rapid decrease in AST and ALT values and to improvement in necroinflammation as a result of increased PLT values, rather than to improvement of fibrosis (17). Similarly, Elsharkawy et al. (18) reported a significant decrease in ALT levels and APRI scores in the 4th week among patients receiving an SOF-based regimen, and suggested that the early decrease in APRI values reflected a diminution of necroinflammation, rather than regression of fibrosis (18). Similarly in the present study, significant regression was observed in APRI and FIB-4 at the 4th week (p<0.001, p<0.001), which we attributed to a rapid decrease in AST and ALT values. Although regression in APRI and FIB-4 non-invasive fibrosis scores is a finding supporting histological improvement, further prospective studies comparing scores with liver biopsy are now needed in order to confirm this.

Several studies have investigated SVR rates among different DAA therapies, although research into these therapies' effects on histological improvement is insufficient. Carvalho et al. (19) evaluated regression in fibrosis developing after one year in patients receiving IFN-based therapy and DAA therapy using TE, APRI and FIB-4. SVR data were accessed for 105 patients receiving DAA and 73 receiving IFN-based therapy, and statistically significant decreased were observed in APRI, FIB-4 and TE values. Fibrosis regression was more significant in the DAA group, independently of patient characteristics, and this was associated only with the therapeutic regimen (19). Another study evaluated changes in fibrosis between groups receiving IFN-based and DAA therapies among 204 patients diagnosed with CHC. TE, APRI, and FIB-4 and biochemical parameters were investigated before treatments and 12 weeks after the EOT. No significant difference was observed between treatment-naive and treatment-experienced patients in all treatment groups, while score changes were significant in both groups (20). In our study, significant regression was observed in APRI and FIB-2 scores before treatment and at SVR12 in patients receiving SOF and PrOD regimens, together with insignificant regression in API scores. Significant decreases were observed in APRI and FIB-4 scores irrespective of whether patients were treatment-naive or experienced, or cirrhotic or non-cirrhotic, while AAR scores increased significantly, and no change was determined in API scores.

Table 5. Comparison of the liver stiffness measurement value measured by TE with other parameters

Liver stiffness	R	p
APRI	0.301	**0.009**
FIB-4	0.172	0.140
AAR	-0.302	**0.008**
API	0.117	0.316
ALT	0.345	**0.002**
AST	0.458	**<0.001**
AFP	0.533	**<0.001**
Total bilirubin	0.329	**0.004**
ALP	0.322	**0.005**
GGT	0.485	**<0.001**
INR	0.511	**<0.001**
WBC	-0.145	0.215
PLT	-0.434	**<0.001**

APRI: AST to Platelet Ratio index, FIB-4: Fibrosis 4 index, AAR: AST-ALT ratio, API: Age Platelet index, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AFP: Alpha fetoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamyl transferase, INR: International normalized ratio, WBC: White blood cell, PLT: Platelet

Examination of the previous literature shows that long-term follow-up has most frequently involved patients receiving pegylated (PEG)-IFN + RBV therapy, and since the length of use of DAA agents is still short, long-term follow-ups have not been performed. In a prospective study from France, patients with and without PEG-IFN + RBV therapy were followed-up for three years. Changes in liver fibrosis were evaluated using non-invasive methods. Liver stiffness measurements for fibrosis performed with TE before treatment, at the EOT, and six months after completion of treatment for liver fibrosis in the treatment group were compared in the treatment group, while initial values and values at the end of one and two years were compared in the non-treatment group. Significant regression was observed in liver stiffness values in the treatment group between baseline and the EOT (p<0.001). EOT measurements in the treatment group differed significantly from first-year measurements in the non-treatment group (p<0.001) (21).

In their study of 392 patients receiving DAA therapy, Bachofner et al. (22) reported significant improvement, with a regression rate of 32.4%, in TE values after treatment compared to baseline (p<0.001). Regressions in APRI and FIB-4 scores were also significant (p<0.001). Liver stiffness values measured before treatment and at SVR12 in our study were 11.6±7.8 kPa and 9.3±6.5 kPa, respectively. This improvement in liver stiffness was statistically significant (p<0.001).

Tada et al. (23) reported that the improvement in liver fibrosis persisted from the end of DAA therapy until the 24th week in CHC patients achieving SVR. Pons et al. (24) investigated early and long-term liver and spleen stiffness following treatment with DAA and reported that improvement in liver stiffness commenced from the 4th week of treatment (p=0.002), and that the greatest regression was observed in the first four weeks. In addition, improvement persisted throughout treatment, significant improvement was also observed at EOT measurements (p=0.014), persisting until the 48th week post-treatment (p=0.003) (24). These two studies showed that significant improvement in liver stiffness persisted for 48 weeks. The patients in the present study were followed-up for 12 weeks after treatment. In terms of grades based on TE measurement,

the proportion of F_{0-1} patients rose from 34.7% to 52% at SVR12, while the proportion of F_4 patients decreased from 34.7% to 20%. Since the healing process is a continuing one, longer follow-ups are required for a more accurate evaluation. We think that fibrosis regression rates in patients with higher degrees of diseases will be greater at long-term follow-up.

A study from Japan evaluated liver stiffness measurements obtained using TE before treatment and at SVR24 in patients diagnosed with CHC and using DAA. Significant regression was observed at SVR24 in ALT, AST, total bilirubin, INR, HGB, APRI, FIB-4, and liver stiffness, and positive correlation was determined between this improvement in liver stiffness and ALT (p=0.04), AST (p=0.04), total bilirubin (p=0.03), and APRI (p=0.002) (25). In our study, the improvement in liver stiffness was positively correlated with APRI (p=0.009), ALT (p=0.002), AST (p<0.001), AFP (p<0.001), total bilirubin (p=0.004), ALP (p=0.005), GGT (p<0.001) and INR (p<0.001), and negatively correlated with AAR (p=0.008) and PLT (p<0.001). We think that the positive correlation between improvement in liver stiffness and APRI, ALT, and AST is associated with improvement in necroinflammation with treatment, while the positive correlation with INR and negative correlation with PLT are associated with improvement in fibrosis and regulation of hepatic synthesis functions.

Study Limitations

There were limitations to the present study. First, the study was done retrospectively. Second, the number of patients is small. Third, noninvasive scores were not confirmed by biopsy.

Conclusion

DAA therapy was effective in all the patients in this study, and successful SVR was achieved. The study findings showed that cure can be achieved in CHC with treatment, and that early regression in fibrosis scores occurs after treatment. This study also shows that the use of non-invasive fibrosis markers is a simple, effective, and practical method for monitoring fibrosis.

Ethics

Ethics Committee Approval: Approval for this study was granted by the Karadeniz Technical University Scientific Research Ethical Committee, Turkey (approval number: 2019/042).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Research Article

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Evaluation of HCV-Core Antigen in Diagnosis of Chronic Hepatitis C Patients under Direct-Acting Antiviral Treatment

Doğrudan Etkili Antiviral Tedavi Kullanan Kronik Hepatit C Hastalarının Tanısında HCV Çekirdek Antijeninin Değerlendirilmesi

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ABSTRACT

Objectives: Recently, with the use of direct-acting antivirals (DAA) for treating chronic hepatitis C (CHC), the success rate has exceeded 90%. The implementation of these strong therapies has reduced the role of monitoring therapy with hepatitis C virus (HCV)-RNA tests. The current study compares the HCV-core antigen test (HCV-Ag) with HCV-RNA in terms of correlation, effectiveness and cost in patients who started DAA and to evaluate the usability of HCV-Ag as a routine laboratory test.

Materials and Methods: This study includes 76 patients with CHC. Patients with positive HCV-RNA, over 18 years old and who will initiate DAA are included. HCV-Ag level was studied in all samples by using ARCHITECT core antigen measurement Abbott method. HCV-RNA and anti-HCV levels compared with HCV-Ag levels.

Results: Of the 76 patients, 44 (57%) were males, 48 (63%) were treatment experienced and 21 (27%) were cirrhotic. All patients were started with DAAs. When compared before and after treatment, HCV-RNA level, HCV-Ag level was found to be significantly different ($p<0.001$). Before treatment, HCV-RNA and HCV-Ag levels were found to be positive correlations (correlation coefficient: 0.419).

Conclusion: The use of DAAs in HCV therapy has eliminated the need for response-guided therapy. It has been demonstrated in the study that HCV-Ag measurement is very successful and cost effective in detecting viremic patients and evaluating virological response, which are the two most important factors in the management of CHC.

Keywords: Hepatitis C virus, correlation, viral load, hepatitis C antibodies

ÖZ

Amaç: Son yıllarda kronik hepatit C (KHC) tedavisinde doğrudan etkili antivirallerin (DEA) kullanılmasıyla başarı oranı %90'ı geçmiştir. Bu güçlü tedavilerin uygulanması, tedavinin hepatit C virüs (HCV)-RNA testleri ile izlenmesinin rolünü azaltmıştır. Bu çalışmanın amacı, DEA başlanan hastalarda HCV çekirdek antijen testi (HCV-Ag) ile HCV-RNA'yı korelasyon, etkinlik ve maliyet açısından karşılaştırmak ve HCV-Ag'nin rutin laboratuvar testi olarak kullanılabilirliğini değerlendirmektir.

Gereç ve Yöntemler: Çalışmamıza 76 KHC hastası dahil edilmiştir. HCV-RNA pozitif olan, 18 yaş üstü ve DEA başlanacak olan hastalar dahil edilmiştir. ARCHITECT-Abbott yöntemi kullanılarak tüm örneklerde HCV-Ag düzeyi çalışıldı. HCV-Ag seviyeleri ile RNA ve anti-HCV seviyeleri ile karşılaştırıldı.

Bulgular: Yetmiş altı hastanın 44'ü (%57) erkek, 48'i (%63) önceden tedavi görmüş ve 21'i (%27) sirotikti. Tüm hastalara DEA başlandı. Tedavi öncesi ve sonrası karşılaştırıldığında, HCV-RNA düzeyi, HCV-Ag düzeyi anlamlı olarak farklı bulundu ($p<0,001$). Tedavi öncesi HCV-RNA ve HCV-Ag seviyeleri arasında pozitif korelasyon (korelasyon katsayısı: 0,419) saptandı.

Sonuç: HCV tedavisinde DEA'larin kullanılması tedavi yanıtının değerlendirilmesinde HCV-RNA takibi yapılmasının önemini azaltmıştır. KHC yönetiminde en önemli iki faktör olan viremik hastaları saptamada ve virolojik yanıtı değerlendirmede HCV-Ag ölçümünün oldukça başarılı ve maliyet etkin olduğu çalışmamızda gösterilmiştir.

Anahtar Kelimeler: Hepatit C virüs, korelasyon, viral yük, hepatit C antikorları

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Introduction

Hepatitis C virus (HCV) infection is a blood-borne disease that affected approximately 185 million people worldwide (1). It has been estimated that HCV accounts for 27% of cirrhosis and 25% of hepatocellular carcinoma (HCC) worldwide (2). In Turkey, the prevalence of anti-HCV positivity was found to be 1% and prevalence increased after 50 years of age most of them unaware of their infection (3). In 2030, it is estimated that approximately 80,000 people may have cirrhosis, 3,770 people may have HCC related to HCV, and 3,420 people will be lost due to HCV infection (4).

The diagnosis of hepatitis C infection is made by detection of HCV-RNA by molecular methods after detection of anti-HCV antibodies by ELISA. HCV-core antigen testing is a convenient, inexpensive alternative, as it is correlated with HCV-RNA, in resource-restricted locations or when the HCV-RNA test is not available. HCV-core antigen tests have been introduced to supplement anti-HCV tests or HCV quantitative real time polymerase chain reaction (qRT-PCR) analyses over the last decade (5,6). This chemiluminescent microparticle immunoassay uses microparticles coated with anti-HCV monoclonal antibodies for the detection of HCV-Ag by capturing. The first in-house HCV-core antigen assays that were shown to have insufficient performance for clinical application mainly due to their low sensitivity were developed in Japan in the early 1990s. Over the years, researchers from Abbott Laboratories (North Chicago, IL) have recently developed the ARCHITECT HCV-Ag method which is used in this study. Despite all the advantages mentioned in the literature the manufacturer of HCV-core antigen assays recently stopped active marketing of these assays in several countries. It will, unfortunately, and probably, never be possible to determine the actual potential and usefulness of HCV-core antigen testing in the management of hepatitis C (7).

The diagnosis and treatment of HCV infection have improved a lot over the years. Over finally, well-tolerated and effective treatments with oral antivirals inhibiting HCV non-structural viral proteins involved in viral replication have been marketed this last decade, allowing the cure of all infected subjects (8). The main goal of chronic hepatitis C (CHC) treatment is to reduce the risk of developing HCC, the morbidity, and mortality associated with this disease, and the need for liver transplantation by the sustained virological response (SVR), which is defined as the inability to detect HCV-RNA in the blood 12 or 24 weeks after treatment is completed (9). The ratio of SVR is over 90% with these direct-acting antivirals (DAA). With these advances in HCV treatment, it would be beneficial to simplify the diagnosis and increase the screening to provide more patients access to new treatments. According to the European Association for the Study of the Liver (EASL) guideline, two main factors in the management of CHC; to detect basal viral load before treatment and to see that viral load becomes negative after treatment. In resource-limited environments where a nuclear acid test (NAT) is not available, using an HCV-c-Ag test to confirm viremia is recommended (10).

The purpose of this study; to compare the HCV-core antigen test with HCV-RNA, which is studied in the patient before and after the treatment of patients using DAA, and to evaluate the usability of core antigen measurement as a routine laboratory test.

Materials and Methods

Seventy-six patients with chronic HCV infection who applied to infectious diseases outpatient were included in this study. Patients were diagnosed with CHC according to the EASL guidelines. The presence of HCV-RNA above the threshold value was used for establishing the diagnosis of HCV. The anti-HCV positivity longer than 6 months was used as the criterion for chronicity (11). All patients were HCV-RNA positive, over 18 years old, and who would start treatment with DAA. Patients used sofosbuvir/ledipasvir (SOF/LDV), ritonavir boosted paritaprevir-ombitasvir-dasabuvir (PrOD), telaprevir (TEL) and bocepravir (BOC) as DAA regimen. Patients with acute hepatitis C and under 18 years of age have been excluded from the study. The demographic, clinical, and virological variables of the patients were obtained by scanning from the hospital electronic data system. Whether patients had cirrhosis or not was obtained from imaging records or biopsy reports. ISHAK Modified Histological Activity index (HAI) scoring system was used for the pathological diagnosis of cirrhosis. HCV treatment was initiated according to guides and our the Health Practice Communiqué (12,13).

Before the treatment started, informed consent was obtained from the patients, and blood was taken into a 1 tube EDTA hemogram tube, centrifugation (5K rpm in 10 min) was performed as soon as they were received and their plasma was separated. At the end of the treatment, plasma of the same patients was obtained. Patients' plasma samples were stored at -80 °C until required for testing. Then, HCV-Ag level was studied in all samples by using the ARCHITECT core antigen measurement Abbott method (Denka Seiken Co., Tokyo, Japan) HCV-RNA and anti-HCV levels before and after treatment, which were routinely studied in our hospital, were obtained using the hospital data system and compared with HCV-Ag levels. The lower detection limit for the HCV-RNA and HCV-Ag levels was 15 IU/mL and 3 fmol/L, respectively. In addition, the HCV genotype was detected using type-specific RT-PCR. Patients with HCV-RNA negative or below the lower limit of measurement at 12 weeks post-treatment were identified as providing SVR.

Ethical approval for the study was received from Kocaeli University Faculty of Medicine Ethics Committee (approval number: 2018/212, date: 11.7.2018).

Statistical Analysis

Statistical evaluation was done with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) package program. Compatibility with normal distribution was evaluated with the Kolmogorov-Smirnov test. Continuous variables were given as mean ± standard deviation and median (25^{th}-75^{th} percentile), and categorical variables were given as frequency (percent). The pre-treatment and post-treatment comparisons were determined by the Wilcoxon-Signed Ranks test since normal distribution assumption was not provided. Relationships between categorical variables were evaluated by chi-square analysis. Spearman correlation analysis was used to analyze the relationships between continuous variables. For statistical significance $p<0.05$ was considered sufficient.

Results

For this study, a total of 76 patients treated with DAAs in the Kocaeli University, Infectious Diseases Outpatient Clinic during the year 2017 were included. Of the 76 patients; 44 (58%) were males and 32 (42%) were females. The average age was 56.97±13.56. It was determined that 46 of the patient's liver biopsy was performed. Nineteen patients were treatment - experienced, and 11 of them were chronic kidney failure. Patients with fibrosis 3 and above as a result of the biopsy were considered cirrhosis. Totally 21 patients had cirrhosis. Of these patients, 17 patients were accepted as cirrhosis as a result of the biopsy, 2 patients with liver imaging, 2 patients with fibroscan fibrosis score 4. The most common genotype in our patients was GT-1b (45, 59%). When the underlying diseases of the patients were evaluated, it was observed that 11 patients, 7 of whom underwent hemodialysis, had chronic kidney failure and eight patients had type 2 diabetes mellitus. There was also a history of liver transplantation in one patient and kidney in one patient. Five of the patients (6.6%) were coinfected with the hepatitis B virus (HBV), and their current HBV-DNA levels were negative. The demographic features are shown in Table 1.

Based on the guidelines, all patients started DAA treatment. Twenty-five patients were treatment-experienced. The most common DAAs for these patients were TEL (35%), SOF + LDV (27%), and BOC (25%) which were pan-genotypic. Treatments initiated to patients are summarized in Table 2.

When compared before and after treatment, HCV-RNA level, HCV-Ag level, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alpha-fetoprotein (AFP) parameters were found to be significantly different ($p<0.001$). However, there was no significant decrease in anti-HCV titer after treatment. A comparison of the laboratory parameters of the patients before and after the treatment is shown in Table 3.

All patients included in our study had a post-treatment response. Subsequently, 73 patients (96.1%) were provided with SVR, and 3 patients (3.9%) had positive HCV-RNA at the 12th week after treatment. It was determined that all patients who did not provide SVR received a TEL regimen. Relationship between cirrhosis and SVR or cirrhosis and age, no significant difference was found respectively ($p=0.567$, $p=0.566$).

In addition, pretreatment HCV-RNA, HCV-Ag, and anti-HCV values were compared and a significant relationship was found between HCV-Ag and HCV-RNA ($p<0.001$) (Table 4). There was no significant relationship between anti-HCV and other parameters. Also, it was observed that the patients had a positive correlation with HCV-RNA and HCV-Ag levels before treatment (Spearman correlation coefficient: $r=0.419$) (Figure 1).

Discussion

The amount of HCV-core antigen in the blood correlates with the level of HCV-RNA, so it is also a test that can be used to demonstrate HCV replication and detect infected individuals (14,15,16,17,18,19,20,21). Studies evaluating the accuracy of these tests, the most studied analyzes (Abbott ARCHITECT HCV-Ag test and Ortho HCV-Ag ELISA) detected HCV viremia at approximately 93% and 99%, respectively (22). Chevaliez et al. (21) demonstrated in the SAPPHIRE I study that the level of HCV-Ag is a good option for detecting patients with viremia and evaluating their response to treatment. Similarly, in our study, it is seen that the HCV-Ag test can be used safely instead of HCV-RNA in the diagnosis and monitoring of treatment success of HCV-infected patients. Kesli et al. (23) reported a high correlation coefficient of 0.864 when comparing HCV-c-Ag levels with HCV-RNA levels. Also, Ergünay et al. (24) found a correlation coefficient of 0.937 between these parameters. Similarly, in this study the correlation coefficient of the two tests was found 0.419 ($p<0.001$) (Figure 1). For this reason, HCV-Ag can also be used as a new serological marker in diagnosis and follow-up. In the 2016 update of the EASL guideline, core antigen level measurement is now recommended as an alternative test in the diagnosis of acute and CHC (25). The results of our study may be useful feedback for the treatment and diagnosis guidelines.

Abbott ARCHITECT HCV-Ag detection is based on a two-stage microparticle-based chemoluminescent analysis. This test provides to determine the HCV-core antigen and anti-HCV in human serum and plasma in 60 minutes (26,27). The HCV-Ag is more durable because of its protein structure but nucleic acid amplification tests are sensitive to environmental contamination. Unlike NAT tests, which require qualified personnel, HCV-Ag measurement can be applied in most laboratories due to its simple methodology (28). Usually, when a patient is infected with HCV, first HCV-RNA is detected in the blood while the core antigen can be detected after 1-2 days. It may seem rational to use in screening of risk groups (intravenous drug addicts, hemodialysis patients, human immunodeficiency virus coinfected patients, and other immunosuppressive patients). Also, it is recommended to use for screening in the blood bank (29). As of the time of the study, in terms of cost, the HCV-Ag measurement per kit is $8, while the PCR method is $25. So HCV-Ag method especially can be used in lower-income countries. The lower detection limit is 3 fmol/L and it was able to detect patients with HCV-RNA levels between 500 IU

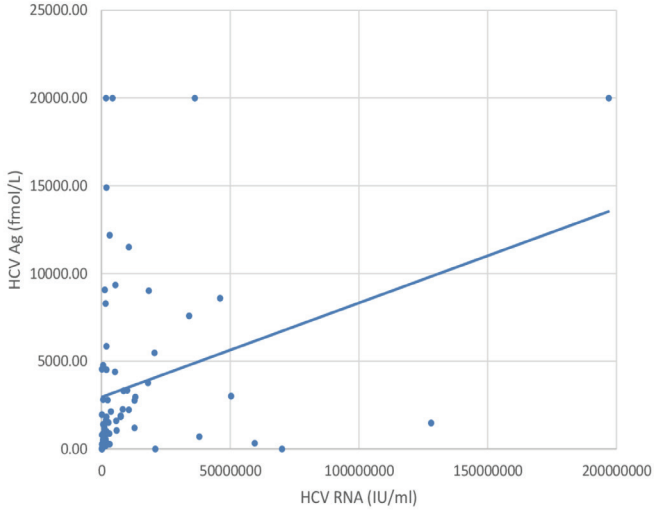

Figure 1. Spearman correlation dynamic between HCV-RNA and HCV-Ag parameters
HCV: Hepatitis C virus

and 3,000 IU/mL depending on HCV genotype (30,31). However, as in our study, most HCV patients have HCV-RNA levels well above these limits at the time of diagnosis. This may indicate that the probability of false-negative detection of HCV-Ag measurement is very low. Nevertheless, Freiman et al. (32) suggested HCV-RNA level detection to excluding false negativity since HCV-RNA low viremia may continue when HCV-Ag detection results in negativity.

In this study, the treatment of CHC with DAAs results in more than 90% SVR, regardless of genotype, cirrhosis, and previous treatment history. According to our findings, 96.1% SVR was observed and 3 patients who had relapsed after treatment were taking the TEL regimen. Şahin et al. (33) in a study in which retrospectively evaluated the results of 53 patients who received triple therapy based on TEL, the rate of SVR was found to be 58.5%. The application of these powerful therapies in recent years reduced the role of monitoring therapy with quantitative HCV-RNA tests (30). Also, to provide more patients access to new treatments, it will be useful to simplify the diagnosis of the disease and increase its screening. Anti-HCV is used for screening and in patients who are found positive, candidates for treatment are detected by PCR for HCV-RNA and HCV genotype. The HCV-Ag immunoassay is an adequate alternative to the two-stage diagnostic process (34). As in Table 3, HCV-Ag, which has a positive correlation with HCV-RNA, has 100% diagnostic power in our study. Of course, this may be due to the high viral load in all our patients at the time of diagnosis.

Table 1. Demographic characteristics of the study patients

Characteristics	Study group (n, %)
Patient	**76**
Gender	
Female	32 (42)
Male	44 (58)
Age	
≥65	52 (68)
<65	24 (32)
Treatment status	
Naive	28 (37)
Experienced	48 (63)
Cirrhosis	
Yes	21 (28)
No	55 (72)
HCV-RNA*, IU/mL	
≥1.0+E6	55 (72)
<1.0+E6	21 (28)
HCV genotype/subtype	
1a	13 (17)
1b	45 (59)
1 (untyped)	10 (13)
2	1 (1)
3	5 (7)
4	2 (3)
Comorbidity	
Chronic renal failure	11 (15)
Diabetes mellitus	8 (11)

*HCV-RNA load belonging to the before treatment status. HCV: Hepatitis C virus

All HCV genotypes are common in the world, genotypes 1, 2, and 3 were found to be 1b of the most dominant genotype according to studies performed in Turkey (68-94%) (35). Therefore, pan-genotypic SOF + LDV and TEL were used most frequently in our patients, followed by the PrOD regimen which was used in only genotype 1b. The influence of HCV genotype on cor antigen level and viral load is another point of interest. The majority of HCV genotypes in our study consisted of type 1 strains (types 1b and 1a, 76%). Therefore, the effect of HCV genotype variation can be considered as minimal in this study. When the parameters of the patients before and after the treatment were compared, ALT, AST, and AFP were significantly different. It is seen in the literature that the ALT level has improved significantly after treatment in most studies because the significant linear relationship has been between the degree of ALT elevation and the amount of liver injury based on the HAI score (36,37).

Considering that 3.8% of hemodialysis patients have anti-HCV positivity in our country, it may be rational to use the HCV-Ag test in hemodialysis patients for screening. Miedouge et al. (38) scanned 2,752 hemodialysis patients who were seronegative with HCV-RNA and HCV-Ag and found that these two tests were correlated and that the HCV-Ag test had a diagnostic power of 99.2%. In our study, 7 chronic kidney failure patients, 7 of whom were on hemodialysis, were included and HCV-Ag and HCV-RNA were correlated. Due to anti-HCV is generally negative in patients in this population, tests that directly measure the virus particles are preferred (39). Therefore HCV-core ag assay is a good, cost-effective option.

Study Limitations

There was no correlation study in the time series and the study was retrospective.

Conclusion

HCV-Ag measurement is a very successful and cost-effective test in detecting pre-treatment viremic patients and to follow-up treatment in patients using DAA. For these reasons, it was concluded that HCV-Ag measurement may be a good alternative laboratory test that can be used routinely.

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Ethics

Ethics Committee Approval: Ethical approval for the study was received from Kocaeli University Faculty of Medicine Ethics Committee (approval number: 2018/212, date: 11.7.2018).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Table 2. Treatment regiments applied to patients based on previous treatment and cirrhosis

Treatment regiment	Treatment status	Non-cirrhotic, (n)	Cirrhotic, (n)	Total, (n)
PRoD	Naive	9	2	11
	Experienced	3	ND	3
SOF + LDV	Naive	8	3	11
	Experienced	3	8	11
PRoD + RBV	Naive	7	ND	7
	Experienced	ND	1	1
SOF + LDV + RBV	Naive	1	ND	1
	Experienced	1	ND	1
SOF + RBV	Naive	3	ND	3
	Experienced	ND	ND	ND
Pro + RBV	Naive	1	ND	1
	Experienced	ND	ND	ND
TEL	Naive	1	ND	1
	Experienced	10	4	14
BOC	Naive	1	ND	1
	Experienced	8	2	10

ProD: Ritonavir boosted paritaprevir-ombitasvir and dasabuvir, SOF + LDV: Sofosbuvir/ledipasvir, RBV: Ribavirin, TEL: Telprevir, BOC: Boceprevir, ND: Not determined

Table 3. Laboratory parameters of the patients before and after the treatment

Laboratory parameters	Before treatment [mean ± SD, median (IQR)]	End of treatment [mean ± SD, median (IQR)]	Significancy, p-value
Anti-HCV	15±7.02 15 (12.9-15.6)	14±2.32 14 (13.3-14.78)	0.140
HCV-RNA	1.2+E7 1.8+E8	ND	**<0.0001**
HCV-Ag	3,648±5,092 1627 (493-4,468)	0.07±0.31 ND	**<0.0001**
ALT	40±27.09 35 (21.5-50)	19±13.09 16 (11.75-21)	**<0.0001**
AST	40±33.3 34 (23-46)	22±14.2 20 (14.2-24)	**<0.0001**
INR	1±0.11 1 (0.9-1.05)	1±0.17 1 (0.9-1.08)	0.156
AFP	7±12.7 4 (2.8-6.3)	3±2.4 3 (1.8-4.08)	<0.001

SD: Standard deviation, per: Percentil, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalized ratio, AFP: Alfa feto protein, ND: Not determined

Table 4. Comparison of patients' HCV-RNA, HCV-Ag and anti-HCV values before treatment

Parameter	HCV-RNA		HCV-Ag		anti-HCV	
	Correlation coenffient	p-value	Correlation coenffient	p-value	Correlation coenffient	p-value
HCV-RNA	-	-	0.419	<0.001	0.029	0.805
HCV-Ag	0.419	<0.001	-	-	0.122	0.302
anti-HCV	0.029	0.805	0.122	0.302	-	-

HCV: Hepatitis C virus

Authorship Contributions

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

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Research Article

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Comparison of Hepatitis B and Hepatitis C Seropositivity of the Syrian Immigrant and Turkish Local People

Suriyeli Göçmen ve Türk Yerel Halkın Hepatit B ve Hepatit C Seropozitifliğinin Karşılaştırılması

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ABSTRACT

Objectives: We compared the hepatitis B surface antigen (HBsAg), anti-HBs, anti-hepatitis C virus (anti-HCV) positivity of local Turkish and Syrian patients under temporary protection status according to age groups and gender and to evaluate the seroprevalence of hepatitis B virus (HBV) and HCV in our study.

Materials and Methods: HBsAg, anti-HBs and anti-HCV test results were compared of Syrian and Turkish patients who applied to University of Health Sciences Turkey, Bursa Yüksek Ihtisas Training and Research Hospital between January 2016 and December 2017 in our study.

Results: HBsAg positivity was higher in Turkish patients than Syrians in the 20-29 and 30-39 age groups. Anti-HBs positivity was higher in Turkish patients compared to Syrians in the 0-9 to 30-39 age groups. Anti-HCV positivity was higher in Syrian patients than Turks in 10-19 to 70-79 age groups. HBsAg, anti-HBs and anti-HCV positivity were higher in male patients than female patients in Syrian and Turkish patients.

Conclusion: It is necessary to develop national HBV vaccination policies, including young adults for Syrian immigrants, especially women in pregnancy age because they are risky for the transmission of hepatitis B infection and to conduct HBV and HCV infection screening and training for young adults who are risky in our country.

Keywords: Anti-HCV, anti-HBs, HBsAg, Syrian, Turkish

ÖZ

Amaç: Çalışmamızda, hastanemize başvuran yerel Türk hastaların ve geçici koruma statüsündeki Suriyeli hastaların hepatit B yüzey antijen (HBsAg), anti-HBs, anti-hepatit C virüs (anti-HCV) pozitifliklerini yaş grupları ve cinsiyete göre karşılaştırmayı ve hepatit B virüs (HBV) ve HCV seroprevalansını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışmamızda Ocak 2016-Aralık 2017 tarihleri arasında Sağlık Bilimleri Üniversitesi, Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi'ne başvuran Suriyeli ve Türk hastaların HBsAg, anti-HBs ve anti-HCV test sonuçları karşılaştırıldı.

Bulgular: HBsAg pozitifliği, 20-29 ve 30-39 yaş gruplarında Türk hastalarda, Suriyeli hastalardan anlamlı yüksek bulundu. Anti-HBs pozitifliği; 0-9, 10-19, 20-29, 30-39 yaş gruplarında Türk hastalarda Suriyeli hastalardan anlamlı yüksek belirlendi. Anti-HCV pozitifliği; 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 yaş gruplarında Suriyeli hastalarda, Türk hastalardan anlamlı yüksek saptandı. HBsAg, anti-HBs ve anti-HCV pozitifliği Suriyelilerde ve Türklerde erkeklerde kadınlardan istatistiksel olarak anlamlı yüksek bulundu.

Sonuç: Suriyeli göçmenlere yönelik genç erişkinleri özellikle hepatit B enfeksiyonunun bulaştırılması açısından riskli grup oldukları için gebelik çağındaki kadınları içeren ulusal HBV aşılama politikalarının geliştirilmesi gerekmektedir. Ülkemizde HBV ve HCV bulaşmasını önlemek için özellikle riskli gruplar olan genç erişkinlere enfeksiyon taraması ve eğitim verilmesi gerekliliktir.

Anahtar Kelimeler: Anti-HCV, anti-HBs, HBsAg, Suriyeli, Türk

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Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are viral pathogens that can cause chronic hepatitis, liver cirrhosis and hepatocellular cancer (1). HBV affects approximately two billion people worldwide. The World Health Organization (WHO) is located Turkey in moderate endemicity region of HBV with 2-8% incidance rate (2). It has been determined that approximately 170 million people are infected with HCV all over the world and HCV seropositivity is 1-2.4% in our country (3,4). HBV and HCV can be transmitted by parenteral contact with infected blood and body fluids, sexually and directly from infected mother to baby (5). With the immigration caused by the civil war that started in Syria in 2011, a total of 3,607,563 Syrians, 162,471 in Bursa as of 2018, are living in temporary refugee status in our country (6). Many studies have emphasized the increase in infectious disease rates in asylum seekers fleeing war due to difficult migration conditions and inadequate living conditions (7,8,9).

In our study, we aimed to compare the hepatitis B surface antigen (HBsAg), anti-HBs, anti-HCV positivity of local Turkish patients and Syrian patients living under temporary protection status in our region admitted to our hospital by age groups and gender and to evaluate the seroprevalence of hepatitis B and C.

Materials and Methods

In our study, the HBsAg, anti-HBs and anti-HCV test results of Syrian and Turkish patients admitted to University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital between January 2016 and December 2017 were compared. HBsAg test results of 124,203 patients (10,834 Syrians and 113,369 Turk); anti-HBs test results of 87,236 patients (7,457 Syrians and 79,779 Turk); anti-HCV test results of 116,777 patients (10,505 Syrians and 106,272 Turk) who applied to our hospital were evaluated. HBsAg, anti-HBs and anti-HCV positivity of the patients were determined according to sex and age groups (<9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, 80-89, 90-99). HBsAg, anti-HBs and anti-HCV positivity of the patients were also grouped into pediatric (<18) and adult (18) age groups. The presence of HBsAg, anti-HBs and anti-HCV antibodies was detected by Chemiluminescent Microparticle Immunoassay method in a fully automated COBAS 4000 device from serum samples obtained by separating 10 cc blood samples of the patients by centrifugation (Roche Diagnostics, Germany). With the manufacturer's recommendation, samples with HBsAg and anti-HCV values below 1 IU/mL were considered negative and samples with 1 IU/L values were considered positive, anti-HBs values below 10 IU/mL were negative, and ≥10 IU/mL positive.

Statistical Analysis

Statistical analyzes were performed using Pearson chi-square and Fisher's chi-square method in SPSS-20 program. P<0.01 and p<0.05 values were considered statistically significant. This study was approved by University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital Research Ethic Committee (approval number: 2011-KAEK-25 2020/10-5).

Results

In our study, HBsAg positivity of Syrian and Turkish patients were compared according to age groups (Table 1). HBsAg positivity was significantly higher in Turkish patients (2.4%, 4.2%) compared to Syrian patients (1.5%, 3.2%) in the 20-29 and 30-39 age groups (p<0.01, p<0.05) (Table 1). Additionally, HBsAg positivity was found to be significantly higher in Turkish patients (4.7%) than Syrian patients (2.5%) in the adult age group (p<0.01) (Table 1).

Anti-HBs positivity of Syrian and Turkish patients were compared according to age groups in our study (Table 2). Anti-HBs positivity (79.4%, 56.9%, 66.2%, 25.7%) was significantly higher in Turkish patients than Syrian patients (66.0%, 39.5%, 24.0%, 20.4%) in 0-9, 10-19, 20-29, 30-39 age groups (p<0.01, p<0.01, p<0.01, p<0.01) (Table 2). Anti-HBs positivity was significantly higher in Syrian patients (56.3%, 65.3%) than Turkish patients (41.3%, 45.2%) in the 60-69, 80-89 age groups (p<0.01, p<0.01) (Table 2). In addition, anti-HBs positivity was significantly higher in Turkish patients (68.3%, 42.4%) than Syrian patients (59.7%, 27.1%) in the pediatric and adult age groups (p<0.01, p<0.01) (Table 2).

Anti-HCV positivity of Syrian and Turkish patients were compared according to age groups in our study (Table 3). Anti-HCV positivity was significantly higher in Syrian patients than Turkish patients (0.0%, 0.1%, 0.2%, 0.3%, 0.5%, 0.8%, 0.9%) in the 10-19, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79 age groups (0.5%, 0.5%, 1.4%, 2.8%, 4.9%, 1.9%, 4.0%) (p<0.05, p<0.01, p<0.01, p<0.01, p<0.01, p<0.05, p<0.01). In addition, anti-HCV positivity was significantly higher in Syrian patients (0.9%, 1.2%) than Turkish patients (0.1%, 0.4%) in the pediatric and adult patient groups (p<0.01, p<0.01).

In our study, HBsAg, anti-HBs, anti-HCV antibody positivity of Syrian and Turkish patients were compared according to gender (Table 4). HBsAg positivity was statistically significantly higher in Syrian and Turk patients among males (5.9%, 6.7%) than females (1.7%, 3.5%) (p<0.01, p<0.01). Also, HBsAg positivity was significantly higher in Turkish female patients (3.5%) than Syrian female patients (1.7%) (p<0.01). There was no significant difference in HBsAg positivity between Syrian and Turkish men (Table 4).

Anti-HBS positivity was statistically significantly higher in Syrian and Turk patients among males (42.6%, 47.0%) than females (26.1%, 42.0%) (p<0.01, p<0.01). In addition, anti-HBs positivity was significantly higher in Turkish males (47.0%) than Syrian males (42.6%) and Turkish females (42.0%) than Syrian females (26.1%) (p<0.01, p<0.01) (Table 4).

Anti-HCV positivity was significantly higher in Syrian and Turk male patients (2.5%, 0.4%) than female patients (0.9%, 0.3%) (p<0.01, p<0.05). In addition, anti-HCV positivity was significantly higher in Syrian males (2.5%) than Turkish males (0.4%) and Syrian females (0.9%) than Turkish females (0.3%) (p<0.01, p<0.01) (Table 4).

Discussion

According to our study, HBsAg, anti-HBs and anti-HCV positivity rates of Syrian immigrants and Turks were found to be compatible with recent studies. In a study, HBsAg positivity

Table 1. Comparison of the HBsAg results of Syrian and Turkish patients by age groups

Age groups	Nationality	HBsAg		p
		Negative (n, %)	Positive (n, %)	
0-9	Syrian	323 (99.7%)	1 (0.3%)	0.714
	Turk	1997 (99.5%)	11 (0.5%)	
10-19	Syrian	748 (99.5%)	4 (0.5%)	0.127
	Turk	3943 (98.8%)	49 (1.2%)	
20-29	Syrian	5435 (98.5%)	80 (1.5%)	**0.001****
	Turk	26464 (97.6%)	641 (2.4%)	
30-39	Syrian	2512 (96.8%)	84 (3.2%)	**0.017***
	Turk	26482 (95.8%)	1164 (4.2%)	
40-49	Syrian	671 (94.2%)	41 (5.8%)	0.397
	Turk	15801 (93.4%)	1117 (6.6%)	
50-59	Syrian	350 (92.1%)	30 (7.9%)	0.468
	Turk	11397 (90.9%)	1142 (9.1%)	
60-69	Syrian	312 (95.7%)	14 (4.3%)	0.279
	Turk	10366 (94.2%)	634 (5.8%)	
70-79	Syrian	145 (97.3%)	4 (2.7%)	0.663
	Turk	7757 (96.4%)	290 (3.6%)	
Pediatric	Syrian	597 (99.7%)	2 (0.3%)	0.163
	Turk	4553 (99.0%)	44 (1.0%)	
Adult	Syrian	9979 (97.5%)	256 (2.5%)	**0.001****
	Turk	103651 (95.3%)	5121 (4.7%)	

HBsAg: Hepatitis B surface antigen, **p<0.01, *p<0.05

Table 2. Comparison of anti-HBs results of Syrian and Turkish patients by age groups

Age groups	Nationality	Anti-HBs		p
		Negative (n, %)	Positive (n, %)	
0-9	Syrian	99 (34.0%)	192 (66.0%)	**0.001****
	Turk	403 (20.6%)	1,558 (79.4%)	
10-19	Syrian	352 (60.5%)	230 (39.5%)	**0.001****
	Turk	1,735 (43.1%)	2,289 (56.9%)	
20-29	Syrian	2,747 (76.0%)	869 (24.0%)	**0.001****
	Turk	5,789 (33.8%)	11,351 (66.2%)	
30-39	Syrian	1,289 (79.6%)	331 (20.4%)	**0.001****
	Turk	12,108 (74.3%)	4,180 (25.7%)	
40-49	Syrian	377 (69.4%)	166 (30.6%)	0.125
	Turk	7,836 (66.2%)	4,008 (33.8%)	
50-59	Syrian	188 (59.7%)	127 (40.3%)	0.192
	Turk	6,055 (63.3%)	3,511 (36.7%)	
60-69	Syrian	124 (43.7%)	160 (56.3%)	**0.001****
	Turk	5,112 (58.7%)	3,601 (41.3%)	
70-79	Syrian	66 (48.5%)	70 (51.5%)	0.054
	Turk	3,775 (57.0%)	2,843 (43.0%)	
80-89	Syrian	17 (34.7%)	32 (65.3%)	**0.006****
	Turk	1,726 (54.8%)	1,422 (45.2%)	
90-99	Syrian	10 (58.8%)	7 (41.2%)	0.627
	Turk	237 (51.5%)	223 (48.5%)	
Pediatric	Syrian	205 (40.3%)	304 (59.7%)	**0.001****
	Turk	1,468 (31.7%)	3,169 (68.3%)	
Adult	Syrian	5,066 (72.9%)	1,882 (27.1%)	**0.001****
	Turk	43,318 (57.6%)	31,824 (42.4%)	

*P<0.05, **p<0.01, HBs: Hepatitis B surface

3.8%, 4.6%, 3.2%, 10%, anti-HBs positivity 41%, 10.7%, 12.9%, 40% and anti-HCV positivity were 1.2%, 1.5%, 6.4%, 2.8% found in Syrian immigrants aged 0-15, 16-40, 41-50 and > 50 (10). Yalçın Bahat et al. (11) established that HBsAg and anti-HCV seropositivity rates in Syrian pregnant women were found to be 1.1% and 0.1%, respectively. İnci et al. (12) determined that HBsAg positivity was found to be 1.8% in pregnant Syrian women and 1.1% in Turkish pregnant women. In a study, anti-HCV positivity was found 3-10% and HBsAg positivity 6% in Syrians (13). Bashour and Muhjazi (14) showed that HCV seroprevalence in Syrians was varied between 2-10% according to anti-HCV test values and hepatitis B seroprevalence was varied between 5-10% according to HBsAg test values. HBsAg positivity was found 1.01% to 4.6% and anti-HCV positivity was determined between 0.4% and 1.57% in studies from different regions in Turkey (15,16,17,18). Significantly higher HBsAg positivity among Turkish people than Syrians in young adult and adult age groups in our study was showed that Turkish people were infected with HBV more than Syrians in young adult and adult age groups (p<0.01, p<0.05). Also, determination of higher

Table 3. Comparison of anti-HCV results of Syrian and Turkish patients by age groups

Age groups	Nationality	Anti-HCV		p
		Negative (n, %)	Positive (n, %)	
0-9	Syrian	302 (99.3%)	2 (0.7%)	0.216
	Turk	1760 (99.8%)	4 (0.2%)	
10-19	Syrian	663 (99.5%)	3 (0.5%)	**0.021***
	Turk	3001 (100.0%)	1 (0.0%)	
20-29	Syrian	5348 (99.5%)	28 (0.5%)	**0.000****
	Turk	25316 (99.9%)	37 (0.1%)	
30-39	Syrian	2515 (98.6%)	36 (1.4%)	**0.000****
	Turk	25784 (99.8%)	47 (0.2%)	
40-49	Syrian	688 (97.2%)	20 (2.8%)	**0.000****
	Turk	15985 (99.7%)	41 (0.3%)	
50-59	Syrian	366 (95.1%)	19 (4.9%)	**0.000****
	Turk	11816 (99.5%)	62 (0.5%)	
60-69	Syrian	303 (98.1%)	6 (1.9%)	**0.035***
	Turk	10636 (99.2%)	81 (0.8%)	
70-79	Syrian	143 (96.0%)	6 (4.0%)	**0.003****
	Turk	7962 (99.1%)	75 (0.9%)	
80-89	Syrian	54 (94.7%)	3 (5.3%)	0.061
	Turk	3605 (98.5%)	56 (1.5%)	
Pediatric	Syrian	528 (99.1%)	5 (0.9%)	**0.003****
	Turk	3615 (99.9%)	4 (0.1%)	
Adult	Syrian	9854 (98.8%)	118 (1.2%)	**0.000****
	Turk	102253 (99.6%)	400 (0.4%)	

*P<0.05, **p<0.01. HCV: Hepatitis C virus

Table 4. Comparison of the HBsAg, anti-HBs, anti-HCV antibody results of Syrian and Turkish patients by gender

Test		Syrian		Turk		p
		Male (n, %)	Female (n, %)	Male (n, %)	Female (n, %)	
HBsAg	Negative	1620 (94.2%)	8956 (98.3%)	34697 (93.3%)	73507(96.5%)	**0.001**** **0.001****
	Positive	100 (5.8%)	158 (1.7%)	2507 (6.7%)	2658 (3.5%)	0.139 **0.001****
Anti-HBs	Negative	826 (57.4%)	4445 (73.9%)	15680 (53.0%)	29105(58.0%)	**0.001**** **0.001****
	Positive	613 (42.6%)	1573 (26.1%)	13902 (47.0%)	21091(42.0%)	**0.001**** **0.001****
Anti-HCV	Negative	1611 (97.5%)	8771 (99.1%)	34430 (99.6%)	71438(99.7%)	**0.001**** **0.017***
	Positive	42 (2.5%)	81 (0.9%)	154 (0.4%)	250 (0.3%)	**0.001**** **0.001****

*P<0.05, **p<0.01. HBsAg: Hepatitis B surface antigen, HCV: Hepatitis C virus

anti-HBs positivity in Turkish patients than Syrian patients in children, young adults and adult age groups in our study shows that hepatitis B immunity is significantly higher in children, young adults and adult age groups in Turks than Syrians ($p<0.01$, $p<0.01$). More common hepatitis B infection among Turks than Syrians in age groups with high contact risk shows that Syrians are more susceptible to hepatitis B infection and have a higher risk of contracting the hepatitis B infection.

Chronic HBV and HCV infection was determined after perinatal HBV and HCV transmission in 90% of newborns, in 20-50% of 1-5 age group, in 5-10% of >5 years (19,20). Chronic HBV and HCV infections can cause serious health problems such as liver cirrhosis and hepatocellular cancer (21). In our country, hepatitis B vaccine has been administered to babies in the routine vaccination program since 1998 as 3 doses at 0, 1 and 6 months. Although hepatitis B vaccine has been in the national vaccination program since 1993 in Syria, the necessary importance was not shown in the vaccination of children; it has been stated that safe and effective vaccination and education are required to prevent hepatitis B infection (22). In addition, studies have emphasized that the prevalence of HBV and HCV infection is high in Syria due to critical security, economic conditions, low infection control and deficiencies in hygienic practices (23,14). Our study shows that Syrians have lower HBV vaccination rates than Turks. Therefore, it is necessary to develop national HBV vaccination policies for Syrian immigrants, which include women of gestational age, as young adults are particularly at risk for the transmission of hepatitis B infection. Also, higher anti-HCV positivity in Syrian patients than Turkish patients in the pediatric and adult age groups shows that Turks are more susceptible to infection and more risky in terms of contracting HCV infection.

Study Limitations

The limitation of our study is that the HBV vaccination history of Syrian and Turkish patients, and the history of HBV and HCV infection were not examined.

Conclusion

According to our study, necessary precautions should be taken to prevent the increase of HBV and HCV infection in our country. For this purpose, it is necessary to provide infection screening and training to young adults, especially pregnant women, who are at risk groups in our country to prevent HBV and HCV transmission.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, Bursa Yüksek İhtisas Training and Research Hospital Research Ethic Committee (approval number: 2011-KAEK-25 2020/10-5).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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Case Report

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Efficacy of Entecavir Treatment in a 8-Year-Old Child with Chronic Hepatitis B

Kronik Hepatit B'li Sekiz Yaşında Çocuk Hastada Entekavir Tedavisinin Etkinliği

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ABSTRACT

Although the incidence of hepatitis B virus (HBV) infection has decreased significantly in Turkey since the introduction of universal immunization programs and blood donor screening, few children are still infected vertically with HBV. In Turkey, entecavir is approved for use for treating chronic hepatitis B (CHB) in children aged 16 years and older. The American Association for the Study of Liver Diseases 2018 Hepatitis B Guidance reported that entecavir can be used for treating CHB in a weight-based dosing in children aged 2 years and older. Eight-year-old children with CHB unresponsive to lamivudine (LAM) treated successfully with entecavir without significant adverse effect. In children younger than 16 years, use of entecavir may be considered for treating CHB if there is no adequate response to LAM.

Keywords: Chronic hepatitis B, hepatitis B virus, entecavir, child

ÖZ

Evrensel bağışıklama programları ve kan bağışçısı taramasının başlamasından bu yana Türkiye'de hepatit B virüsü (HBV) enfeksiyonu insidansı önemli ölçüde azalmasına rağmen, az sayıda çocuk hala vertikal olarak HBV ile enfekte olmaktadır. Türkiye'de entekavir, 16 yaş ve üzeri çocuklarda kronik hepatit B (KHB) tedavisinde kullanım için onaylıdır. Amerikan Karaciğer Hastalıkları Araştırmaları Derneği 2018 Hepatit B Rehberi, entekavirin 2 yaş ve üzeri çocuklarda vücut ağırlığına göre KHB tedavisinde kullanılabileceğini bildirmiştir. Lamivudine (LAM) yeterli yanıt alınamayan, sekiz yaşında KHB'li bir çocuk hastada entekavir ile tedavi başarılı sonuçlandı ve belirgin bir yan etki gözlenmedi. On altı yaşından küçük çocuklarda da, LAM yeterli yanıt yoksa, KHB tedavisinde entekavir kullanımı düşünülebilir.

Anahtar Kelimeler: Kronik hepatit B, hepatit B virüsü, entekavir, çocuk

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Introduction

It is known that more than 360 million people (6% of the world's population) are chronically infected with hepatitis B virus (HBV) worldwide. The incidence of HBV infection has decreased dramatically since the introduction of universal immunization programs and blood donor screening in various countries. However, a significant number of children are still infected with HBV each year, chronic HBV infection often develops and appropriate follow-up is required (1). Although chronic HBV infection mostly follows a benign course during childhood and adolescence, complications such as cirrhosis and hepatocellular carcinoma (HCC) can sometimes develop before adulthood. In the literature, the rates of development of cirrhosis and HCC before adulthood in children with chronic HBV infection have been reported as 3-5% and 0.01-0.03% (2,3).

There are five drugs approved by the US Food and Drug Administration for the treatment of children with chronic hepatitis B (CHB): Interferon-alfa, lamivudine (LAM), adefovir, entecavir (ETV), and tenofovir (4).

In this case report, we aimed to present a 8-year-old pediatric patient whose treatment was successful after starting ETV for his CHB treatment.

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Case Report

A 4.5-year-old boy was admitted to the pediatric gastroenterology outpatient clinic with hepatitis B surface antigen (HBsAg) positive (quantitative HBsAg 468.9 IU/mL), very high hepatitis B virus (HBV)-DNA level (>10^7 IU/mL), and persistently normal alanine aminotransferase (ALT) levels [upper limit of normal (ULN) approximately 40 IU/L]. According to the The European Association for the Study of the Liver 2017 guideline, the patient was diagnosed with hepatitis B e antigen (HBeAg)-positive chronic HBV infection (previously termed "immune tolerant" phase) (5). From his previous history, we learned that her mother had HBeAg positive chronic HBV infection and was given both the vaccine and hepatitis B immunoglobulin (HBIG) within 12-24 hours after birth.

At the age of 6.5-year-old, serum ALT levels began to exceed 2 times the ULN. All other possible causes of elevated serum ALT levels were investigated and excluded. We decided that he passed into HBeAg-positive CHB phase because of the presence of serum HBeAg positive, high HBV-DNA levels and high ALT. Since most patients may enter the HBeAg-negative infection phase by representing spontaneous HBeAg seroconversion and HBV-DNA suppression, we followed his for 6 months without liver biopsy, with monitoring serum HBeAg, ALT, and HBV-DNA levels for every months. However serum HBeAg positivity, high HBV-DNA levels and high ALT persisted for 6 months, then liver biopsy performed. In the histology activity index examination performed according to the Ishak grading and staging system, moderate liver necroinflammation (grade: 8) and fibrosis (stage: 2) were detected. When he was 8-year-old, LAM (3 mg/kg/day) was started for the treatment of CHB. Although serum ALT levels returned to normal limits (biochemical response), it was considered appropriate to switch to another oral antiviral agent from LAM, since the HBV-DNA level was measured as 154,000 IU/mL at the 24th week of antiviral treatment. Because of there was no other approved antiviral drug in this age group, switching to another drug was not considered at that time. At the 13th month of LAM treatment, serum HBV-DNA level was found to be 3120 IU/mL. However, at that time, the American Association for the study of liver diseases (AASLD) 2018 Hepatitis B Guidance was published. Since it was reported that ETV can be used in children aged 2 years and older in the AASLD 2018 Hepatitis B Guidance, it was planned to switch from LAM to ETV for the treatment of CHB. Written consent from his parent and approval from the Republic of Turkey Ministry of Health Turkish Medicines and Medical Devices Institution (REİYS-2019-02-171344) were obtained before ETV was started for the treatment of CHB. When he was 8-year-old, ETV was started at 0.5 mg/day on a weight basis as recommended in the AASLD 2018 Hepatitis B Guidance. The serum HBV-DNA level was still detectable despite a decrease of >1 $\log_{10}$ IU/mL 12 months after the start of ETV therapy (partial virological response). Approximately 2 years after initiation of ETV therapy, loss of HBeAg and anti-HBe seroconversion (serological response) occurred with undetectable serum HBV-DNA. No adverse reaction related to ETV was observed in our patient since the beginning of the treatment. If the patient's HBeAg seroconversion and serum undetectable HBV-DNA remain stable, we will plan to discontinue ETV therapy after at least 12 months of consolidation therapy is completed.

Discussion

When both vaccine and HBIG are administered to newborns of HBeAg positive mothers within 12-24 hours after birth, 90% protection can be achieved. In newborns of HBeAg negative mothers, the protection rate rises up to 98% (6,7,8). In her previous history, our patient's mother had HBeAg positive chronic HBV infection and there was transmission despite properly vaccination and HBIG administration.

In Turkey, treatment with 3 oral antiviral drugs has been approved when starting treatment for children aged 2-18 years with CHB: LAM, ETV and tenofovir. LAM is used from 2 years of age as recommended in the guideline published by the AASLD in 2018. Tenofovir can be used in children aged 12 years and older, as recommended in the 2013 guideline published by The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (4) and the AASLD 2018 Hepatitis B Guidance (9). ETV is used for the treatment of CHB in children aged 16 years and older, as recommended in the ESPGHAN guideline published in 2013 (4). According to the Turkish Health Practice Communiqué, if the HBV-DNA level is above 50 IU/mL at week 24, it is possible to switch to another oral antiviral agent. In the AASLD 2018 Hepatitis B Guidance, it was reported that ETV can be used from the age of 2 years (9). While our patient was at the 24th week of LAM treatment, his HBV-DNA level was found to be 154.000 IU/mL, therefore it was deemed appropriate to switch to ETV.

To the best of our knowledge, this is the first report in Turkey on the use of ETV in a 8-year-old child.

We think that ETV can be used as an alternative antiviral agent to LAM in children with CHB in Turkey, even if they are younger than 16 years of age.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.H.E., M.E., Design: H.H.E., M.E., Data Collection or Processing: H.H.E., M.E., Analysis or Interpretation: H.H.E., M.E., Literature Search: H.H.E., Writing: H.H.E.

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