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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.

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Scientific and Ethics Responsibility

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

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

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

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

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

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

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

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

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

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

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.

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

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

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

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

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

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

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

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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.

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

Review Articles

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

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

Letters to the Editor

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

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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.

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

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

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

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

Checklist for Submitted Articles:

Articles must be complete. They must include the following:

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• Title Page

• Article sections

• Turkish and English titles

• Abstract (250 words) (Turkish and English)

• Keywords (minimum 3; maximum 6)

• Article divided into appropriate sections

• Complete and accurate references and citations

• List of references styled according to "journal requirements"

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

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CONTENTS

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Viral Hepatitis Journal 2022;28(2):41-46

Acute Serious Hepatitis of Unknown Cause in Children

Çocuklarda Görülen Nedeni Bilinmeyen Akut Ciddi Hepatit

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ABSTRACT

On April 5, 2022, an increase in cases of acute hepatitis of unknown etiology was reported in previously healthy children under the age of 10 in the United Kingdom. Since there is no link between these patients, called acute non-HepA-E hepatitis, and viral hepatitis agents (hepatitis A, B, C, D, and E), the possible etiology, and pathogenesis of this emergency is being investigated. One of the alarming features of this epidemic is the high requirement for liver transplantation in a fraction of the cases. In cases other than hepatitis A, B, C, D, and E, a case definition is made by looking at a series of clinical pictures, including serum transaminase levels and age. As of August 26, 2022, 513 cases of acute hepatitis have been reported in Europe and 1,010 globally. Adenovirus was detected in 75% of cases tested in the UK, but data for other countries are still lacking. The role of other etiologic agents is still under investigation. The exact disease pathogenesis has not yet clear. Evidence of human-to-human transmission of the disease remains unclear. Epidemiological studies are critical in clarifying the uncertainties regarding the existence of links between the cases reported to date. Continuing the national and international surveillance activities of the countries in an organized manner is the most basic issue required for the elimination of the epidemic.

Keywords: Acute non-HepA-E hepatitis, children, unknown hepatitis, hepatitis epidemic

ÖZ

Birleşik Krallık tarafından 5 Nisan 2022'de önceden sağlıklı olan 10 yaşın altındaki çocuklarda etiyolojisi bilinmeyen akut hepatit olgularında artış bildirilmiştir. Akut HepA-E dışı hepatit olarak adlandırılan bu hastalık ile viral hepatit ajanları (hepatit A, B, C, D ve E) arasında bir bağlantı bulunmadığından, bu acil durumun olası etiyolojisi ve patogenezi araştırılmaktadır. Bu salgının endişe verici özelliklerinden biri, olguların bir kısmının karaciğer nakline ihtiyaç duymasıdır. Hepatit A, B, C, D ve E dışındaki olgularda serum transaminaz düzeyleri ve yaş gibi bir dizi klinik tabloya bakılarak olgu tanımı yapılmaktadır. Avrupa'da 513 ve dünya çapında 1.010 akut hepatit olgusu 26 Ağustos 2022 itibariyle rapor edilmiştir. Birleşik Krallık'ta test edilen olguların %75'inde adenovirüs tespit edilmiş olup, diğer ülkelere ilişkin veriler eksiktir. Diğer etiyolojik ajanların rolü halen araştırılmaktadır. Hastalık patogenezi henüz net değildir. Hastalığın insandan insana bulaştığına dair kanıtlar belirsizliğini korumaktadır. Epidemiyolojik çalışmalar, bugüne kadar bildirilen olgular arasındaki bağlantıların aydınlatılması açısından oldukça önemlidir. Ülkelerin ulusal ve uluslararası gözetim faaliyetlerinin organize bir şekilde devam ettirilmesi salgının ortadan kaldırılması için gerekli olan en temel hususdur.

Anahtar Kelimeler: Akut HepA-E dışı hepatit, çocuklar, bilinmeyen hepatit, hepatit salgını

Cite this article as: Kahraman Kılbaş EP, Altındiş M. Acute Serious Hepatitis of Unknown Cause in Children. Viral Hepatitis Journal 2022;28(2):41-46

Introduction

As of January 2022, more than normal cases of hepatitis in children have started to occur in the world (1,2). As of the end of April 2022, although the number of cases is higher in Europe, cases have also been reported in North America and Asia (3,4,5,6). On July 8, 2022, it was reported that the number of cases was over 1,010 in 35 countries (Austria, Belgium, Bulgaria, Cyprus, Denmark, France, Greece, Ireland, Israel, Italy, Latvia, Luxembourg, Republic of Moldova, Netherlands, Norway, Poland, Portugal, Serbia, Spain, Sweden, United Kingdom, Argentina, Brazil, Canada, Colombia, Costa Rica, Mexico, Panama, United States of America, Japan, Singapore, Indonesia, Maldives, occupied Palestinian territories and Qatar). These reports indicate that the disease affects children aged 16 years and younger and is more common in those aged

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1-5 years (4,5,6,7). The possible etiology and pathogenesis of this emergency is being investigated, since there is no link between these patients, called acute non-HepA-E hepatitis, and viral hepatitis viruses (hepatitis A, B, C, D, and E) (4,5,6,8).

One of the alarming features of this epidemic is the high requirement for liver transplantation in a proportion of cases (4,6). fifteen of the 270 confirmed cases in the UK through 19 July 2022 required liver transplantation (4).

Further surveillance studies are ongoing in countries where cases are identified, examining patients' clinical and exposure histories, and where environmental and food toxicology and virological testing is performed. The World Health Organization (WHO) and the European Center for Disease Prevention and Control (ECDC) are supporting the countries with the epidemic and collecting data with ongoing research. All available data is collected more quickly and effectively by countries through institutions such as the Hepatitis Networks and European Association for Liver Research, the European Society for Clinical Microbiology and Infectious Diseases, and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (9).

In this review, it is aimed to examine the present status of hepatitis cases of uncertain etiology in children.

Case Description

Case definitions are made by WHO, ECDC and the UK Health Security Agency. Case description; based on the clinical presentation including age, time of presentation, liver enzyme levels in the absence of acute viral hepatitis markers except acute hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis E virus (HEV) and hepatitis D virus (HDV) during chronic HBV disease (4,6,8).

Nowadays, WHO/ECDC/WHO has not been able to provide a description for approved cases of acute non-HepA-E hepatitis, owing to the lack of determination of the underlying etiology and the possibility of other microorganisms and agents other than infectious agents that may cause the disease (4,6). The ECDC and the UK Health Safety Agency have defined a approved case of acute non-HepA-E hepatitis by definition as a case of acute hepatitis with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels more than 500 (IU)/L in children under 11 years of age at any time from 1 January 2022. In addition, possible case definitions of the WHO are as follows:

Likely: Children aged 16 years and younger presenting with acute hepatitis (non-HepA-E) with serum transaminase >500 IU/L (AST or ALT) presenting after October 1, 2021.

Epi-linked: A person presenting with acute hepatitis (non-HepA-E*) of any age who is a close contact of a probable case occurring after 1 October 2021 (2).

Regional Distribution

As of 19 July 2022, the UK Health Safety Agency in the UK reported that it had detected a total of 270 children aged 9 and younger with acute hepatitis of unknown etiology. Fifteen of them are known to be liver transplant patients (4). On 26 August 2022, the European Union and the European Economic Area, 27 countries, except the United Kingdom, declared more than 513 cases of non-HepA-E acute hepatitis [18]. Additionally, the total number of cases declared globally is 1010 (10). As of 26 August 2022, ECDC reported that 513 cases of acute hepatitis of unknown etiology had been reported in children aged 16 years and younger in Europe. He stated that 513 of the cases were classified as probable by 21 countries and none of them could be found to be epidemiologically related. Notifying countries; Austria [6], Belgium [14], Bulgaria [1], Cyprus [2], Denmark [8], France [9], Greece [12], Ireland [26], Israel [5], Italy [36], Latvia [1], Luxembourg [1], Netherlands [15], Norway [6], Poland [18], Portugal [20], Republic of Moldova [1], Serbia [1], Spain [46], Sweden [12] and United Kingdom [273] (11) (Table 1).

Clinic and Prognosis

So far, it is known that most children affected by acute non-HepA-E hepatitis are 10 years old or younger. Unlike the mean, 12 out of 13 cases declared in Scotland were five years old or younger (5). Six of nine patients identified in Alabama were reported to be less than five years old (7).

The predominant symptoms seen in patients are abdominal pain, vomiting, and diarrhea reported prior to hospital admission (6). In addition, ALT and AST enzymes were found to be elevated with icterus (5,6). Elevated serum aminotransferase levels exceeding 500 IU/L were also detected in patients. Baker et al. (7) They reported that nine affected children in Alabama had ALT levels between 603 and 4696 IU/L and AST between 447 and 4000 IU/L.

WHO and ECDC reported that majority cases were free of fever (4,6). Cases in Scotland also reported no fever in the few weeks prior to hospitalization (5). However, fever was demonstrated in five (55.6%) of nine cases in Alabama (7).

In cases in Alabama, 1/3 of children have reported upper respiratory symptoms prior to hospitalization (7). Vomiting and diarrhea were reported in more than 2/3 of cases in Alabama and Scotland (5,7). Seven of the Alabama cases had hepatomegaly and one patient had encephalopathy at the time of acceptance to the hospital. While seven patients recovered without liver transplantation, the violence of acute non-A-E hepatitis emerges when compared to the two cases who recovered after transplantation (7).

Possible Etiologies and Hypotheses

ECDC works in close cooperation with relevant countries, WHO and other relevant institutions to investigate the etiology of acute hepatitis syndrome of unknown origin in children. The current hypothesis put forward in the ECDC Rapid Risk Assessment; a co-factor that normally affects young children with mild adenovirus infection triggers a more serious infection or immune-mediated liver injury. These co-factors are;

- Increased susceptibility due to decreased exposure to microorganisms in the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) pandemic,
- History of SARS-CoV-2 infection or other infection,
- Co-infection with SARS-CoV-2 and/or a different agent,
- Toxins are in the form of drugs or environmental exposure (12).

Adenovirus was detected in 75% of cases tested in the UK and data for other countries are still lacking. Most of the cases reported so far have been confirmed as adenovirus type 41 (in 35/27 cases). Adenovirus-associated virus-2 has also been detected in a small number of cases in the UK using meta-genomics in liver and blood samples. However, in most other cases, appropriate samples were not obtained, emphasizing the importance of drawing whole blood to accurately characterize the type of Adenovirus detected. In addition, adenovirus type 41 infection has not previously been associated with such a clinical presentation in healthy children (13).

The role of other etiologic agents is still under investigation. The exact disease pathogenesis is not yet clear. Evidence for human-to-human transmission of the disease remains unclear. Cases in the EU/EEA have been reported to be almost entirely sporadic (11).

Laboratory Research

Serological testing for HAV-HEV is recommended in suspected cases (4,8). Epstein-Barr virus (EBV) was identified by molecular methods in six of nine cases in Alabama. However, the absence of immunoglobulin M antibody suggested that these patients had EBV reactivation, not acute infection (7).

Although SARS-CoV-2 presence has been detected in a small number of cases, molecular tests are recommended among suspected cases of acute non-HepA-E hepatitis (14). In the exhaustive report of Baker et al. (7), it was reported that the cells were free of viral inclusions and no adenovirus was detected by electron microscopy and immunohistochemical staining. Further testing of liver biopsies from severe cases may provide more in-depth information on the role and immunopathology of Adenoviruses in this disease (9).

The laboratory tests that should be performed in cases with suspected acute non-HepA-E hepatitis in the current guidelines are as follows:

- Polymerase chain reaction (PCR) test on blood/serum samples for adenovirus, enterovirus, HAV, HCV, HEV, human herpesviruses types 1, 2, 3, 4, 5, 6 and 7,

- Serological tests for SARS-CoV-2, HAV, HBV, HCV, HEV, EBV and citomegalovirus,

- Blood culture if fever is present,

- Studying multiplex PCR respiratory viruses panel (adenovirus, enterovirus, influenza virus, human bocavirus and SARS-CoV-2) from nasopharyngeal swab as soon as possible,

- Study of multiplex PCR gastrointestinal system viruses panel (adenovirus, sapovirus, norovirus, enterovirus) in stool, and,

- *Salmonella* spp. etc. stool culture is required for bacterial enteric pathogens (4,14) (Figure 1).

Anti-streptolysin O serological tests, nasopharyngeal swab culture for group A β-hemolytic *Streptococci*, and serum/urine testing for leptospirosis should be considered if clinically indicated. Toxicological screening can also be done using blood and urine samples (14).

Detection of Adenovirus

It is recommended to collect the following samples for adenovirus testing.

- Whole blood or plasma taken into a purple capped EDTA tube,

- Nasopharyngeal swab, sputum or bronchioalveolar lavage [must be taken into Viral Transport Medium (VTM) or Universal Transport Medium (UTM)],

- Stool sample (or VTM/UTM rectal swab). A stool sample should be preferred over a rectal swab,

- If a liver biopsy has already been performed from a natural liver explant or autopsy as a clinical indication:

*Formalin-fixed, paraffin-embedded liver tissue,

*Fresh liver tissue should be frozen on dry ice or liquid nitrogen as soon as possible and stored at ≤-70 °C.

For all these samples, nucleic acid amplification test (PCR etc.) should be preferred. Testing whole blood by PCR is more sensitive than testing plasma by PCR and is recommended (15).

Discussion

Cases of severe acute hepatitis of unknown source in children have currently been declared in 19 countries worldwide. The rapid increase in the disease is a cause for concern and requires careful surveillance and coordinated studies to determine its possible etiology and transmission routes.

Detection of newly emerging cases is critical. In addition to surveillance, surveillance studies should be conducted by investigating epidemiological links. Marsh et al. (5) in a study conducted in Scotland, they showed that two children had close contact with two other cases in one setting, although no epidemiological link has been identified so far in the Alabama cases (7).

Another aspect of the involvement of microorganisms in the etiology of acute non-HepA-E hepatitis is the need to explore the hypothesis established for the potential role of immunopathological mechanisms. In the liver biopsies examined in Alabama cases, adenoviruses were not detected as a result of electron microscopy and immunohistochemical examination methods. For this reason, research to detect other microorganisms is important (7).

If adenoviruses are indeed associated with the etiology of acute non-HepA-E hepatitis, non-molecular testing for adenoviruses in blood and stool samples may preclude detection of cases. Therefore, it is crucial to provide up-to-date guidelines for adenovirus detection and to report cases and establish basic but reliable methods for adenovirus identification, including lateral flow testing (9). Moreover, considering the higher efficiency of whole blood for detection of adenovirus compared to plasma, it is reported that molecular tests for adenoviruses in cases of suspected acute non-HepA-E give more accurate results using whole blood instead of serum/plasma samples (4,7).

If adenoviruses were to have a definitive role in the current cases, various infection control precautions would be essential,

including appropriate hand cleaning and surface disinfection practices (due to its long-term stability and being a non-enveloped virus) (16,17).

Considering the higher-than-normal prevalence of adenoviruses among non-HepA-E acute hepatitis cases, the possibility of being an etiologic agent seems more robust, but other possible hypotheses mentioned earlier should not be ignored and should be carefully examined. Since microorganisms cannot be detected in the etiology of acute non-HepA-E hepatitis, continued investigation of toxicological and potential environmental factors should be a priority (9). In addition, given the limited surveillance capacity in most regions, the number of cases may be underestimated.

Common transmission measures for non-HepA-E acute hepatitis cases; regular hand washing and respiratory hygiene should be practiced. Based on the available information, WHO has not yet proposed any restrictions on travel and/or trade with the UK or other countries where cases have been detected.

WHO recommendations for the surveillance of the disease are as follows;

- Member states should be encouraged to identify, investigate and report potential cases that fit the case definition.

- Epidemiological data and risk factors should be made available by member states to WHO and partner organizations through agreed reporting tools.

- These data must be recorded as any epidemiological link between cases may provide clues to trace the origin of the disease.

- The time of occurrence of the cases and close contacts with the geographical regions where they occur should be reviewed in terms of possible risk factors (6).

Conclusion

Epidemiological studies are very important to clarify the uncertainties about the existence of links between the cases reported to date. The fact that there are no cases in our country yet may be due to patients that do not show symptoms and experience mild illness. Continuing the national and international surveillance works of the countries in an organized manner is the most basic issue required to eliminate the epidemic.

Ethics

Peer-review: Externally peer-reviewed.

Table 1. Summary of cases of severe acute hepatitis of unknown etiology published by ECDC on 26 August 2022 (18)

Country name	Number of cases	Hospitalised	Intensive care unit	Transplanted
Austria	6	3	0	0
Belgium	14	0	1	0
Bulgaria	1	1	0	0
Cyprus	2	2	0	0
Denmark	8	0	0	0
France	9	0	0	0
Greece	12	10	1	0
Ireland	26	25	5	2
Israel	5	2	0	0
Italy	36	31	0	1
Latvia	1	1	0	0
Luxembourg	1	1	0	0
Moldova	1	1	1	0
Netherlands	15	13	1	4
Norway	6	6	1	0
Poland	18	18	1	0
Portugal	20	17	0	0
Serbia	1	1	0	0
Spain	46	27	6	1
Sweden	12	8	3	1
United Kingdom	273	191	69	13
Total number of cases	513	358	89	22
Adenovirus positivity	218/404	-	-	-
SARS-CoV-2 positivity	96/445	-	-	-
HHV7 positivity	34/109	-	-	-

ECDC: European Center for Disease Prevention and Control, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, HHV: Human herpesvirus

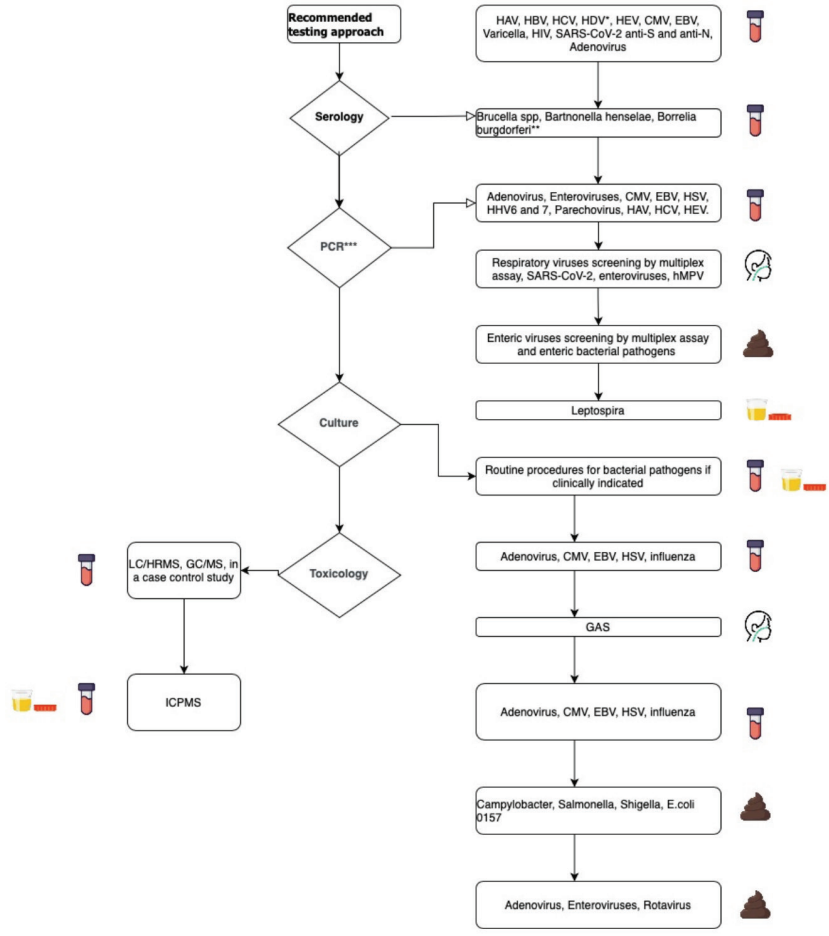

Figure 1. *Salmonella* spp. etc. stool culture is required for bacterial enteric pathogens (4,14)

HAV: Hepatitis A virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HDV: Hepatitis D virus, HEV: Hepatitis E virus, CMV: Citomegalovirus, EBV: Epstein-Barr virus, HIV: Human immunodeficiency virus, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, HSV: Herpesvirus, HHV: Human herpesvirus LC: Liquid chromatography, HRMS: High resolution mass spectrometry, GC: Gas chromatograph, MS: Mass spectrometry, GAS: Group A *Streptococcus*

Authorship Contributions

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

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Eliminating Viral Hepatitis in Turkey: Achievements and Challenges

Türkiye'de Viral Hepatitin Ortadan Kaldırılması: Başarılar ve Zorluklar

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ABSTRACT

After the declaration Global Health Sector Strategy on Viral Hepatitis by the World Health Organization in 2016, the Turkish Government defined a national strategy covering 2018-2023 to reach goals by 2030. Following a participatory decision process and a series of workshops, the strategy was built on eight separate subheadings. Apart from the official Prevention and Control Program, two separate road maps for hepatitis B and C were developed to obtain targets accessible with the cooperation of the Viral Hepatitis Society and the Turkish Association for the Study of the Liver in 2018 and 2020, respectively. Up to 2023, achievements and the current situation of the National Viral Hepatitis Prevention and Control Program and the hepatitis B virus and hepatitis C virus road maps were assessed in detail on June 28th, 2022, by the subject matter experts in Turkey. Besides the officially reported achievement rate (42%) of the Program in 2021, participants mentioned undesirable effects of the coronavirus disease-2019 pandemic, unregulated migration, low levels of professional and public awareness, and barriers to access to anti-viral treatment. Recommendations focused on increasing the efficiency of screening and surveillance by integrating the viral carrier identity of individuals into the national health information system, simplifying the drug supplement and treatment initiation process and insisting on education to raise awareness.

Keywords: COVID-19, HBV, HCV

ÖZ

2016 yılında Dünya Sağlık Örgütü tarafından Viral Hepatite İlişkin Küresel Sağlık Sektörü Stratejisi ilan edildikten sonra Türk Hükümeti, 2030 yılına kadar hedeflere ulaşmak için 2018-2023'ü kapsayan ulusal stratejiyi tanımladı. Katılımcı bir karar süreci ve bir dizi çalıştayın ardından strateji sekiz ayrı alt başlık üzerine inşa edildi. Resmi Önleme ve Kontrol Programı dışında, sırasıyla 2018 ve 2020 yıllarında Viral Hepatitle Savaşım Derneği ve Türk Karaciğer Araştırmaları Derneği iş birliği ile (sırasıyla; 2018 ve 2020) Türkiye'de de hedeflerin erişilebilir hale getirilmesi için hepatit B ve C'ye yönelik iki ayrı yol haritası geliştirilmiştir. Ulusal Viral Hepatit Önleme ve Kontrol Programı ile hepatit B virüs ve hepatit C virüs yol haritalarının 2023 yılına kadar elde edilen kazanımları ve mevcut durumu 28 Haziran 2022 tarihinde Türkiye'nin önde gelen kanaat önderleri tarafından detaylı olarak değerlendirilmiştir. Programın 2021'de resmi olarak bildirilen başarı oranının yanı sıra (%42), katılımcılar koronavirüs hastalığı-2019 pandemisinin istenmeyen etkilerine, düzensiz göçe, düşük düzeyde profesyonel ve kamu bilincine ve anti-viral tedaviye erişimin önündeki engellere dikkat çekti. Öneriler, bireylerin viral taşıyıcı kimliğinin ulusal sağlık bilgi sistemine entegre edilerek tarama ve sürveyansın etkinliğinin artırılmasına, ilaç takviyesi ve tedaviye başlama sürecinin basitleştirilmesine ve farkındalığın artırılmasına yönelik eğitimde ısrar edilmesine odaklandı.

Anahtar Kelimeler: COVID-19, HBV, HCV

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Introduction

Viral hepatitis continues to be a global health problem despite innovative health technologies and improving living conditions. It seems to have a priority for health policymakers in the next several years. In Turkey, the prevalence of hepatitis B and C were reported as 4.0% and 0.3-1.0% (1,2). The seropositivity rates also indicate that the total amount of hepatitis B virus (HBV) carriers might be more than 3.5 million actually. But only 12% of these HBV carriers are aware of their status (3) (Figure 1). Despite prevention policies, unregulated migration, changing demographic features, and persistent awareness challenged the achievement of predicted goals (4,5).

Global Health Sector Strategy on Viral Hepatitis (GHSS) was declared by the World Health Organization (WHO) in 2016 for the sake of moving toward a world where viral hepatitis transmission has stopped and barriers to access to safe and effective treatment have been removed. For this, it is aimed to prevent the transmission of hepatitis viruses, reduce complications and deaths related to viral hepatitis, improve patient care, and reduce the socio-economic negative effects of viral hepatitis in social areas. Also, WHO set targets to eliminate viral hepatitis as a public health risk by 2030. By this, 90% reduction in the risk of new infections, 80% of eligible people with chronic hepatitis B and C infections treated, and 65% reduction in hepatitis-related mortality were declared as goals to be achieved (6).

In Turkey, prevention efforts have been implemented since 2013 before the declaration of GHSS (Table 1). Epidemiologic data point out a demonstrable reduction in seropositivity in the last decades as an indicator of the success of existing national health care policy in the manner of prevention and treatment (7). In a study, where 26,001 adult patients were included, hepatitis B surface antigen (HBsAg) and anti-HBs were positive in 4.2% and 16.8% of patients, respectively. When the 20 years included in the study are divided into three periods namely 1995-2002, 2003-2009, and 2010-2015 and each period is analysed separately. It was reported that the rate of HBsAg positivity decreased from 5.3% to 4.8% and 3.1% (8).

Although there is a decrease in the prevalence of HBV in the country, people who migrate to Turkey are in a position to affect the prevalence of HBV in the country. A huge amount of immigrants from Syria (3.6 million) live in Turkey (4). In addition, Turkey also stands on the road of immigration from Afghanistan and other Central Asian countries as well as from East-European countries placed in the former Soviet Union. The aforementioned people are employed informally in household services and the care of children and disabled people. Moreover, the higher prevalence of viral hepatitis in these countries (9-12) (Table 2) and persistent low-level awareness remain a threat to the program's success (4). From this standpoint, it can be stated; that viral hepatitis continues to remain high in the long term (13).

Methods

1. Defining the Strategy

Turkish Health Authority has been handling the issue in a detailed and extended manner consistent with a global strategy soon after its declaration. For this issue, workshops were held in İstanbul and Ankara before the final workshop on April 3rd, 2018. The Turkish Viral Hepatitis Prevention and Control Program were announced by The Ministry of Health on September 12th, 2018. In this program, eight strategies were planned to be implemented in long term (Table 3).

Apart from the comprehensive "Turkish Viral Hepatitis Prevention and Control Program" managed by Ministry of Health, two road map projects were carried out to facilitate the national program and determine achievable, smart targets. The first of which was to target the elimination of hepatitis C virus (HCV) in June 2018 with the cooperation of Viral Hepatitis Society (VHSD) and Turkish Association for the Study of the Liver (TASL), "Hepatitis C Elimination Roadmap Recommendations and Workshop in Turkey" (14) was created. Then, in 2020, the "National Hepatitis B Elimination Roadmap" (15) was created in cooperation with VHSD and TASL.

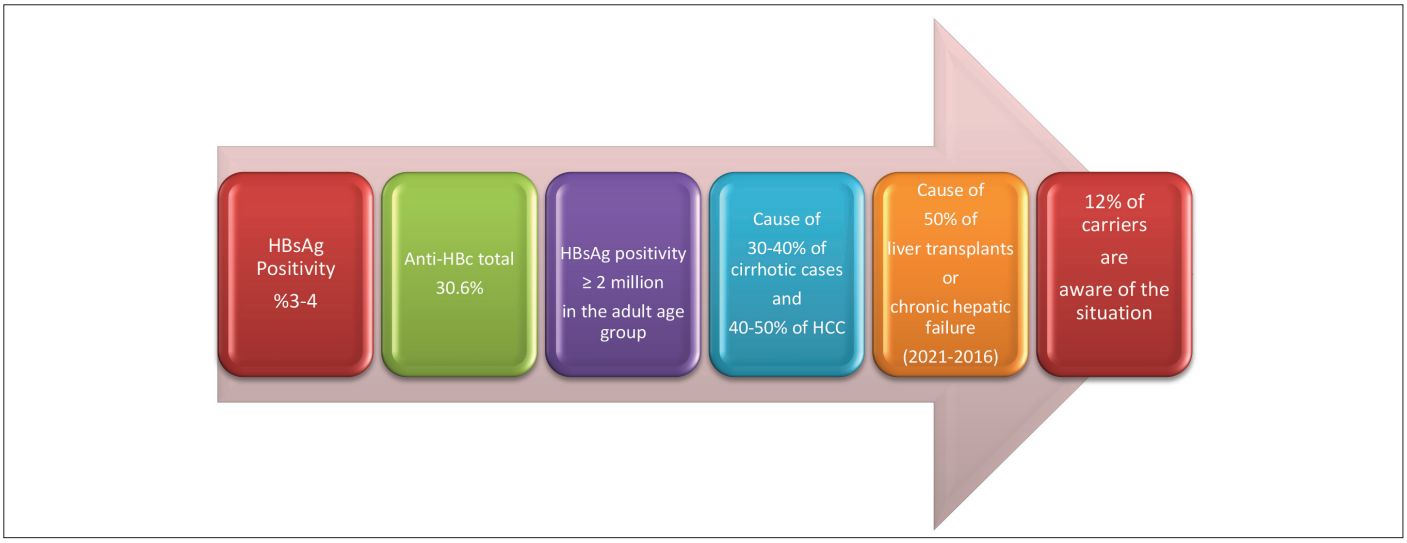

Figure 1. Epidemiologic features of hepatitis B virus infection in Turkey

Elimination of Hepatitis C Virus

At the workshops of "Hepatitis C Elimination in Turkey, Roadmap Recommendations and Workshop Reports" held in Ankara, İstanbul, and İzmir. The practical applications of the countries having a national elimination plan were reviewed. The content of the national hepatitis C elimination plan specific to Turkey was discussed and local recommendations were outlined. The resulting reports were prepared based on especially treating physicians' opinions about the current situation and recommendations for solutions under the title of a roadmap. Especially, Professor Jeffrey V. Lazarus explained how the idea of HCV elimination emerged in the world, the WHO's proposed targets for HCV elimination, the micro-elimination approach and its benefits, and the best practices to date in HCV elimination in other countries. Moreover, Professor Lazarus shared the results of the research conducted in 2017, which includes the current status of HCV in Turkey and solution suggestions on which topics it should be under if an elimination plan is to be carried out. The attending physicians shared their ideas about how these solution proposals can be transferred to Turkey. The status of HCV infection in Turkey and the recommended approach steps for HCV elimination are grouped under seven strategies as listed below (Figure 2).

1. Establishing a national HCV elimination plan

a. A specific, quickly applicable, traceable national HCV elimination plan should be implemented as soon as possible.

b. The targets of the program need to be adopted by The Ministry of Health and specialized associations operating in the field of HCV. Responsible units and teams should be determined and assigned.

Table 1. Achievements of national hepatitis program before the declaration of GHSS

Definition of achievements
1. Inclusion of hepatitis B vaccine in the childhood vaccination program in 1998
2. Development of the surveillance system and inclusion of acute hepatitis in the scope of compulsory notification
3. Inclusion of hepatitis A vaccine in the childhood vaccination program in 2012
4. Inclusion of nucleic acid test in the blood transfusion safety panel as well as serological tests.

GHSS: Global Health Sector Strategy on Viral Hepatitis

Table 2. Prevalence of hepatitis in some countries where immigrants originate

Geographic region	Hepatitis B	Hepatitis C	Reference
Syria, country estimated, (%)	5.6	2.8	Bashour and Muhjazi (9)
Aleppo, (%)	10.5	10.14	-
Hassakeh, (%)	10.6	-	-
European part of Russia, (%)	-	0.7-3.8	Lovo et al, (10)
North Caucasian of Russia, (%)	-	2.1	-
Far-East part of Russia, (%)	-	2.5	-
Mongolia, (%)	-	10.7	-
Middle East, (%)	2-7	-	MacLachlan and Cowie (11)
Eastern and Southern Euro, (%)	2-7	-	-
Central Asia, (%)	≥8	-	-
Kazakhstan, (%) (0.95 CI)	-	0.7 (0.7-0.8)	Botheju et al. (12)
Kyrgyzstan, (%) (0.95 CI)	-	2.0 (1.7-2.4)	-
Uzbekistan, (%) (0.95 CI)	-	9.6 (5.8-14.2)	-

CI: Confidence interval

Table 3. Eight Strategies announced by The Turkish Ministry of Health for implementing prevention and control program

Strategy	Targeted achievements
Strategy 1.	Raising awareness
Strategy 2.	Increasing immunization
Strategy 3.	Strengthening viral hepatitis surveillance
Strategy 4.	Reducing vertical transmission
Strategy 5.	Increasing access to treatment
Strategy 6.	Providing safe blood products
Strategy 7.	Prevention of viral hepatitis transmission in injecting drug users
Strategy 8.	Prevention of healthcare-associated transmission

c. Subpopulations available for immediate improvements should be allocated to micro-elimination projects.

2. Increasing awareness

a. Public announcements could be prepared for conceiving that HCV infection is an easily recognizable and easily treatable disease.

b. Develop training activities by Provincial Health Directorate to raise the contribution of family physicians or internal medicine specialists to the process of diagnosis, treatment, and follow-up of HCV infection.

3. Getting screening to be more effective and comprehensive

a. It could be developed software warning physicians before interventional/surgical procedures (surgical services, dental clinics, etc.) about positive patients and compelling them to consult with relevant departments/specialists.

b. Cases defined as anti-HCV positive in donor screening should be registered to the national health informatics system.

c. Anti-HCV positive cases could be periodically directed to the treatment and follow-up process.

d. Population-based screening programs could be conducted in regions with high HCV prevalence (eg. Hatay, Ordu, Nevşehir, Manisa, Kütahya).

e. Encouraging family physicians to evaluate for HCV. In this context, the cost of HCV assessment might be kept out of the physician's predefined budget.

f. Integration of the Ministry of Justice into the health information system could allow screening of prisoners to have priority.

g. Diagnosis, treatment, and follow-up procedures of HCV in outpatients and inpatients in people who inject drug (PWID) centers can be standardized.

h. Anti-HCV screening can be included in the routine pregnancy follow-up program.

i. Previous gastrointestinal cancer screening projects successfully implemented such as "faecal occult blood screening" can serve as a reference point.

j. Defining subpopulations with priority for assessment.

- Existing liver disease patients,
- Intravenous drugs users,
- Prisoners,
- Having a history of liver or renal transplantation,
- Haemodialysis patients,
- Infected with HIV.

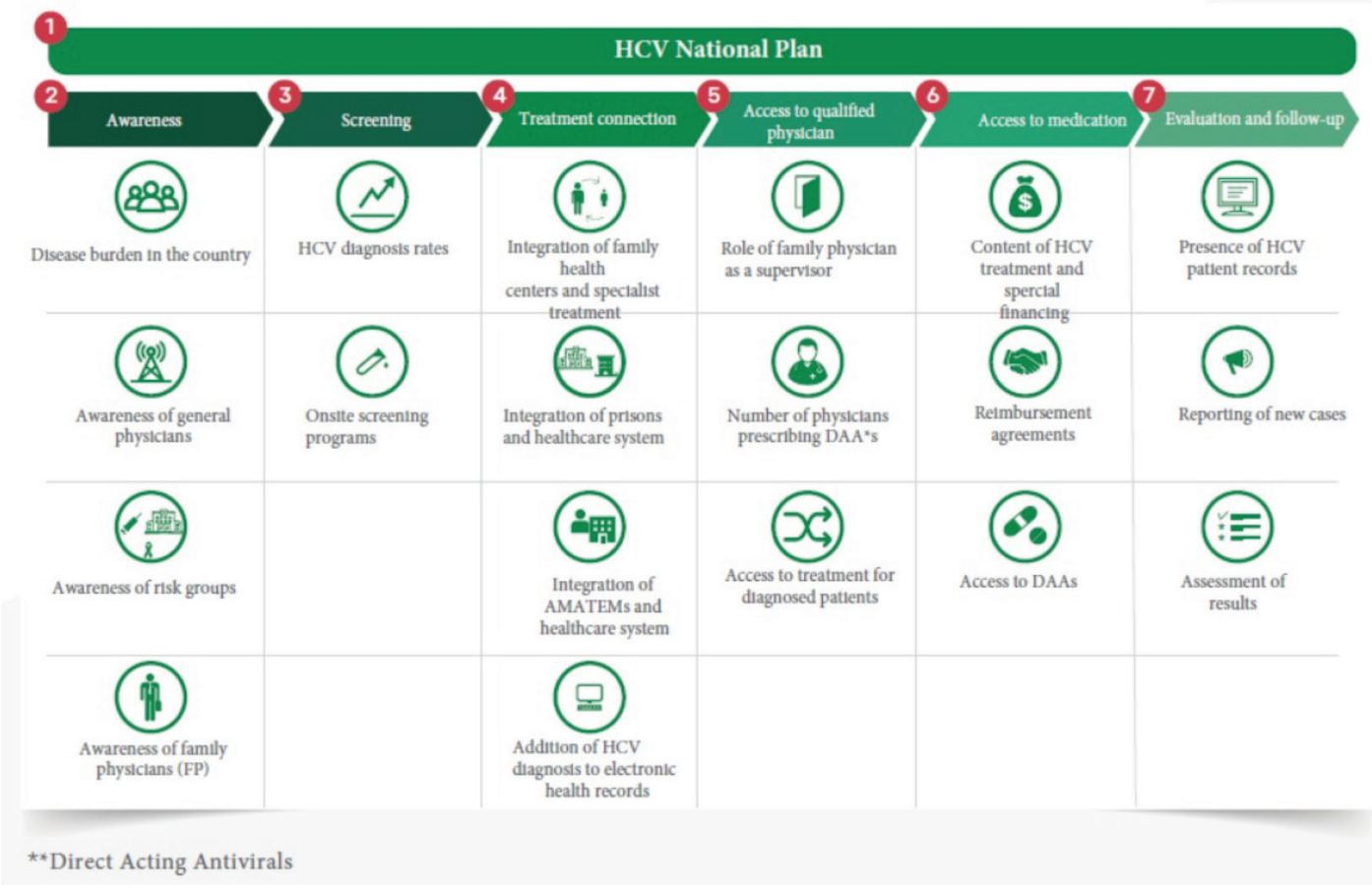

Figure 2. Roadmap for elimination of hepatits C virus infection
HCV: Hepatitis C virus

4. Improving treatment connection

a. Information systems can be developed to enable or facilitate the access of patients with anti-HCV positive (pre-operation evaluation, dental procedures, or blood bank) to infectious diseases or gastroenterology departments.

b. A direct referral chain can be established between PWID centers and infectious diseases or gastroenterology departments, or relevant specialist physicians can be assigned to PWID centers at certain times.

5. Facilitating accession to qualified physicians and medication

a. Family physicians or internists should have an active role in HCV diagnosis, treatment, and follow-up processes.

b. The follow-up of patients infected with HCV should be conducted in a centralized system.

6. Simplifying the accession to medication

a. Effective anti-viral regimens should be prescribed unrestrictedly by all infectious diseases or gastroenterology specialists in all hospitals in all provinces.

b. Biopsy and fibrosis stage assessment, which is essential for using direct-acting anti-viral therapy in patients who have not received treatment before, should be removed.

c. Patients in PWID centers should be treated by all physicians occupied in the centers regardless of specialty on-site or infectious disease and gastroenterology specialists may be assigned to these institutions on certain days.

d. Every patient, including immigrants, should have access to direct-acting anti-viral agents.

e. Patients should be able to receive all their treatments at the proper timing without delay.

f. Physicians should be able to make their selection of direct-acting anti-viral agents to give optimal treatment to their patients.

7. Optimizing evaluation and monitoring

A. A centralized system designed to monitor HCV-infected patients should be implemented.

B. Models that predict the benefits and treatment costs of HCV treatment and elimination should be developed.

Micro-elimination programs in some patient populations, achieving rapid success, and sharing it in appropriate environments will lay the groundwork for raising awareness about the issue. Subpopulations having priority for micro-elimination are listed below.

1. Patients are currently followed in the health system under the following categories

a. Advanced liver disease,

b. Advanced chronic kidney disease,

c. Haematological diseases (haemophilia, thalassemia, etc.) that require blood product usage,

d. History of transplantation and those receiving immunosuppressive treatment,

e. Patients who have already been found to be anti-HCV positive.

2. Demographic or individual characteristics accompanied by high risk

a. Born before 1970,

b. Living/living in areas known to have a high prevalence of HCV,

c. Using intravenous drugs,

d. Prison inmates.

Elimination of Hepatitis B Virus

A participatory project was carried out with opinion leaders and relevant stakeholders to develop and facilitate the implementation of the Hepatitis B Elimination Roadmap in the direction defined by the Ministry of Health "Turkish Viral Hepatitis Prevention and Control Program". The main purpose of the study was to stop the transmission of hepatitis B in Turkey in the short term, prevent the progression of the disease, improve the quality of life, and ensure its elimination in the long term. After evaluation of the current status in 2020, the "National Hepatitis B Elimination Roadmap" (15) was created in cooperation with VHSD and TASL.

The project process consisted of five stages:

1. Review of current hepatitis B strategies and plans,

2. Conducting preliminary interviews,

3. Conducting workshops,

4. Preparation of the Hepatitis B Elimination Roadmap within the scope of the National Hepatitis Elimination Program,

5. Evaluation of National Hepatitis B Elimination Roadmap projects.

2. Current Situation in 2022

Turkish Viral Hepatitis Prevention and Control Program was implemented by the Turkish Ministry of Health, General Directorate of Public Health, Department of Infectious Diseases, and Early Warning covering the years 2018-2023.

In the evaluation of the Viral Hepatitis Prevention and Control Program of Turkey conducted by the Ministry of Health in 2021. The reported achievement rate was reported as 42%. Also, officially declared, a great part of activities (44%) were ongoing and the remaining 14% were waiting for started (Figure 3). The 14% parts, which have not yet started, mostly

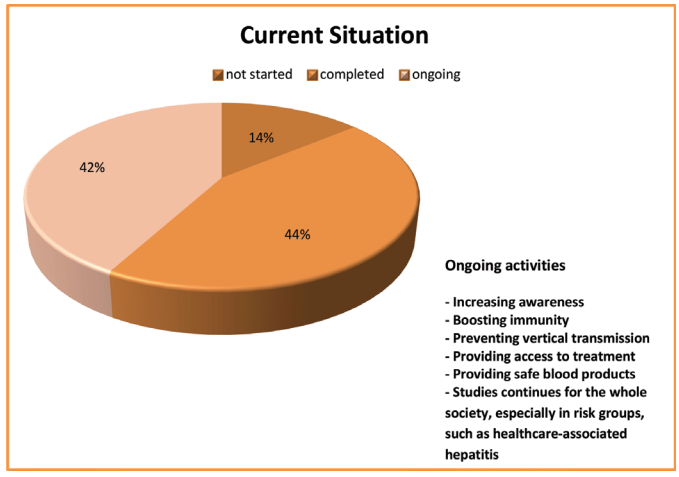

Figure 3. Turkish Viral Hepatitis Prevention and Control Program (2019-2023), evaluation in 2021

require the contribution of other ministries, this was the reason for the delay.

Training and raising awareness seemed to have priority in the implementation process. In this context, completed activities were reported as listed below

- The Viral Hepatitis Educator Guide and educational slide sets were prepared and shared by the Ministry of Health in 2019.

- Before the pandemic, 104 family physicians were trained in Konya and Niğde. Also, the training of the family physician was carried out in Çorum, in the late phase of the pandemic.

- In the southeast region of Turkey, training sessions were completed online.

- Meetings were organized in various provinces to raise public awareness of hepatitis among the public, and posters were posted on billboards.

Additionally, The National Haemovigilance Guide for safe blood transfusion was updated in 2020.

The Viral Hepatitis Prevention and Control Program by Ministry of Health was re-evaluated in the scope of Hepatitis C Elimination Roadmap Recommendations and Hepatitis B Elimination Roadmap Recommendations one year later, on June 28th, 2022. Being aware of the fact that six months are left until 2023, completed and ongoing activities were revised under the guidance of the government's improvements and gained experience. The recommendations were summarized as listed below.

1. Generally, the program should be implemented in the field prevention should be prioritized, and the progress of the program should be shared with reports at regular intervals. Stakeholders must motivate each other for the success of the program.

2. Viral hepatitis awareness and screening should first be started by healthcare associate professionals working with doctors and nurses. Screening and training of personnel working in hospitals should be obligated.

3. From June 2022, it is planned to organize face-to-face training in big cities until the end of 2022. For instance, İstanbul Provincial Health Directorate Public Health Department will organize a training program dedicated to physicians having the intention to collaborate in İstanbul in cooperation. A series of face-to-face training sessions will be organized with the participation of 50-100 family physicians. Increasing HBV and HCV awareness and screening rate of risky groups will be put as goals of these sessions. The family medicine or family medicine specialty associations should be identified as stakeholders and their support and participation should be requested at the organization stage.

4. Alternative methods for adult education such as Flipped Classroom could be put into practice with the collaboration of educational sciences.

5. Evaluation of training sessions performed in the province of Niğde revealed that learning efficiency was about 70% considering pre-test and post-test scores. The reflection of knowledge in practice should be the most important parameter to be monitored at certain periods.

6. The pre-test-post-test success performance can be considered a reference to gain the right to free of charge participation in the training meetings organized by the relevant associations operating in the field of hepatitis.

7. There are a significant number of individuals who have been exposed to hepatitis viruses in Turkey. Positive individuals should be obligated to take a place in a periodic in follow-up process beyond verbally informed. This task can be handled by disease card or special information integrated in national health information system.

8. According to the Centers for Disease Control, absolute screening of adults is recommended in regions with a prevalence of more than 0.1%. The frequency of HCV in Turkey is 0.3-1.0% (1,2). For this reason, anti-HCV and HBsAg should be checked and documented in everyone over the age of 18 and younger ones in risk categories. The avoidance of repeated tests would create a resource for precise diagnosis (HCV-RNA polymerase chain reaction confirmation) and effective treatment.

9. Accurate and reliable surveillance data should be collected and handled by the Ministry of Health and used in national health policymaking.

10. Intuitional-based hepatitis B and C screening data collecting activities should be centralized and confirmed carrier status could be transmitted to relevant professionals and institutions. Electronic prevention practices developed during the coronavirus disease-2019 (COVID-19) pandemic would be a model for a hepatitis-specific e-disease management system.

11. An electronic identity card specific to the prevention of communicable disease could be designed in close collaboration between the General Directorate of Health Information Systems of the Ministry of Health and the Turkish Ministry of Health General Directorate of Public Health, Communicable Diseases and Early Warning Department. The proposed digital could be tested in pilot projects before it is rolled out across the country.

Hepatitis C Virus Specific Recommendations

1. Prisons and PWID centers should be prioritized in HCV screening.

2. In actual state, HCV treatment can be given in 60 hospital pharmacies at 44 provinces/in Turkey. An arrangement is required to get available HCV treatment in every province.

3. Micro-elimination projects can be launched in the provinces of Konya and Niğde where family physicians' training is completed.

4. Rapid testing, shifting away from centralized management and focusing on local practices, and simplified treatment regimens are needed to increase access to treatment for people at risk.

Hepatitis B Virus Specific Recommendations

1. The HBV vaccination rate is an actual performance measure for family physicians in HBV vaccination is outstanding. The actual rate of three doses of HBV vaccination in infants is 98%. The infrastructure of this success should also be applied to the screening of HBV. It is necessary to create a performance measurement policy with a central approach. Encouraging family

reduction in regional the prevalence of hepatitis in their region can be rewarded by encouraging family physicians.

2. Keeping in the mind an annual pregnancy rate of one million, HBsAg screening during pregnancy is the most accessible target in this scope.

3. The widely shared misunderstanding of "noting is needed for a carrier" among many community members and health professionals should be changed. The concept of "being a carrier of HBV does not mean that you do not have the disease" would be getting a community education subject focused especially on hepatitis B carriers. Awareness among society and family physicians about surrogacy should be increased. The perception of "if the patient is a carrier, nothing is needed" should be changed by regular training.

4. Improving access to treatment: In HBV-infected patients with certain charecteristics, treatment should be started without liver biopsy.

Discussion

Viral hepatitis seems to continue to be a major public health problem in the coming decades. Despite global health insurance coverage and successful infant vaccination programs, reaching WHO's goals for the elimination of viral hepatitis in 2030 is challenged by several factors.

Concerning the existing policy changes aligned with the GHSS, unpredictable geopolitical states, and uncertain economic conditions weighed especially COVID-19 hinder the purpose of improvement in the process.

Besides the changing demography due to unregulated migration, widely existing awarelessness might be overcome by digitalization transformation. Gained experience in controlling infectious diseases during pandemics might be an advantage for defining and raising the efficiency of anti-viral treatment. Integrating the viral status of individuals in their electronic health identity would decline the transmission rate and raise the rates of early access to treatment.

Decentralizing the drug supplying system, reorganizing of patient referral system for providing accession to qualified specialists, and integrating family physicians into the disease management process would increase treatment attendance and resulting treatment success rates.

The treatment protocols and relevant reimbursement rules should be modified in favor of early treatment taking into account non-invasive novel diagnostic technologies (16). In this respect, it should be encouraged to develop new economic assessment models considering cost-effectiveness and economic burden in the long term.

Conclusion

Turkey is one of the candidates having a possibility of reaching goals defined by WHO. In addition to the existing healthcare workforce and infrastructure, considering great achievements in health information systems, it can be hoped major drawbacks could be overcome. But this seems to be possible by defining problems and rational solutions with close collaboration among different stakeholders.

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Research Article

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What is the Current Situation of HBV, HCV and HIV Seroprevalence Among Syrian Refugees? Patients Evaluated Preoperatively Over Ten Years

Suriyeli Mültecilerde HBV, HCV ve HIV Seroprevalansında Mevcut Durum Nedir? On Yıllık Bir Süre Boyunca Preoperative Olarak Değerlendirilen Hastalar

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ABSTRACT

Objectives: Migration can change the demographic dynamics of host populations in terms of communicable diseases in destination countries. This is a potential public health challenge for the health authorities. Hepatitis B virüs (HBV) and hepatitis C virüs (HCV) infections can lead to the development of chronic liver diseases, cirrhosis and hepatocellular carcinoma, whereas human immunodeficiency virus (HIV) infection can lead to the development of serious opportunistic diseases. The aim of this study was to evaluate the seroprevalence of HBV, HCV and HIV in Syrian refugees and Turkish patients who were evaluated preoperatively in our hospital.

Materials and Methods: Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody, anti-HCV and anti-HIV results of Syrian refugee and Turkish patients who applied to surgical clinics approximately 2011-2021 were retrospectively reviewed.

Results: The study comprised 54,446 patients: Turkish patient group (n=20569) and Syrian refugee patient group (n=33877). The Syrian refugee patients had a significantly higher HBsAg seropositivity rate and a significantly lower anti-HBs seropositivity rate than the Turkish patients (p=0.002 and p<0.001, respectively). The anti-HCV and anti-HIV seropositivity rates were similar. The annual preoperative prevalence of HBsAg seropositivity in the Syrian refugee patients tended to significantly decrease gradually from 2011 to 2021 (p<0.001 for ≤30 and p=0.001 for >30 years old).

ÖZ

Amaç: Göç, hedef ülkelerdeki bulaşıcı hastalıklar açısından ev sahibi popülasyonun demografik dinamiklerini değiştirebilir. Bu, sağlık otoriteleri için potansiyel bir halk sağlığı sorunudur. Hepatit B virüs (HBV) ve hepatit C virüs (HCV) enfeksiyonları kronik karaciğer hastalıkları, siroz ve hepatosellüler karsinom gelişimine neden olurken, insan immün yetmezliği virüsü (HIV) enfeksiyonu ciddi fırsatçı hastalıkların gelişmesine neden olabilir. Bu çalışmanın amacı, hastanemizde preoperatif olarak değerlendirilen Suriyeli mülteciler ve Türk hastalarda HBV, HCV ve HIV seroprevalansını değerlendirmektir.

Gereç ve Yöntemler: 2011-2021 yılları arasında cerrahi kliniklere başvuran Suriyeli mülteci ve Türk hastaların hepatit B yüzey antijeni (HBsAg), hepatit B yüzey antikoru (anti-HBs), hepatit B çekirdek antikoru, anti-HCV ve anti-HIV sonuçları retrospektif olarak incelendi.

Bulgular: Çalışma 54,446 hastadan oluşuyordu: Türk hasta grubu (n=20569) ve Suriyeli mülteci hasta grubu (n=33877). Suriyeli mülteci hastalarda Türk hastalara göre anlamlı düzeyde daha yüksek HBsAg seropozitiflik oranı ve önemli ölçüde daha düşük bir anti-HBs seropozitiflik oranı vardı (sırasıyla; p=0,002 ve p<0,001). Anti-HCV ve anti-HIV seropozitiflik oranları benzerdi. Suriyeli mülteci hastalarda HBsAg seropozitifliğinin yıllık preoperatif prevalansı 2011 yılından 2021 yılına kadar kademeli olarak önemli ölçüde azalma eğilimindeydi (<30 yaş için; p<0,001 ve >30 yaş için; p=0,001).

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Conclusion: Although HBV seroprevalence gradually decreases and HCV and HIV seroprevalence is low; screening, information and treatment programs should be given due importance because of the serious disease potential and preventable conditions with precautions. Additionally, preoperative screening of refugee patients coming for major surgery may be important for the safety of healthcare professionals.
Keywords: Anti-HIV, hepatitis B, hepatitis C, prevalence, Syrian refugees, Turkey

Sonuç: HBV seroprevalansı giderek azalmasına ve HCV ve HIV seroprevalansının düşük olmasına rağmen; ciddi hastalık potansiyeli ve tedbirlerle önlenebilir durumlar nedeniyle tarama, bilgilendirme ve tedavi programlarına gereken önem verilmelidir. Ek olarak, majör cerrahi için gelen mülteci hastaların cerrahi öncesi taranması sağlık çalışanlarının güvenliği için önemli olabilir.
Anahtar Kelimeler: Anti-HIV, hepatit B, hepatit C, prevalans, Suriyeli mülteciler, Türkiye

Introduction

Migration is recognized as an independent social determinant of health. Large-scale migration can contribute to a change in the demographic dynamics of host populations in terms of communicable diseases in destination countries. Current mass movement from high or medium prevalence regions is a potential public health challenge for health authorities in countries with low prevalence of infectious diseases (1).

The Syrian civil war, which has been ongoing since 2011, led to the biggest refugee crisis since World War II. 3.658 million refugees were reported in Turkey in September 2019 (2,3). Refugees bring many infectious diseases that endanger the health of both themselves and the host population (4). Infections caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) lead to the development of chronic liver diseases, cirrhosis and hepatocellular carcinoma, while human immunodeficiency virus (HIV) infection can lead to the development of serious opportunistic infections. According to the World Health Organization (WHO), an estimated number of 500 million people live with chronic viral hepatitis, making HBV and HCV one of the most virulent infectious diseases worldwide (5,6). At least 1.3 million deaths per year can be attributed to chronic liver disease caused by HBV and HCV (6,7). Also, viral hepatitis is largely responsible for the global increase in liver cancer.

More than 90% of the Syrian refugee population live in the community and mostly in big provinces such as İstanbul, Gaziantep, Hatay and Şanlıurfa. Hatay province hosts 435,953 Syrian refugees (8). Our city, which is close to the war zone, is at a higher risk of infectious diseases compared to other regions, as there are many applications for emergency and elective operations to our institution, which is a third level training and research hospital. In order to minimize the risk of occupational contamination, every patient may be potentially infected and there is a need to take protective measures accordingly. In addition, it is important to know the current prevalence of these diseases in establishing appropriate health policies for refugees. The aim of this study is to compare the seroprevalence of HBV, HCV and HIV between Syrian refugees and Turkishs patients who were evaluated preoperatively in our hospital.

Materials and Methods

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Hatay Mustafa Kemal University (approval number: 22/04/2021-05). Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody immunoglobulin G (anti-HBc IgG), hepatitis C virus antibody (anti-HCV) and human immunodeficiency virus antibody (anti-HIV) results of Syrian refugees and Turkish patients of all age groups who applied to Hatay Mustafa Kemal University Health Practice and Research Hospital between 2011-2021 to be operated in surgical clinics were retrospectively screened and a comparison was made between the two groups. Serum samples were tested for HBsAg, anti-HCV, anti-HIV, anti-HBc IgG, and anti-HBs using commercial immunoenzymatic assays (Abbott Architect i2000SR, Illinois, USA). Anti-HIV reactivity was always confirmed by a western blot assay, which identifies both HIV-1 and HIV-2 strains. The demographic data of the patients were analyzed retrospectively from the hospital electronic information system and patient files. Duplicate records were removed.

Patient characteristics were determined as age, gender, race and year of admission to the hospital. Patients with positive HBsAg but with normal alanine aminotransferase and aspartate transaminases levels and negative HBV-DNA were accepted as HBV carriers. Patients with HBsAg and anti-HBc IgG negative but positive for anti-HBs were considered vaccinated. Detection of anti-HBc IgG positivity alone was accepted as isolated anti-HBc IgG positivity. Patients who were found to be negative for all three parameters (HBsAg, anti-HBs and anti-HBc) were considered to have never encountered hepatitis B.

Statistical Analysis

All analyses were carried out using SPSS, version 23 software (SPSS Inc, Chicago IL, USA). The Shapiro-Wilk normality test was used to examine normality of distribution. Categorical variables were presented as frequencies (percentages) and compared with chi-square test. Non-normally distributed continuous variables were presented as median with interquartile range (25^{th} and 75^{th} percentiles) and compared with the Mann-Whitney U test between the groups.

Results

The study is comprised of 54,446 patients, divided into two groups: Turkish patient group (n=20569) and Syrian refugee patient group (n=33877). The median age of the patients was 41 (28-59) years and 44.8% (n=24396) were male. The epidemiological characteristics and preoperative seroprevalance of HBV, HCV, HIV serological markers in the Syrian refugee and Turkish patients are shown in Table 1.

Although the Syrian refugee patients were significantly younger than the Turkish patients, Syrian refugee patients had a significantly higher HBsAg seropositivity rate and a significantly lower anti-HBs seropositivity rate than the Turkish patients (p<0.001, p=0.002 and p<0.001, respectively). The anti-HBc, anti-HCV and anti-HIV seropositivity rates were similar between the two groups (p=0.258, p=0.457 and p=1.000, respectively) (Table 1).

The comparisons of seropositivity of HBV markers between two groups according to age are shown in Table 2. Syrian refugee patients 15-year-old or younger and in the 16-30 age group had a significantly higher rate of HBsAg seropositivity than the Turkish patients in the same age groups (p=0.007 and p=0.002, respectively). However, the rates of HBsAg seropositivity between two groups were similar in other age groups (Table 2).

The annual preoperative prevalance of HBsAg seropositivity in the Syrian patients (both in 30-year-old or younger and in over 30-year-old patients) tended to significantly decrease gradually from year 2011 to year 2021 (p<0.001 and p=0.001, respectively). However, no significant changes were seen in the prevalance of HBsAg seropositivity in the Turkish patients in the same age groups (p=0.910 and p=0.483, respectively) (Figure 1). Although anti-HCV seropositivity was similar between Syrian refugee and Turkish patients in <15, 16-30, 46-60 and >60 age groups, it was significantly higher in Syrian refugee patients in the 31-45 age group (p=0.037) (Table 3).

Discussion

Millions of people around the world emigrate from their homeland due to economic, political and war reasons. Hatay, a border city that has received heavy immigration due to the Syrian civil war that started in 2011, and many people who were injured in the war applied to our hospital due to the need for urgent surgical operations. It is important to determine the infectious disease prevalence of our city due to migration and patient transfers. To the best our knowledge, this is the first preoperative hepatitis serology study conducted in Syrian refugee patients from Hatay.

The Center for Disease Control and Prevention recommends screening for HBV infection in people from countries with an HBsAg prevalence greater than 2%. Turkey is a moderately endemic country for HBV with a prevalence of 4% (2-8%) (9). Vaccination against HBV in Turkey started in 1998 and vaccination rates reached 98% in 2016 (10). Vaccination against HBV in Syria started in 1991 and the pre-war vaccination rate reached 83% in 2008 (11,12). Also, Syria is one of the moderately endemic countries for HBV (13).

It is well known that the HBsAg seropositivity increases with age. In the current study, although the Syrian refugee patients were significantly younger than the Turkish patients, Syrian refugee patients had a significantly higher HBsAg seropositivity rate (2.3% versus 1.9%). This finding is consistent with results from earlier studies conducted in in the general patient population of

Table 1. Comparison of epidemiological characteristics and preoperative seroprevalance of HBV, HCV, HIV serological markers in the Turkish and Syrian patients (n=54446)

	Turkish patients (n=20569)	Syrian patients (n=33877)	p-value
Age, years	42 (28-59)	41 (28-58)	**<0.001**
Gender, male	9268 (45.1)	15128 (44.7)	0.360
HBsAg, positive	397 (1.9)	789 (2.3)	**0.002**
Anti-HBc, positive	216 (36.6)	323 (33.8)	0.258
Anti-HBs, positive*	7512 (42.5)	12231 (40.8)	**<0.001**
Anti-HCV, positive	223 (1.1)	390 (1.2)	0.472
Anti-HIV, positive	1 (0)	1 (0)	1.000

Continuous data are expressed as median and interquartile range (IQR)=25th-75th percentile. Categoric data are expressed as number (n) and percentages (%). Statistically significant values are shown in bold. *: ≥10 mIU/mL. HBsAg: Hepatitis B surface antigen, anti-HBc: Anti-hepatitis B core antigen, anti-HBs: Anti-hepatitis B surface antigen, HCV: Hepatitis C, HIV: Human immunodeficiency virus, HBV: Hepatitis B virus

Table 2. Comparison of preoperative seroprevalance of HBV serological markers in the Turkish and Syrian patients by age

Age group, years	Positive HBV serological markers								
	HBsAg			Anti-HBc			Anti-HBs*		
	Turkish patients (n=20569)	Syrian patients (n=33877)	p-value	Turkish patients (n=20569)	Syrian patients (n=33877)	p-value	Turkish patients (n=20569)	Syrian patients (n=33877)	p-value
15	2 (0.1)	21 (0.7)	**0.007**	3 (15.0)	3 (6.3)	0.349	1086 (70.0)	2027 (70.7)	0.613
16-30	32 (0.7)	100 (1.4)	**0.002**	28 (26.7)	23 (13.9)	**0.009**	2505 (66.0)	3939 (59.8)	**<0.001**
31-45	95 (1.8)	184 (2.0)	0.283	39 (36.1)	55 (31.3)	0.398	994 (22.9)	1607 (20.9)	**0.013**
46-60	134 (3.0)	240 (3.5)	0.215	50 (37.0)	81 (37.3)	0.956	1131 (30.0)	1753 (29.0)	0.313
60 +	134 (2.8)	244 (3.2)	0.181	96 (43.2)	161 (46.0)	0.518	1796 (42.7)	2905 (42.6)	0.853

Continuous data are expressed as median and interquartile range (IQR)=25th-75th percentile). Categoric data are expressed as number (n) and percentages (%). Statistically significant values are shown in bold. *: ≥10 mIU/mL. HBsAg: Hepatitis B surface antigen, anti-HBc: Hepatitis B core antigen, anti-HBs: Anti hepatitis B surface antigen

Syrian refugees, have reported rates ranging from 2.3% to 5.7% (14,15,16). When evaluated according to age groups, HBsAg seropositivity was significantly higher in Syrian refugee patients under the age of 15 and in the 15-30 age group. There was no difference in other age groups. This may be due to the fact that refugee children who came to Turkey missed a large number of vaccination periods due to the collapse of the vaccination system in their country of origin (17,18).

In the present study, the annual preoperative prevalence of HBsAg seropositivity in Syrian refugee patients (both ≤30 and >30 years old) tended to gradually decline significantly from 2011 to 2021. However, there was no significant change in the prevalence of HBsAg seropositivity in Turkish patients in the same age group during the same period. This may be due to the collapse of the vaccination system in the country of origin during the first period of war and migration and more crowded living environments such as camps. In the later period, it can be attributed to the inclusion of all Syrian refugee children in the national vaccination program and the improvement of socioeconomic conditions (such as free access to health and treatment, children's education, work permits and free access to vocational training) (17,19,20).

Anti-HBs seropositivity was significantly lower in Syrian refugee patients compared to Turkish patients (40.8% and 42.5%, respectively). However, no difference was found between Syrian refugee and Turkish patients in terms of anti-HBs seropositivity under the age of 15. This may be due to the fact that all Syrian refugee children who arrived in Turkey are included in the national vaccination program (19). According to the data of the Turkish Ministry of Health, the number of Syrian refugee children vaccinated was reported as 59,743 in 2014, 100,244 in 2015, 148,172 in 2016 and 269,085 in 2017 (19). Anti-HBs seropositivity was lower in Syrian refugee patients compared to Turkish patients in the 16-30 age (p<0.01) and 31-45 age (p=0.013) groups. This was attributed to the poor socioeconomic conditions in the war zone and the absence of vaccination tracking (17,18). No significant difference was found between Syrian refugee and Turkish patients over the age of 46. In accordance with this study, Özkaya et al. (15)

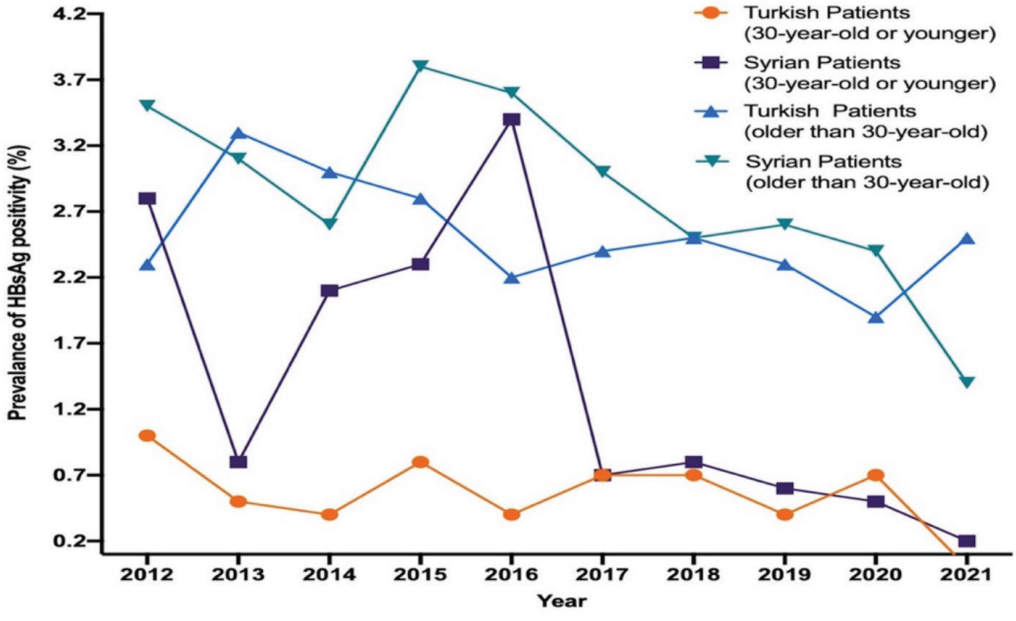

Figure 1. Annual trends of preoperative prevalance of HBsAg seropositivity
HBsAg: Hepatitis B surface antigen. Figure was plotted with Prism 8.0 (GraphPad Software, La Jolla, CA, USA)

Table 3. Comparison of seropositivity of HCV serological marker in the Turkish and Syrian patients by ages

Age group, years	Positive HCV serological marker		
	Anti HCV		
	Turkish patients (n=20569)	Syrian patients (n=33877)	p-value
<15	2 (0.1)	2 (0.1)	1.000
16-30	18 (0.4)	37 (0.5)	0.493
31-45	17 (0.3)	51 (0.6)	**0.037**
46-60	44 (1.0)	59 (0.9)	0.411
60 +	142 (3.0)	239 (3.2)	0.545

Continuous data are expressed as median and interquartile range (IQR)=25th-75th percentile. Categoric data are expressed as number (n) and percentages (%). Statistically significant values are shown in bold. HCV: Hepatitis C virus

found a significant difference in anti-HBs seropositivity between Syrian refugees (34.9%) and Turkish patients (43.4%).

According to WHO data, Syria is among endemic areas with a low anti-HCV seropositivity rate (21). Consistent with this, anti HCV seropositivity was 1.2% in Syrian refugee patients and 1.1% in Turkish patients in this study. There was no significant difference between Syrian refugee and Turkish patients in terms of anti-HCV seropositivity. Anti-HCV seropositivity was significantly higher in Syrian refugee patients aged 31-45 (p=0.037). However, it was similar to Turkish patients in other age groups. Consistent with this study, Özkaya et al. (15) reported 1.8% anti-HCV seropositivity. In another study, Aşgın and Satılmış (14) reported it as 1%. Tümtürk and Yeşil (16) found 2.46% in a study they conducted on a small population (244 Syrian refugees). In a meta-analysis, Chemaitelly et al. (22) reported the anti-HCV seropositivity rate as 48.8-75% in hemodialysis patients, 21% in drug users and 20.5% in hemophilia patients in the Syrian population. These high rates may be due to the presence of serious risk factors in patients.

Syria has very low HIV prevalence (23). In this study, 1 HIV (+) patient was identified in 33,877 Syrian refugee patients and only 1 in 20,569 Turkish patients. Inci et al. (24) did not find any anti HIV (+) patients among 300 Syrian refugees in their study. In another study conducted by Tümtürk and Yeşil (16), they did not find any anti HIV (+) patients among 244 Syrian refugees.

Study Limitations

We have some limitations in this study. This study was conducted on Syrian refugee patients, who had a high population, but had preoperative anesthetic evaluation in a single center. Therefore, multi-center studies are needed as our results may not reflect the serological data of all Syrian refugees. Since this study was retrospective, the medical history and risk factors of the patients could not be obtained.

In this study, information on HBV, HCV and HIV seroprevalence of high population of Syrian refugees who came for emergency and elective surgical operations from the ongoing Syrian civil war since 2011 was presented. In the Syrian refugee population, HBsAg seroprevalence was high and anti HBsAg seroprevalence was low. However, due to the vaccination studies conducted in Turkey, especially in the pediatric age group in Syrian refugees, HBsAg seroprevalence has gradually decreased and anti-HBs seroprevalence has increased gradually in the 10-year period. HCV and HIV rates are very low in both Turkish and Syrian populations.

Conclusion

As a result, although HBV seroprevalence decreases gradually and HCV and HIV seroprevalence is low, due attention should be paid to screening, information and treatment programs due to the serious disease potential and preventable conditions. In addition, healthcare professionals' strict adherence to standard protection measures, training, vaccination against HBV and preoperative screening of refugee patients coming for major surgery may be important for the safety of healthcare professionals.

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Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of Hatay Mustafa Kemal University (approval number: 22/04/2021-05).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: M.S.Ç., T.B., M.Ç., Concept: M.S.Ç., T.B., M.Ç., Design: M.S.Ç., T.B., M.Ç., Data Collection or Processing: M.S.Ç., T.B., M.Ç., Analysis or Interpretation: M.S.Ç., T.B., M.Ç., Literature Search: M.S.Ç., T.B., M.Ç., Writing: M.S.Ç., T.B., M.Ç.

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Research Article

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The Direct Medical Cost of Regular Monitoring of Patients with HBeAg-Negative Chronic Hepatitis B Virus Infection

HBeAg Negatif Kronik Hepatit B Virüs Enfeksiyonu Olan Hastaların Direkt Maliyet Analizi

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ABSTRACT

Objectives: Patients with hepatitis B e antigen-negative chronic infection (inactive carriers) account for most of the people living with hepatitis B virus (HBV). This study investigated the direct medical cost of monitoring patients within this group.

Materials and Methods: A total of 293 outpatients receiving regular monitoring in a large university hospital were included in the study. Direct medical costs included laboratory tests, imaging, liver biopsies and co-payments. Linear mixed effect models were applied to investigate the effect of follow-up time on the annual cost of monitoring. We made quarterly, semi-annual and annual monitoring cost trajectories in accordance with international guideline recommendations.

Results: The average annual direct medical cost per patient was 160 USD and the average laboratory visit cost per patient was 68.5 USD. HBV DNA testing contributed to a majority percentage of the total cost (59.6%). As follow-up time increased, the total annual cost (β=-2.07) and annual cost for DNA testing (β=-1.03) decreased. The cost trajectory of the first two years of monitoring remained above the semi-annual follow-up strategy. After three years, the cost trajectory of monitoring, while reducing slightly, remained between the semi-annual and annual follow-up strategy trend lines.

Conclusion: Due to high-patient numbers, the total cost of monitoring presents a large economic burden. Taking into consideration the generally benign nature of the disease; the length of intervals between outpatient hospital visits could be reviewed and alternative strategies implemented with the aim of reducing expenditure.

Keywords: Hepatitis B virus, chronic hepatitis B, hospital costs, health costs, direct service costs

ÖZ

Amaç: Hepatit B e anti-jen negatif kronik enfeksiyon olan hastalar (inaktif taşıyıcılar), hepatit B virüsü (HBV) ile enfekte bireylerin büyük çoğunluğunu oluşturmaktadır. Bu çalışmada, bu gruptaki hastaları izlemenin doğrudan tıbbi maliyetinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Büyük bir üçüncü basamak üniversite hastanesinde düzenli olarak poliklinik takibi yapılan 293 hasta çalışmaya dahil edilmiştir. Laboratuvar testleri, görüntüleme tetkikleri ve muayene katılım payı ücretleri direkt maliyetin hesaplanmasında kullanılmıştır. Toplam yıllık izlem maliyetinin zaman ile nasıl değiştiğini araştırmak için doğrusal karma modeller oluşturulmuştur. Uluslararası rehberlerin takip önerilerine göre üç ayda bir, altı ayda bir ve yılda bir takip yapıldığında oluşabilecek maliyetler hesaplanmış ve bu maliyetlerin seyirleri merkezimizin izlem stratejisi ile karşılaştırılmıştır.

Bulgular: Hasta başına düşen ortalama yıllık maliyet 160 dolar, hasta başına düşen ortalama poliklinik viziti maliyeti ise 68,5 dolar olarak hesaplandı. Toplam maliyetin büyük çoğunluğunu HBV DNA testi oluşturdu (%59,6). Takip süresi arttıkça yıllık izlemin toplam maliyeti (β=-2,07) ve HBV-DNA testinin yıllık toplam maliyeti (β=-1,03) azalıyordu. Hastaların ilk iki yıllık takibi içinde yapılan toplam harcamanın seyri, altı ayda bir takip stratejisine göre daha fazlaydı. Üç yıl ve sonrasında ise maliyetin seyrinde azalma gözlemlenmekte birlikte bu seyir altı ayda bir takip ile yılda bir takip maliyeti arasındaydı.

Sonuç: Hasta sayısının fazla olması sebebiyle izlem maliyeti ekonomik yük oluşturmaktadır. Bu gruptaki hastaların benign seyri göz önüne alındığında, poliklinik takipleri arasındaki zamana yönelik maliyet etkin stratejiler planlanmalıdır.

Anahtar Kelimeler: Hepatit B virüs, kronik hepatit B, hastane maliyetleri, sağlık harcamaları, direkt hizmet giderleri

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Introduction

Hepatitis B virus (HBV) infection is a global health issue. According to the World Health Organization, an estimated 3.8% of the world's population is living with HBV infection. In 2019 alone, a total of 820,000 (450,000-950,000) people died from HBV infection-related causes (1). Turkey is an intermediate-endemic country with a prevalence of hepatitis B surface antigen (HBsAg) positivity considered to be 4%-4.6% (2,3). Based on a systematic review in the year 2011, it was estimated that the total number of chronic hepatitis B (CHB) cases in Turkey was around 3.3 million (3).

HBV infection can cause acute hepatitis or go on over years to develop chronic infection leading to cirrhosis and hepatocellular cancer (HCC). No virological cure exists for HBV infection and current antiviral drugs only rely on the control of HBV replication. Due to the years of continued follow-up, including implementation of oral antiviral agents when indicated; as well as other associated complications; HBV infection continues to present a heavy economic burden. In a study from China, the direct annual medical cost per CHB patient was 1380 US dollar (USD), with a 4.4 fold increase of direct expenditures when HCC developed (4). In the Republic of Korea, the total socio-economic cost of patients with hepatitis B increased from 127.1 million USD in 2002 to 459.1 million in 2015, mainly due to an increase in medication costs (5). Similarly, previous studies conducted in Turkey revealed the cost of antiviral drugs accounted for most of the expenditure in the CHB patients (6,7).

Patients with hepatitis B e antigen-negative chronic infection (previously termed: inactive carriers) account for the majority of people living with HBV infection. This phase of the disease is characterised by <2000 IU/mL HBV-DNA levels and the presence of anti-HBe (hepatitis B e antibody) (8). Some individuals may have HBV-DNA levels between 2000 and 20000 IU/mL with persistently normal alanine aminotransferase (ALT) levels and minimal necroinflammatory activity. This state, in which the use of antiviral drugs is not required, does offer a very good prognosis. However, lifelong monitoring is still required to detect reactivation of active hepatitis, cirrhosis and hepatocellular carcinoma. European Association for the Study of the Liver and Asian Pacific Association for the Study of the Liver recommends that patients with HBeAg-negative chronic infection should be followed up every 6-12 months with serum ALT and HBV-DNA (8,9). Turkey Viral Hepatitis Diagnosis and Treatment Guide 2017 recommends that patients should be followed every 6-12 months with ALT, HBV-DNA, alpha-fetoprotein (AFP) and liver ultrasound (US) (10). Due to the sheer size of the patient group with this disease, the frequency of follow-up and laboratory tests used in monitoring has a heavy impact on health expenditure.

The objective of this study was to investigate the direct medical cost of monitoring patients with HBeAg-negative chronic infection and identify trends regarding laboratory testing and imaging costs.

Materials and Methods

Study Design and Patient Selection

This retrospective study was conducted based on the electronic records of patients with HBeAg-negative chronic infection followed by İstanbul Medeniyet University, Department of Infectious Disease and Clinical Microbiology. To qualify for inclusion, patients aged ≥18 years and referred to the infectious diseases clinic between June 1st 2016 and June 1st 2017 were reviewed using the International Classification of Diseases-10 (ICD-10) codes. ICD-10 codes used for identification of patients from the hospital database were as follows: B18 (Viral hepatitis), Z22.5 (Carrier of viral hepatitis), K74 (Fibrosis and cirrhosis of liver), C22.0 (Hepatocellular carcinoma), Z13.9 (Special screening examination, unspecified), Z20.5 (Contact with and exposure to viral hepatitis), Z24.6 (Need for immunization against viral hepatitis) and R94.5 (Abnormal results of liver function studies).

From among this group, we selected the patients who had at least one positive HBV-DNA (<2000 IU/mL or 2000-20000 IU/mL) and one HBsAg positivity in the past. We then excluded any patients whose history showed use of antiviral drugs, as well as patients who had >12 months of undocumented activity gaps during the monitoring. Other exclusion criteria included having autoimmune hepatitis, alcoholic hepatitis, hemochromatosis or Wilson disease, immunosuppression (human immunodeficiency virus coinfection, malignancy, the use of immunosuppressive agents), hepatitis C virus or hepatitis D virus coinfections and pregnancy. A total of 293 patients were included in the study.

Direct Medical Cost Calculation

Costs in healthcare services can generally be broken down into 3 main types; these include direct medical costs, direct non-medical costs and indirect costs. Direct medical costs account for such expenditures as laboratory protocols, diagnostic testing, hospitalization, prevention protocols, rehabilitation, and pharmaceuticals used (11). Direct non-medical costs include the additional costs in accessing healthcare such as transportation, meals, care provided by family, and other out-of-pocket expenses. The indirect costs include expenses incurred due to loss of production as a result of work absence, disability, and mortality; as well as time losses attributed to seeking out specific medical services (11,12).

In this study, only direct medical costs were calculated; these included laboratory tests, imaging, biopsies and co-payments. A laboratory visit was defined as the outpatient visit in which laboratory testing was ordered and a 8.58 USD co-payment was charged. Control visits were not included in the direct medical cost analysis because; in accordance with Turkish Social Security Institution (SGK), there is no charge for control appointments that fall within ten days of the first outpatient visit. The direct medical cost was calculated by multiplying the total number of medical resources by unit cost for each laboratory visit of the patient. We used the Turkish SGK's pricing as of 01.07.2017. The unit costs can be found in Supplementary Table 1. A mean exchange rate across the study period (01.01.2005-01.01.2018) was calculated in the USD to Turkish lira (TL) conversion. The daily mean exchange rate was 1.95 TL. All the patients had social health insurance.

Statistical Analysis

Descriptive statistics were presented as numbers and percentages (n, %), mean ± standard deviation and median with interquartile range (IQR). Normality was assessed with the Shapiro-Wilk test. Non-normal distributed variables in a paired group were

compared using Wilcoxon signed-rank test. The patients were divided into four groups according to the duration of follow up: <36 months group, 36-71 months group, 72-108 months group and >108 months group. Cost per laboratory visit between the groups was compared to the <36 months group using Student's t-test. After dividing the follow-up duration into one-year intervals, we calculated the annual expenditure of follow-up, as well as the annual expenditure for laboratory and/or imaging tests. Linear mixed effect models were implemented to investigate the effect of follow-up time on the cost of monitoring while allowing the effect of time to vary across patients (random effect). In order to compare our monitoring strategy with the guideline recommendations; cost trajectories based on patients being followed up with ALT, HBV DNA, AFP and US every three months (quarterly), every six months (semi-annual) or once a year were estimated. Statistical analyses were performed with R version 4.0.2 (A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/), using packages "compareGroups" and "lme4". A double-sided p-value of ≤0.05 was accepted as significant. Approval for our study protocol was granted by the Ethics Committee of İstanbul Medeniyet University (approval number: 2017/0231).

Results

Of the 293 patients (female: 51.5%), the mean age was 47.3±12 (Table 1) with the median monitoring of 60 (IQR: 30-107) months. HBV-DNA level at the last visit [median (IQR): 227 (42-815)] was lower than the levels at the first visit [median (IQR): 306 (89-1223)], (p<0.001).

ALT (n=2932, count per visit: 0.80) test was the most common test being requested and it was followed by HBV-DNA (n=2385, count per visit: 0.65). With 59.55% of the total cost, HBV-DNA was the test that received the most funding (Table 2). Hospital visit copayments were second, accounting for 13.7%. Hepatobiliary US, upper abdomen US and total abdomen US was the third largest cost in regard to total expenditure (4.99%). The spending on liver biopsies, which was the most expensive procedure during monitoring, accounted for 3.15%. The average annual direct medical cost per patient was 160 USD and the average laboratory visit cost per patient was 68.5 USD.

The cost per laboratory visit was decreasing with the duration of follow-up (Figure 1A). There was a statistically significant difference for the cost per laboratory visit between <36 months group and 72-108 months group (76.1±12 vs 65.6±9.7 respectively, p<0.0001) and between <36 months group and >108 months group (76.1±12 vs 53.9±7.8 respectively, p<0.0001), (Figure 1B).

As the follow-up time increased, the total annual cost (β=-2.07, se=0.67, p<0.001), as well as annual spending on ALT (β=-0.04, se=0.005, p<0.001), co-infection serology (β=-0.17,

Table 1. Characteristics and the outpatient follow-up parameters of the patients with HBeAg-negative chronic hepatitis B virus infection, (n=293)

Gender, n (%)	
Female	151 (51.5%)
Male	142 (48.5%)
Age, years, mean ± SD	47.3±12.7
Follow-up time, months, median (IQR)	60 (30-107)
Follow-up time, n (%)	
<36 months	91 (31.1%)
36-71 months	81 (27.6%)
72-108 months	53 (18.1%)
>108 months	68 (23.2%)
Total hospital visit, median (IQR)	20 (12-31)
Total laboratory visit, median (IQR)	10 (6-16)
ALT, IU/L, median (IQR)*	
First visit	20 (16-28)
Last visit	20 (15-28)
HBV-DNA, IU/mL, median (IQR)**	
First visit	306 (89-1223)
Last visit	227 (42-815)

*: First visit vs last visit, p=0.78; **: First visit vs last visit, p<0.001, IOR: Interquartile range, SD: Standard deviation, HBV: Hepatitis B Virus, HBeAg: Hepatitis B e antijen

Table 2. Total count of tests/visits and the total cost of the patients in American dollars

	Total count	Total cost (USD)*	Cost (%)
Complete blood count	2309	3904.8	1.7
ALT	2932	1818.07	0.79
AST	2741	1545.12	0.67
Albumin	991	558.63	0.24
APTT	530	1792.59	0.78
Alfa-fetoprotein	1805	6613.7	2.88
HBsAg	1369	5787.87	2.52
Anti-HBs	633	2854.61	1.24
Anti-HBc IgM	19	85.68	0.04
Anti-HBc IgG	97	437.44	0.19
Anti-HCV	292	1316.82	0.57
Anti-HIV	161	680.68	0.3
Anti-HAV IgG	202	910.95	0.4
HBeAg	903	3817.71	1.66
Anti-HBe	856	3860.27	1.68
HBV-DNA	2385	136729.79	59.55
Anti-HDV	674	3229.48	1.41
Hepatobiliary US	113	649.73	0.28
Total abdomen US	340	4561.52	1.99
Upper abdomen US	723	6235.68	2.72
Upper abdomen MRI	64	3517.53	1.53
Liver biopsy	47	7225.71	3.15
Hospital visit	3688	31466.32	13.7
Total		229600.69	100

*Total costs on Turkish lira can be found in Supplementary Table 2, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, aPTT: Activated partial thromboplastin time, HBsAg: Hepatitis B surface antigen, anti-HBs: Anti-hepatitis B surface antigen, anti-HBc IgM: Anti-hepatitis B core antigen immunoglobulin M, IgG: Immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, HAV: Hepatitis A Virus, HBV: Hepatitis B virus, USD: United States dollar, MRI: Magnetic resonance imaging

se=0.04, p<0.001) and HBV-DNA (β=-1.03, se=0.42, p<0.05) was decreasing (Table 3). The annual cost of HBV serology and the US remained stable during the monitoring. Total spending on AFP had a statistically significant positive relationship with time (β=0.05, se=0.02, p<0.05).

Figure 2 shows the cost trajectories of monitoring the patients with HBeAg-negative chronic infection at İstanbul Medeniyet University, Department of Infectious Diseases and the cost trajectories of hypothetical strategies with quarterly, semi-annual and annual monitoring. In the first two years of monitoring, the cost trajectory of the patients remained above the semi-annual follow-up strategy trend line. After three years, the cost trajectory of patients had fallen to between the semi-annual follow-up trend line and annual follow-up trend line.

Discussion

In accordance with current guidelines (8), HBV infection phases are classified by clinicians as HBeAg-positive chronic infection, HBeAg-positive CHB, HBeAg-negative chronic infection, HBeAg-negative CHB and HBsAg-negative phase. This study quantifies the annual cost of following a patient with HBeAg-negative chronic infection by reviewing the relevant trends in laboratory and imaging costs in a tertiary care hospital in Turkey. Patients with HBeAg-negative chronic infection account for 40-64% of HBV infected patients (13,14,15). Due to the large patient numbers involved, investigating the cost of follow-up will assist in the planning of more cost-effective strategies without compromising on the quality of care.

In this study, the average annual direct medical cost per patient was calculated as 160 USD with the average laboratory visit cost being 68.5 USD. A Tosun and Ayhan (16) study conducted in the mid-2000s found the initial assessment of a subject with HBsAg positivity to cost 153 USD. The follow-up laboratory testing (HBV-DNA excluded) recommended for every 3-6 monthly monitoring was cost at 55.1 USD (16). Six years later, Karahasanoğlu et al. (7) found that the one-year monitoring of 158 inactive carriers cost to be 178.1±161.74 USD. To date, these two studies had been the only studies investigating the cost of monitoring patients with HBeAg-negative chronic infection in Turkey. Across their study periods, these studies used daily mean USD exchange rates of 1.3 TL and 1.5 TL, respectively. We used a mean rate of 1.95 TL. While the lira costs associated with laboratory tests and imaging haven't varied much over years, the further depreciation of the local currency against the USD can account for added expenditures.

According to international guidelines, patients with HBeAg-

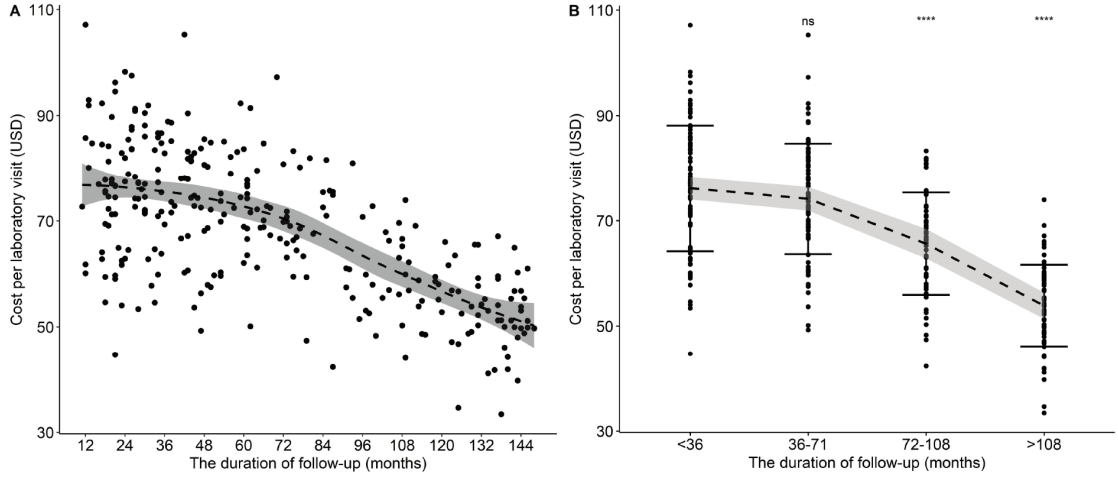

Figure 1. Cost per laboratory visit by the duration of follow up (A). Comparison of the cost per laboratory visit in the patients who monitored <36 months, 36-71 months, 72-108 months and >108 months (B); p-values show the comparisons against the <36 months group, ****: p<0.0001, ns: Not significant

Table 3. The fixed effect estimates of follow up time on the annual expenditures of laboratory tests (USD)

	Annual expenditures (USD)						
	ALT	AFP	HBV serology	Co-infection serology	HBV-DNA	US	Total
Intercept, β (se)	1.16*** (0.03)	3.68*** (0.12)	10.16*** (0.46)	4.17*** (0.22)	82.7*** (2.40)	6.40*** (0.31)	139.76*** (3.70)
Time, β (se)	-0.04*** (0.005)	0.05* (0.02)	-0.11 (0.08)	-0.17*** (0.04)	-1.03* (0.42)	0.06 (0.05)	-2.07** (0.67)

HBV serology expenditures include the total cost of HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgM and anti-HBc IgG. Co-infection serology expenditures include anti-HCV, anti-HIV, anti-HAV IgG, anti-HDV. US expenditures include the total cost of hepatobiliary US, upper abdomen US and total abdomen US. β: fixed-effects coefficients, se: Standard error. *p<0.05, **p<0.01, ***p<0.001. USD: United States dollar, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBsAg: Hepatitis B surface antigen, anti-HBs: Anti-hepatitis B surface antigen, anti-HBc IgM: Anti-hepatitis B core antigen immunoglobulin M, IgG: Immunoglobulin G, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus, HAV: Hepatitis A virus, HBV: Hepatitis B virus, AFP: Alpha-fetoprotein

negative chronic infection and HBV-DNA <2000 IU/mL should be monitored every 6-12 months (8). Fluctuations of HBV-DNA and ALT can be observed in some patients. Due to this, strict monitoring is recommended in the patients after initial HBsAg positivity (8,17). In our study, the total annual expenditure and annual expenditures of ALT and HBV-DNA were decreasing with time. In addition, our cost trajectory at the first two years of monitoring was between quarterly monitoring and semi-annual monitoring trend lines. This could be explained by the fact that concentrated efforts were undertaken to distinguishing HBeAg-negative chronic infection from HBeAg-negative CHB through more frequent monitoring in the initial years.

Increased serial monitoring and liver fibrosis assessments tend to better detect the transition to HBeAg-negative CHB in the patients who experienced ALT and/or HBV-DNA fluctuations while under monitoring. In a study from Taiwan, the annual transition from inactive to active hepatitis B was found to be 1.55% (18). In Western countries, the transition to HBeAg-negative CHB is rare and when an increase in ALT occurs, causes other than HBV infection; drugs, alcohol etc. should be excluded first (17,19,20,21). Immunosuppression or co-infection with other hepatotropic viruses could trigger a reactivation. In our study, we observed that the cost of HBV-DNA and hospital visit co-payments attributed to the majority of expenditure. Due to the benign course in healthy individuals with HBeAg-negative chronic infection, less frequent hospital visits (i.e. yearly) could help reduce HBV-DNA and co-payment expenditure.

HCC ranked seventh among new cancer cases in 2020 (22). The burden from HBV related HCC cases varies highly geographically and is not strictly related to HBV prevalence (23,24). In most cases, it originates from hepatocytes in cirrhotic tissue. Studies conducted among the patients with HBeAg-negative chronic infection revealed favourable outcomes for cirrhosis and HCC. A study from Taiwan, a high burden country with a 20% prevalence, reported that the annual rate of cirrhosis was 0.28% (40 person/14484 person-years) (25). Tong and Trieu (26) followed 146 patients for 8±6.3 years; reporting only 2 (1.4%) developed HCC. Prospective cohort studies from Japan (27), Greece (21), and Italy (28) all failed to detect cirrhosis or HCC. In a low cancer prevalence setting, very low-risk of cancer development, lifelong US screening for HCC doesn't present as being very cost-effective (29). However, personalized surveillance of high-risk patients; such as those with a family history of cirrhosis or HCC, as well as the subjects with persistently high viremia, should continue during monitoring (30).

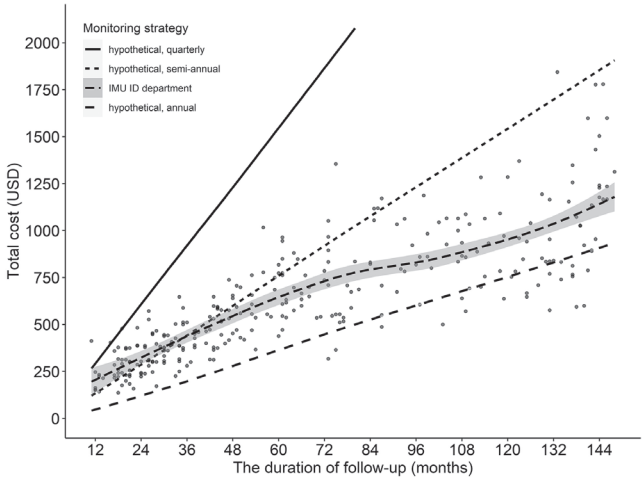

Figure 2. Cost trajectory of the patients monitored in İstanbul Medeniyet University Infectious Disease Department (IMU ID), and comparison with hypothetical scenarios of quarterly, semi-annual and annual monitoring. Only, ALT, HBV DNA, AFP and upper abdomen US were used in the total cost calculation

ALT: Alanine aminotransferase, HBV: Hepatitis B virus, AFP: Alpha-fetoprotein, US: United States

This study showed that we routinely used liver US for cirrhosis/HCC surveillance as the annual spending on US remained stable with time. Suspicious hyperechoic nodular lesions depicted in US reports increase MRI evaluations in the patients without cirrhosis or advanced fibrosis. While this approach is understandable as a part of the HCC diagnostic process, we observed repeated MRI scans for confirmed benign lesions such as hemangiomas, adenomas and focal fatty changes. Rather than requesting repeated MRI scans for benign lesions, more efficient communication between radiologists and clinicians could have a more positive impact on the cost-effectiveness of monitoring. Additionally, limiting laboratory/imaging requests for targeted monitoring could also reduce expenditures. For example, per unit cost of total abdomen US and upper abdomen US was 2.3 times and 1.5 times more expensive than the hepatobiliary US, respectively. Implementing a stepwise laboratory/imaging diagnostic pathway as a component of individualized patient monitoring could positively impact cost-effectiveness (31).

Study Limitations

This study has some limitations. Firstly, we used the mean USD rate over the study period to most accurately investigate the trend of dollar-denominated annual costs. The actual cost will vary depending on the USD rate on the date of the lab visit. Secondly, we did not adjust dollar figures to account for inflation from 2005 to 2017. Thirdly, this study does not include non-reimbursed and out-of-pocket costs. Additionally, while we only extracted the expenditures that predominantly related to hepatitis B monitoring, other laboratory tests may have also been requested due to different health conditions. It is considered that costs were likely underestimated. Lastly, the change in costs in relation to the long-term clinical outcomes of the cohort could not be fully evaluated due to the retrospective design of the study.

Conclusion

Due to high patient numbers, the total cost of monitoring presents a large economic burden. After confirming HBeAg-negative chronic infection through stricter monitoring in the initial years, the length of the interval between outpatient hospital visits should be reviewed; and extended where possible. This study contributes to policymaking with regard to monitoring patients with HBeAg-negative chronic infection, as well as provides data for decision analysis studies in health economics.

Ethics

Ethics Committee Approval: Approval for our study protocol was granted by the Ethics Committee of İstanbul Medeniyet University (approval number: 2017/0231).

Informed Consent: This retrospective study was based on hospital records and informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: H.V., H.Ç., P.E., Y.Ç., F.A. Design: H.V., A.N.E., H.Ç., P.E., Y.Ç., F.A., Data Collection and Processing: A.N.E. Analysis or Interpretation: H.V., A.N.E., Literature Search: A.N.E., H.Ç., P.E., Writing: A.N.E., H.Ç., P.E., F.A., Critical Review: H.Ç., P.E., Y.Ç., F.A.

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

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Research Article

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Hepatitis C Genotype Distribution Changing Through Years in the Kahramanmaraş Region

Kahramanmaraş Yöresinde Yıllar İçinde Değişen Hepatit C Genotip Dağılımı

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ABSTRACT

Objectives: Chronic hepatitis C virus (HCV) infection still continues to be a significant health problem in the entire world. In addition to this, knowing about the existing genotypes in a region is highly important in terms of guiding antiviral treatment and understanding the epidemiology in that region. In our study, we examined the varying genotype distribution in our region and affecting factors.

Materials and Methods: To determine the HCV genotype distribution in Kahramanmaraş in Turkey, patients who were determined to be HCV-positive in the last 4.5 years and whose genotypes were studied retrospectively searched from records and included in the study.

Results: Genotype 1 was the most prevalent genotype (47%) in Kahramanmaraş. The second most prevalent (45%) genotype was genotype 3. Additionally, genotypes 2 and 4 were seen at the rates of respectively 2% and 6%. While there was male dominance in genotypes 1, 2, and 3, genotype 4 had female dominance (69%). There was a very high male dominance in genotype 3 (95%), and the mean age of the patients was 26.4.

Conclusion: The epidemiology of HCV may show serious variations at locations that receive intense migration and where increased drug usage is observed. The main point in preventing HCV infection should be the identification and elimination of risk factors.

Keywords: Hepatitis C virus, genotype, risk factors, Kahramanmaraş

ÖZ

Amaç: Kronik hepatit C virüs (HCV) enfeksiyonu tüm dünyada halen önemli bir sağlık sorunu olmaya devam etmektedir. Bununla birlikte bir bölgedeki mevcut genotiplerin bilinmesi anti-viral tedaviye rehberlik etmesi ve o bölgedeki epidemiyolojiyi anlamak için çok önemlidir. Bizde çalışmamızda bölgemizdeki değişen genotip dağılımını ve etki eden faktörleri irdelemeyi amaçladık.

Gereç ve Yöntemler: Kahramanmaraş genelindeki HCV genotip dağılımını belirlemek için son 4,5 yıl içinde bölgemizde HCV pozitif saptanan ve genotip çalışılan hastalar retrospektif olarak kayıtlardan taranarak çalışmaya alındı.

Bulgular: Genotip 1 Kahramanmaraş'ta en yaygın (%47) genotipti. İkinci en yaygın (%45) genotip ise genotip 3'tü. Ayrıca genotip 2 ve 4 sırasıyla %2 ve %6 oranında görülüyordu. Genotip 1,2,3'te erkek hakimiyeti varken genotip 4'te kadın ağırlıklıydı (%69). Genotip 3'te ise ciddi bir erkek hakimiyeti (%95) vardı ve genotip 3 hastaların yaş ortalaması 26,4'tü.

Sonuç: Yoğun göç alan ve artmış uyuşturucu kullanımının olduğu yerlerde HCV epidemiyolojisi çok ciddi değişimler gösterebilmektedir. HCV enfeksiyonunu önlemede temel nokta ise risk faktörlerinin belirlenmesi ve ortadan kaldırılması olmalıdır.

Anahtar Kelimeler: Hepatit C virüsü, genotip, risk faktörleri, Kahramanmaraş

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Introduction

The hepatitis C virus (HCV) may lead to both acute and chronic hepatitis. The acute process limits itself, rarely causes liver failure and usually leads to chronic infection. Chronic HCV infection shows a progressive course for long years, and at the end, it may result in cirrhosis, hepatocellular carcinoma and requirement of liver transplantation. About 15-45% of infected individuals completely recover within the 6 months after infection without any treatment. The remaining 55-85% develop chronic HCV infection. The risk of cirrhosis in individuals with chronic HCV infection within 20 years is between 15% and 30%. There are 399,000 deaths every year in connection to chronic HCV infection and complications. Additionally, approximately 71 million people living with hepatitis C are considered as a global health problem. According to the World Health Organization, the regions most affected around the world are the Eastern Mediterranean Region and Europe, and the prevalence in these regions were estimated respectively as 2.3% and 1.5% for 2015 (1). The prevalence of chronic HCV infection in healthy individuals in Turkey is reported between 0.6% and 2% (2).

HCV is a small RNA virus belonging to the Hepacivirus species in the Flaviviridae virus family. As in other RNA viruses, the genome of HCV also shows differences based on geographical regions. HCV has 7 types and 67 subtypes that are defined. In the entire world, the most prevalent type is genotype 1 (44%), which is followed by genotype 3 (25%) in the second place, genotype 4 (15%) in the third place and genotypes 2, 5 and 6 in decreasing prevalence (3,4). While genotype 1 is the most frequent type on high- and medium-income levels, genotype 4 is the most frequent type on low-income levels (4). Molecular epidemiology studies have shown that these HCV genotypes and subtypes are differently distributed in different parts of the world, and certain genotypes are dominant in some regions. Type 2 in Ghana, type 5 in South Africa, type 6 in Vietnam, type 4 in Egypt and Syria, type 1b in Japan, type 3 in Pakistan and type 1 in Turkey are the most frequently seen genotypes (4).

Genotype 1, especially its subtypes 1a and 1b, are the most prevalent ones in Europe and the USA. Moreover, genotype 3 carries an increasingly higher significance as it is the second most prevalent genotype reported in all European countries except for Italy and Romania (5). While genotype 4 in Central Africa and the Middle East, genotype 5 in South Africa and genotype 6 in Southeast Asia constitute the most frequently distributed regions for these genotypes, genotype 7 was recently determined in Central African immigrants in Canada (6). Especially genotype 3a is the prevalently seen genotype in intravenous drug addicted individuals in Europe and the United States (7).

As the effectiveness of most existing and new treatments shows differences based on the genotype of HCV, it is clinically important to know about the distribution of HCV genotypes. Treatment times and success rates vary based on HCV genotypes and subtypes (8). Additionally, in monitoring the effects of the intense flows of migration towards Turkey and Europe in recent years on the dynamics of hepatitis C, the most suitable instrument will be genotyping. Thus, in our study, we aimed to examine the HCV genotype distribution changing by years in the Kahramanmaraş region and affecting factors.

Materials and Methods

Patients who were admitted to and found to be anti-HCV positive at family health centers, districts, state hospitals and faculty of medicine laboratories in Kahramanmaraş between January 2015 and June 2019 were determined. Among these patients, those for whom HCV RNA and HCV genotyping was made were included in the study. The study was started by obtaining approval from the Local Ethics Board of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University and permission from the Provincial Directorate of Health. The data were provided by the information processing department from the automation system of the relevant hospital. The collected data were analyzed in the computer environment, the data on patients whose genotypes were studied were gathered, and the demographic characteristics of these patients were recorded.

Statistical Analysis

The data were analyzed by using the SPSS 18 statistical software. Data analysis was performed using frequency analysis and chi-square test. All values were considered statistically significant when $p<0.05$.

Results

In the last 4.5 years in our region of study, 2,189 HCV-positive patients were determined, genotypes were studied in 553 of these patients, and the genotypes of 497 were determined. In the other 56 patients, genotypes could not be determined due to HCV-RNA negativity. Three hundred fifty-one (70.6%) of the patients were male, and 146 (29.4%) were female. The mean age of the patients was 42.7±20.8 (range: 18 to 89 years). Genotype 1 was determined in 235 (47%) patients, 8 (2%) patients had genotype 2, 225 (45%) had genotype 3, and 29 (6%) had genotype 4. Among the patients infected with genotype 1, 123 (52%) were male, 112 (48%) were female, and their mean age was 56.8 (range: 21 to 89 years). Additionally, among the genotype 1 patients, the subtype of 8 (3%) was reported as 1a, while the subtype of 45 (19%) was 1b (Table 1). Among the patients infected with genotype 2, 5 (62.5%) were male, 3 (37.5%) were female, and their mean age was 47 (range: 19 to 82 years). Among the genotype 3 patients, 214 (95%) were male, 11 (5%) were female, and the mean age was 26.4 (range: 18 to 72 years). Among these genotype 3 patients, the subtype of 15 (6%) was genotype 3a. Among the genotype 4 patients, 9 (31%) were male, 20 (69%) were female, and the mean age was 53.8 (range: 22 to 68 years). Among these genotype 4 patients, 25 (86%) were of Syrian nationality, while 4 (14%) were Turkish citizens. Moreover, 2 (25%) of the genotype 2 patients were of Syrian nationality. Three (1%) of the genotype 3 patients were of Azerbaijani nationality. The differences in the distributions of the genotypes based on sex were significant ($p<0.001$). We determined that genotype 3 was seen more in the male patients, while genotype 4 was seen more in the female patients (Table 2). Especially the mean age of the genotype 3 patients was significantly lower than those infected with the other genotypes (Figure 1). No genotype 5 or 6 patients were encountered in our region of study.

Discussion

HCV is a virus with high genetic variation. In hepatitis C, genotype determination is an important parameter for treatment selection and determining the duration of the selected treatment. However, in recent times, pangenotypic drugs offered in the market have caused us to question the necessity of looking at genotypes for patients to be treated. Moreover, genotype determination provides us with information on the course of the disease. For example, genotype 1 may show that the disease progresses more severely in these patients, the risk of hepatocellular cancer development is higher in such individuals, and these individuals should be more closely monitored due to this issue (9).

HCV has been divided into seven main genotypes and several subtypes. The geographical distribution of HCV is also heterogenous. While genotypes 1, 2 and 3 have a global distribution, genotypes 4, 5, 6 and 7 are limited with some geographical regions (e.g. South Africa, Southeast Asia, Egypt and Central Africa) (10). In recent studies, it was determined that the most frequently observed type of HCV in Turkey is genotype 1, while the most prevalent subtype is 1b. The distribution of other genotypes in these studies was reported as genotypes 3, 2 and 4 in decreasing order (11,12,13,14).

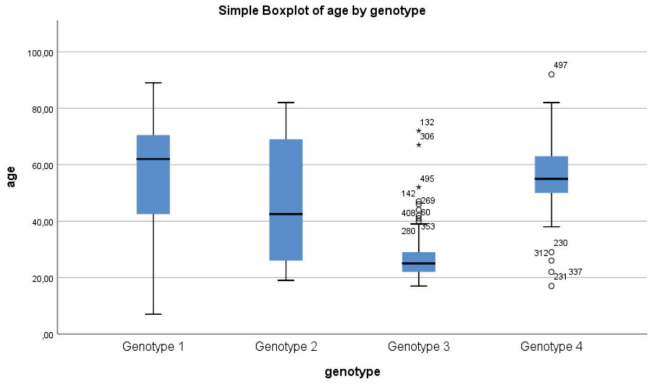

Figure 1. Genotype distribution based on age

In our region of study, in a single-center study by Kirişci et al. (15) conducted in 2013, genotype 1 (60%) was the most prevalent genotype. In the same study, genotype 3 was encountered by 40%, while no other genotypes were observed (15). In a study again in 2013 which only included the data of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University and was presented as a poster at an international conference, 95% genotype 1 and 5% genotype 3 patients were determined, and no other genotypes were encountered. However, in recent years, a serious change has taken place in the genotype distribution in the region.

In our study containing the data of the last 4.5 years and covering the entirety of the aforementioned region, the type that was seen the most frequently was genotype 1 (47%). On the other hand, in comparison to the study in 2013, we observed that the genotype 1 rate decreased (60% vs. 47%). Additionally, the genotype 3 rate was observed to increase from 40% to 45%. These values were similar to those in the world. Furthermore, it was determined that genotype 2 and 4 patients that had not been encountered in the mentioned previous study started to be seen in our region of study. The reasons for these results may be that the province has been rapidly receiving migration from Syria since 2010, and the rate of drug abuse among the youth has increased.

The case is similar to ours in different regions of Turkey. In a genotype study conducted in İzmir in western Turkey by Çetin Duran et al. (16), previously unencountered genotype 5 patients

Table 1. Genotype and subtype distribution

	n	%	Subtype / (n, %)
Genotype 1	235	47.3	1a/8/3 1b/45/19 Undefined subtype/182/77
Genotype 2	8	1.6	2a/1/12.5 2c/1/12.5 Undefined subtype/6/75
Genotype 3	225	45.3	3a/15/6.6 Undefined subtype/210/93.3
Genotype 4	29	5.8	Undefined subtype/29/100
Total	497	100.0	

Table 2. Genotype distribution based on sex

			Genotype				Total	p
			Genotype 1	Genotype 2	Genotype 3	Genotype 4		
Sex	Male	n	123	5	214	9	351	<0.001
		%	35.0%	1.4%	61.0%	2.6%	100.0%	
	Female	n	112	3	11	20	146	
		%	76.7%	2.1%	7.5%	13.7%	100.0%	
Total		n	235	8	225	29	497	
		%	47.3%	1.6%	45.3%	5.8%	100.0%	

were determined, and the authors concluded that the reason for this was the migration received by the region.

Genotype distributions based on age groups may show variations based on the geographical location and societies in which they are seen. Niu et al. (17) reported that genotypes 1 and 2 were seen more in the age group of 40-60, while genotype 3 cases were seen in younger patients. Kartashev et al. (18) showed that genotype 1 patients were mostly in the age group of 45-55, genotype 1a was seen in 55-66-year-olds, genotype 1b was seen in those over 65, genotype 2 was seen in those over 65, and genotypes 3 and 4 were seen in the age group of 45-55. Another study determined that, while the median age of patients infected with genotypes 1, 2 and 4 was 50 and higher, that in those infected with genotype 3 was 41,7. In contrast, in Pakistan, it was determined that all genotypes were mostly seen in the age group of 25-45 (19). A study conducted in Algeria reported that genotype 1 patients could be usually gathered in the age interval of 50-70 (20). The mean age of genotype 1 patients in Turkey was reported in the range of 50-60 (11,21,22). In our study, the mean ages of the genotype 1, 2 and 4 patients were similar to those reported in the aforementioned studies. However, the mean age of the genotype 3 patients in our study was found as 26.4. This value was lower than those reported in Turkey and other countries. This may be explained by the increasingly higher intravenous drug addiction in the young population in our region of study.

Genotype distributions may also vary based on sex. Janahi et al. (23) determined in Bahrain that the frequency of male cases in all genotypes was higher than females. However, the lowest frequency in female patients was seen in genotype 3. Likewise, in a study covering the period of 2008-2015 and Belgium, the prevalence of male cases was higher in all genotypes (24). Kartashev et al. (18) found genotypes 1b and 2 more frequent in women, while they found genotypes 1a, 3 and 4 more frequent in men. In our study, there was a male dominance in all patients of genotypes 1, 1a and 1b. It is seen that the female dominance in the study previously conducted in our region of study turned into a male dominance in recent years. Additionally, the male sex was more prevalent among the genotype 2 and 3 patients. Among the genotype 4 patients, as opposed to the case in the studies mentioned above, the female sex was more prevalent. This may have been caused by the higher rate of the female sex among those migrating from Syria to our region of study. Indeed, 25 of the genotype 4 patients were of Syrian origin, and most of these were female patients.

Study Limitations

Since our study is retrospective, it does not contain much information about HCV transmission risk. The limitations of our study are that genotype could not be checked in all patients with positive anti-HCV, and subtype analysis could not be performed in patients with all genotypes.

Conclusion

It was seen that there have been serious changes in the genotype distribution in comparison to previous studies conducted in our region of study. As in the case in the whole world, the most frequently encountered genotype was also determined in our study as genotype 1, but it was observed that its prevalence decreased in comparison to the past. In this study, genotype 2 and 4 patients, who were not encountered at all in previous studies in our region of study, were determined. This shows that the epidemiology of HCV may change in time especially in regions receiving migration. Therefore, in our region, there is a need to increase social awareness and prevent intravenous drug use.

Ethics

Ethics Committee Approval: The study was started by obtaining approval from the Local Ethics Board of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University and permission from the Provincial Directorate of Health.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.G., M.İ., Design: K.G., Data Collection or Processing: K.G., M.A., A.R.Ş., B.K., Analysis or Interpretation: K.G., B.K., A.R.Ş., M.A., Literature Search: K.G., M.İ., Writing: K.G.

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Research Article

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Implications of Hepatitis B and C on the Human Immunodeficiency Virus Infections

Hepatit B ve C'nin İnsan Bağışıklık Yetmezliği Virüsü Enfeksiyonları Üzerindeki Etkileri

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ABSTRACT

Objectives: Viral hepatitis and human immunodeficiency virus (HIV) infections are still significant causes of morbidity and mortality. This study investigatedaimed to investigate the effect of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection on HIV infection, investigate the epidemiological characteristics of co-infected patients and thus help identify risk factors for co-infection, evaluate the results and clinical information, and shape the treatment of patients.

Materials and Methods: This descriptive, cross-sectional study from January 2013 to July 2021 was conducted carried out on 758 patients, including 502 infected with HIV, 196 co-infected with HBV/HCV, and 60 co-infected with HCV/HIV. Comparison between groups in terms of categorical characteristics was analyzed with the Pearson chi-square test or Fisher-Freeman-Halton test. The changes in HIV infection in the presence of co-infections were examined with the multivariate multinomial logistic regression model.

Results: We found differences in our HIV-infected patients co-infected with HBV or HCV in gender, nationality, transmission routes, HIV viral load, and CD+4 T-cell count ($p<0.001$). There was no difference between the groups regarding age, opportunistic infection status, and malignancy status.

Conclusion: Our findings indicate that HBV and HCV may affect HIV infection infections. Our approach can focus on these points in co-infected patients, and we can effectively manage their treatment and follow-up.

Keywords: Human immunodeficiency virus, hepatitis B virus, hepatitis C virus, co-infection

ÖZ

Amaç: Viral hepatit ve insan bağışıklık yetmezlik virüsü (HIV) enfeksiyonları hala önemli morbidite ve mortalite nedenleridir. Bu çalışmada, hepatit B virüs (HBV) ve hepatit C virüs (HCV) enfeksiyonlarının HIV enfeksiyonu üzerindeki etkisinin araştırılması, ko-enfekte hastaların epidemiyolojik özelliklerinin ortaya çıkarılması ve böylece viral hepatit/HIV ko-enfeksiyonu için risk faktörlerinin belirlenmesi, sonuç ve klinik bilgilerin değerlendirilmesi ve hastaların tedavisinin şekillendirilmesine yardımcı olunması amaçlanmıştır.

Gereç ve Yöntemler: Ocak 2013'ten Temmuz 2021'e kadar olan bu tanımlayıcı, kesitsel çalışma, 502'si HIV ile enfekte, 196'sı HBV/HCV ile ko-enfekte ve 60'ı HCV/HIV ile ko-enfekte olmak üzere 758 hasta üzerinde gerçekleştirildi. Kategorik özellikler açısından gruplar arası karşılaştırma Pearson ki-kare testi veya Fisher-Freeman-Halton testi ile analiz edildi. Ko-enfeksiyon varlığında HIV enfeksiyonundaki değişiklikler çok değişkenli çok terimli lojistik regresyon modeli ile incelendi.

Bulgular: HBV veya HCV ile ko-enfekte HIV positiv hastalarda cinsiyet, ülke, bulaşma yolları, HIV viral yükü ve CD+4 T- hücre sayısında anlamlı farklılıklar bulduk ($p<0,001$). Gruplar arasında yaş, fırsatçı enfeksiyon ve malignite durumu açısından ise fark yoktu.

Sonuç: Bulgularımız HBV ve HCV'nin HIV enfeksiyonlarını etkileyebileceğini göstermektedir. Yaklaşımımıza göre HBV ve/veya HCV'nin HIV ko-enfeksiyonlarında, anlamlı noktalara odaklanarak tedavi ve takiplerinin etkin bir şekilde yönetilebilmesi mümkün olabilir.

Anahtar Kelimeler: İnsan bağışıklık yetmezlik virüsü, hepatit B virüs, hepatit C virüs, ko-enfeksiyon

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Introduction

Viral hepatitis and human immunodeficiency virus (HIV) infections are still significant causes of morbidity and mortality in vulnerable populations and developing countries (1). World Health Organisation (WHO) reports that hepatitis B virus (HBV) and hepatitis C virus (HCV) are responsible for 96% of hepatitis deaths and that deaths are due to chronic liver disease and liver cancer (2). An estimated 257 million people lived with chronic HBV infection and 71 million chronic HCV infections in 2016 (2). On the other hand, at the end of 2019, an estimated 38 million people lived with HIV (3). Co-infections with HBV and HCV are common in HIV-infected individuals due to the similarity of transmission routes. These infections' estimated prevalence varies by geographic region (4). Approximately 5-10% of HIV-positive patients are infected with HBV and 15-25% with HCV in various studies (5,6,7). In Turkey, an estimated 3,6 million people are infected with HBV, 800,000 people with HCV, and 25,000 people with HIV; also, HBV/HIV and HCV/HIV co-infection rates were 4,4% and 0,9%, respectively (8,9,10,11).

HIV accelerates liver disease progression in viral hepatitis; HIV hurts the natural course and progression of HBV infection. HBV/HIV co-infected individuals have a higher DNA replication rate and a lower spontaneous clearance rate (12). In addition, HIV accelerates cirrhosis, end-stage liver disease, hepatocellular cancer, and an increase in liver-related death rates with an increase in the rate of fibrous formation in the liver (13).

The rate of liver disease progression is increased in HCV/HIV co-infected individuals compared to individuals infected with HCV alone (14). Liver cirrhosis can occur in a shorter time in HIV-positive people co-infected with HCV than in HIV monoinfected ones (15). Comorbid conditions such as cardiovascular disease, cognitive impairments, kidney disease, osteoporosis, bone fractures, and diabetes are more common in HCV/HIV co-infected patients than HIV monoinfected patients (16,17). People with HBV/HIV infection, HCV/HIV infection, and HBV/HCV/HIV infection have higher mortality rates than people with any disorder alone (18,19,20).

It has been found that HIV has a significant effect on the course of HBV and HCV, but the opposite has not been shown reliably, and the impact of HBV and HCV on the natural history of HIV is controversial. This study aimed to investigate the effect of HBV and HCV infection on HIV infection, investigate the epidemiological characteristics of co-infected patients and thus help identify risk factors for co-infection, evaluate the results and clinical information, and shape the treatment of patients.

Materials and Methods

Study Population

This descriptive, cross-sectional study from January 2013 to July 2021 was carried out on 758 patients, including 502 infected with HIV, 196 co-infected with HBV/HCV, and 60 co-infected with HCV/HIV, in the Faculty of Medicine, Clinical Laboratory, PCR Unite of Kocaeli University and Department of Infectious Diseases and Clinical Microbiology of Health Science University, Antalya Training and Research Hospital in Turkey. Not all patients were treated; they were naive.

HBV and HCV were diagnosed by clinical standards of care and practice guidelines. Patients with positive hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) were included in the study.

Ethics committee approval for this study was obtained from the Kocaeli University Clinical Studies Ethics Committee (approval number: KOU KAEK 201345).

Sampling

The plasma HIV-1 RNA detection and quantification levels samples from confirmed HIV-positive patients were measured using real-time-PCR (Abbott TagMan 2000, Illinois-Des Plaines USA) (lower limit as quantification, 10 IU/mL).

CD4+ T-cell counts were analyzed with BD Simultest™ CD4/CD8 (Becton, Dickinson, and Company BD Biosciences 2350 Qume Drive San Jose, CA 95131 USA).

HBsAg and HCV Ab measurements were determined using chemiluminescence immunoassays (Cobas e 601 analyzers, Roche Diagnostic, Mannheim, Germany).

Statistical Analysis

Descriptive statistics of the data obtained were calculated as the arithmetic mean, standard deviation, median value, first (25^{th}) and third quartile (75^{th}) (IQR: 75^{th}-25^{th}), absolute and relative frequencies, depending on the type and distribution of the features. The conformity of the numerical type features to the normal distribution was examined using the Shapiro-Wilks test. Since it was determined that numerical measurements did not show normal distribution, the Kruskal-Wallis test was used to compare the groups, and the post-hoc Dunn test determined the groups that differed. Comparison between groups in terms of categorical characteristics was analyzed with the Pearson chi-square test or Fisher-Freeman-Halton test. In addition, considering the univariate test results described above, the changes in HIV infection in the presence of co-infections were examined with the multivariate multinomial logistic regression model. The statistical significance level was accepted as $p<0.05$, and SPSS (v25) software was used for calculations.

Results

While the rate of men (66.7%) in the HIV + HCV group was significantly lower than only the HIV (86.8%) and HIV + HBV (90.8%) groups, the rate of women in the HIV + HCV group was considerably higher than the other two groups. The frequency of Turkish nationality (63.3%) in the HIV + HCV group was significantly lower than only HIV (96%) and HIV + HBV (93.9%). Baseline demographic, clinical, and laboratory characteristics of patients are shown in Table 1.

In the HIV + HCV group and HIV + HBV group, the frequency of those with homosexual transmission routes was significantly lower than in the HIV group. Still, the frequency of those with heterosexual transmission routes was considerably higher. In addition, the frequency of those with intravenous drug use (IVDU) route in the HIV + HCV group was significantly higher than in the other two groups.

The mean HIV-1 RNA load in the HIV + HBV group was significantly lower than in the other two groups ($p<0.001$). In the

Table 1. Baseline demographic and laboratory characteristics of the study patients

Characteristic			Patient with HIV-1 infection, (n=502) HIV + HCV, (n=60)	Patient with co-infection		p-value
				HIV + HBV, (n=196)	HIV + HCV, (n=60)	
Age, mean year (range)*	Mean		38 (18-80)	40 (18-77)	39 (18-77)	0.080
	SD		12,442	12,482	13,014	
	Percentiles	25	29.00	31.00	30.00	
		50	36.00	38.00	39.00	
		75	46.00	46.00	47.00	
Age group, n (%)[b]	18-24 25-29 30-39 40-49 >50		52 (10.4) 98 (19.5) 158 (31.5) 101 (20.1) 93 (18.5)	16 (8.2) 23 (11.7) 70 (35.7) 46 (23.5) 41 (20.9)	4 (6.7) 10 (16.7) 19 (31.7) 17 (28.3) 10 (16.7)	0.286
Gender, n (%)	Female Male		66 (13.2)[a] 435 (86.2)[a]	18 (9.2)[a] 178 (90.8)[a]	20 (33.3)[b] 40 (66.7)[b]	**<0.001**
Nationality, n (%)	Turkish Non-Turkish		482 (96.0)[a] 20 (4)[a]	184 (93.9)[a] 12 (6.1)[a]	38 (63.3)[b] 22 (36.7)[b]	**<0.001**
HIV transmission route, n (%)	Heterosexual Homosexual IVDU Unknown		253 (50.4)[a] 224 (44.6)[a] 2 (0.4)[a] 23 (4.6)[a]	122 (62.2)[b] 68 (34.7)[b] 1 (0.5)[a] 5 (2.6)[a]	36 (60.0)[b] 8 (13.3)[b] 14 (23.3)[a] 2 (3.3)[b]	**<0.001**
Baseline HIV-1 RNA load, mean copy/mL (range)*	Mean		2.2+E7 (0-1+E10)	1.2+E6 (8.5+E2-6.0+E7)	2.1+E6 (7.1+E8)	**<0.001**
	SD		4.4+E8	5.1+E6	12.8+E7	
	Percentiles	25	8.3+E3	2.9+E4	5.3+E3	
		50	4.6+E4	1.0+E5	7.6+E4	
		75	2.3+E5	6.5+E5	2.3+E5	
HIV-1 RNA load group, copy/ml, n (%)	<1+E5 1+E5-2+E5 2+E5-5+E5 >5+E5		313 (62.4)[a] 53 (10.6)[a] 53 (10.6)[a] 83 (16.5)[a]	95 (48.5)[b] 22 (11.2)[a] 25 (12.8)[a] 54 (27.6)[a]	32 (53.3)[ab] 12 (20.0)[b] 5 (8.3)[a] 11 (18.3)[ab]	**0.004**
Baseline CD4+ T cell count, mean cell/mm^3 (range)*	Mean		484 (0-1900)	363 (5-1659)	616 (0-1800)	**<0.001**
	SD		787,380	234,561	1658,820	
	Percentiles	25	237.00	220.75	123.25	
		50	378.00	356.00	242.00	
		75	588.25	476.50	506.50	
CD+4 T-cell count group, cell/mm^3	≤200 >200		103 (20.5)[a] 399 (79.5)[a]	48 (24.5)[ab] 148 (75.5)[ab]	20 (33.3)[b] 40 (66.7)[b]	**0.049**
Exist of sexually transmitted diseases, n (%)	None Exist		38.1 (75.9)[a] 12.1 (24.1)[a]	178 (90.8)[b] 18 (9.2)[b]	55 (91.7)[b] 5 (8.3)[b]	**<0.001**
Sexually transmitted diseases status, n (%)	HPV Leishmaniasis Syphilis Syphilis + HPV		13 (2.6)[a] 0 (0.0)[a] 107(21.3)[a] 1 (0.2)[a]	1 (0.5)[ab] 0 (0.0)[a] 17 (8.7)[b] 0 (0.0)[a]	0 (0.0)[b] 1 (1.7)[b] 4(6.7)[b] 0 (0.0)[a]	**<0.001**
Opportunistic infections status, n (%)[b]	TBC PCP CMV PML		13 (20.9) 4 (30.8) 5 (38.5) 4 (30.8) -	9 (4.6) 4 (30.8) 3 (33.3) - 2 (22.2)	2 (3.3) 1 (50.0) 1 (50.0) - -	0.390
Malignancy status, n (%)[b]			9 (1.8)	5 (2.6)	3 (5.0)	0.198

*Kruskal-Wallis test, [a]Pearson chi-square test, [b]Fisher-Freeman-Halton test, CMV: Cytomegalovirus, HBV: Hepatitis B, HCV: Hepatitis C, HIV: Human immunodeficiency virus, IVDU: Intravenous drug use route, PCP: Pneumocystis jiroveci pneomonia, PML: Progressive multifocal leukoencephalopathy, SD: Standart deviation, TBC: Mycobacterium tuberculosis, HPV: Human papillomavirus

HIV + HBV group, the frequency of those with HIV-RNA <1+E5 copies/mL was significantly lower than in the HIV group, but the other group differences were insignificant. In the HIV + HCV group, the frequency of HIV-RNA between 1+E5-2+E5 copies was significantly higher than in the other two groups (p=0.004). In the HIV + HBV group, the frequency of HIV-RNA loud >5+E5 documents was substantially higher than in the HIV group only (p=0.004).

There was a significant difference between HIV and HIV + HBV (p=0.003) and HIV + HCV (p=0.010) in CD4+ T-cell count. It was seen that the mean CD4+ T-cell count in the HIV + HBV group was significantly lower than in the other two groups. The rate of those with CD4 count ≤200 cells/mL in the HIV + HCV group was considerably higher than the group with only HIV, and the frequency of those with >200 cells/mL was significantly lower (p<0.001).

The frequency of other sexually transmitted co-infections in the HIV + HCV and HIV + HBV groups was significantly lower than in the HIV group. The source of this was syphilis infection (p<0.001).

HIV-1 RNA load and CD4 count were expressed as categorical, with a significant difference between the groups in both cases. However, there was no significant difference between the mean age and age distribution groups.

Significant results are defined above in Table 1. These are univariate test results, and the features found to be substantial were modeled together, and the comparison of the three groups was re-evaluated with the multivariate model. The results obtained are given in Table 2.

Comparing HIV + HBV vs. HIV, the incidence of HIV + HBV in men was significantly higher by 2,298 times (p=0.007). In addition, the frequency of HIV + HBV in those with other sexually transmitted co-infections was markedly lower by 0.313 times (p<0.001). Apart from this, no other difference was observed compared to HIV + HBV and HIV.

Comparing HIV + HCV vs. HIV, HIV + HCV frequency was found to be 2.773 times higher in those with HIV-1 RNA loads between 1.0+E5-2.0+E5 compared to those with HIV-1 RNA load <1.0+E5 (p=0.023). In addition, the frequency of HIV + HCV in "homosexual, heterosexual and unknown" transmission routes was significantly lower than those transmitted through IVDU (p<0,001). Apart from this, no other difference was observed compared to HIV + HCV and HIV.

Discussion

This is the first national study of HIV-HBV and HIV-HCV co-infected individuals characterizing HBV, HCV, and HIV parameters. This study analyses the effect of HBV and HCV infection on HIV infection. Characterizing HBV and HCV in HIV-infected patients advances our understanding of HBV and HCV in this setting to focus on HIV treatment efforts.

As epidemiological characters, there were significant changes in gender and nationality in our study. The number of women and non-Turkish individuals in HCV + HIV co-infected patients was higher than in the other two groups. In addition, in multivariate analysis, the number of men was more elevated in HBV + HIV patients. We found 63% of HCV + HIV co-infected patients from Central Asia and the Russian Federation (data not shown). In Central Asia, including Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan, the pooled mean prevalence of HCV infection was 13.5% [95% confidence interval (CI): 10.9-16.4%] among non-specific clinical populations and 51.3% (95% CI: 46.9-55.6%) among people who inject drugs (21). Since their independence from the Soviet Union, public health and healthcare infrastructure have deteriorated in these countries, resulting in a re-emergence of infectious diseases, making it the region with one of the highest HCV prevalence levels worldwide (22,23,24). In our study, 23.3% of 60 HCV + HIV patients were IVDUs, taller and more significant

Table 2. Multivariate analysis of factors affecting HBV and HCV infection in HIV-infected people

			Patient with coinfection					
			HIV + HBV			**HIV + HCV**		
Variable	**Risk**	**Reference**	**OR**	**p-value**	**95% CI**	**OR**	**p**	**95% CI**
Nationality	Turkish	Non-Turkish	0.511	0.102	0,228-1,142	0.144	**0.001**	0.059-0.351
Gender	Male	Women	2,298	0.007	1,251-4,224	0.791	0.569	0.353-1,772
Presence of malignancy	Exist	None	1,313	0.642	0.416-4,145	3.446	0.095	0.807-14,713
HIV-1 RNA load, copies/mL	1.0+E5-2.0+E5	<1.0+E5	1,572	0.121	0.888-2,781	2.773	**0.023**	1,152-6,673
	2.0+E5-5.0+E5	<1.0+E5	1,535	0.132	0.879-2,680	0.891	0.844	0.282-2,814
	>5.0+E5	<1.0+E5	2,131	0.001	1,371-3,313	1.461	0.399	0.605-3,531
CD4+ T-cell count, cells/mm^3	>200	≤200	1,098	0.666	0.717-1,682	0.708	0.349	0.343-1,460
Presence of coinfection	Exist	None	0.313	**0.001**	0.183-0,537	0.383	0.096	0.124-1,187
HIV-1 transmission route	MSM	IVDU	0.762	0.828	0.066-8,750	0.010	**0.001**	0.002-0.057
	Heterosexual	IVDU	1,212	0.877	0.106-13,805	0.026	**0.001**	0.005-0.131
	Unknown	IVDU	0.486	0.588	0.036-6,632	0.018	**0.001**	0.002-0.157
	Intercept	-	-	0.367	-	-	**0.001**	-

CI: Confidence interval, p: p-value, OR: Odds ratio, MSM: Men who have sex with men, HBV: Hepatitis B virus, HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

than the other two groups (p<0.001). The route of homosexual transmission was more elevated in HIV monoinfected patients than the others. WHO estimated that 52% of the 15.6 million global PWID have evidence of hepatitis C exposure (25). In Central Asia, the number of PWID is higher (26). Viral hepatitis is not circulating in the homosexual community, so it may follow individuals carefully in Turkey.

We found that HIV-infected men were more affected by HBV than HCV women. In some studies, similar results were reported (27,28,29). Interestingly, both HCV and HIV mono-infected individuals generally predominate in the male population (30,31,32). On the other hand, there are conflicting reports regarding the high incidence of infection in male or female individuals. This is not apparent but may be due to different methodological methods or epidemiological differences in study populations. Higher incidence in males than females in HIV-positive patients co-infected with HBV or HCV; may be related to problems where men are more likely to develop risky behaviors and men have higher rates of homosexuality and injecting drug use than women (33,34). According to age groups, there was no difference between the three groups in this study. However, it was observed that the prevalence increased with age in all three groups and peaked in the groups, especially in the 30-39 age range. These findings concord with those reported previously (35,36,37). This may be because younger patients are more exposed to risky behaviors than older patients.

In our study, HIV-1 RNA load was higher in HBV/HIV co-infected patients. HIV infection adversely affects all stages of the natural history of hepatitis B, leading to increased persistent infection rates, higher HBV-DNA levels, lower rates of hepatitis B e antigen loss, and increased liver-related complications and death rates at low CD+4 T-cell counts (38). Whether HBV infection does affect HIV infection is not well known. Before the general availability of highly active antiretroviral therapy, clinical studies evaluating the impact of HBV on HIV progression have shown inconsistent results (39,40). Some studies have found no difference in HIV progression between those with and without chronic HBV (41,42). It has been suggested that a persistent immune activation state may upregulate HIV replication in patients with chronic HBV infection (41,42). Patients co-infected with HIV/HBV have been shown to have a 3.6 - to 6.8 - fold risk of progression to AIDS in early prospective cohort studies compared to those without co-infection (39,43). In the Swiss HIV Cohort Study; the negative impact of HBV on HIV has been demonstrated: It has been shown that HBsAg-positive patients have significantly impaired CD4+ T-cell recovery in the first three years of antiretroviral treatment compared to HIV-positive patients without HBV infection, despite similar virological efficacy of antiretroviral therapy (44). A recent study has observed that anti-HBc in HBV + HIV co-infected patients hurts the CD4/CD8 ratio increase. In the subset of patients with low immune status, a significant increase in CD8+ T-cell counts was also demonstrated up to 24 months after initiating effective antiretroviral therapy (45). We also found an immunological difference in HBV/HIV co-infected patients; the immunological effect of HBV on HIV should be kept in mind in planning the treatment of HIV patients co-infected with HBV and in the follow-up of these patients.

In the subgroup analysis, the number of HCV + HIV co-infected patients was higher than the CD4+ T-cell count of ≤200 cells/mm^3. Chun et al. (46) had found that untreated HIV-positive patients with and without anti-HCV antibodies at the time of HIV diagnosis had an increased risk of AIDS or death to a similar extent. Similar results had been shown in the other studies (47,48,49). In one study, a higher CD4+ T-cell count (>200 cells/μL) was associated with a reduced risk of HIV-positive patient co-infection with HCV or HBV (50). In that study, increased differentiation was observed in CD4+ Th17 effector cells in HCV-infected hepatocytes. It was stated that this might cause HCV negatives to have higher CD4+ T-cell counts than positives. Although there have been different immunological results in HCV + HIV co-infected patients, this may lead to the hypothesis that treating HCV during the treatment of these patients will result in immunological recovery by increasing the CD4+ T-cell count.

We found that the frequency of syphilis co-infection was higher in the HIV monoinfected group than in the other two groups. This can be interpreted as HBV and HCV in HIV-infected patients reducing the risk of a second co-infection. Virus-virus interactions strongly influence co-infection; in the most comprehensive superinfection exclusion test to date, prophage arrays reduced culture co-infection by other prophages and had a weaker effect on extrachromosomal virus co-infection (51). The presence of viral co-infections minimizes the risk of bacterial co-infection. The relationship between HIV and syphilis can be explained by behavioral factors and genital ulceration facilitating HIV transmission in syphilis patients (52). HIV syphilis co-infection rates vary between 8-25% (53,54,55). HIV serology in syphilis patients and syphilis serology in HIV patients should be screened. In HIV-positive patients co-infected with HBV and HCV, syphilis screening should be performed, although syphilis was found less common in our study.

Conclusion

We found differences in our HIV-infected patients co-infected with HBV or HCV in gender, nationality, transmission routes, HIV viral load, and CD+4 T-cell count. Our findings may indicate that HBV and HCV may affect HIV infections. Our approach can focus on these points in co-infected patients, and we can effectively manage their treatment and follow-up.

Ethics

Ethics Committee Approval: Ethics committee approval for this study was obtained from the Kocaeli University Clinical Studies Ethics Committee (approval number: KOU KAEK 201345).

Informed Consent: Patients' informed consent couldn't be required due to the study's retrospective design.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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Evaluation of Direct-acting Antiviral Agents and Clinical Responses in Chronic Hepatitis C Patients

Kronik Hepatit C Hastalarında Doğrudan Etkili Antiviral Ajanların ve Klinik Yanıtların Değerlendirilmesi

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ABSTRACT

Objectives: Direct-acting antiviral (DAA) agents have made a breakthrough for treating chronic hepatitis C virus (HCV) with their high efficacy and tolerability. In this study, the end of treatment response of DAA treatment regimens was analyzed with respect to epidemiological data.

Materials and Methods: A total of 143 patients, over 18 years of age, who were treated with the diagnosis of HCV infection were analyzed retrospectively. The comorbid diseases, co-infection status (hepatitis B virus and human immunodeficiency virus-co-infection), genotype distribution and transmission routes were noted. The changes in the laboratory parameters were evaluated before treatment, at the first month and at the end of treatment and after treatment at the 12th week.

Results: When the genotype distributions of the patients were examined, it was found that 75.5% of the patients (n=108) were genotype-1, 4.2% (n=6) were genotype-2, 12.6% (n=18) were genotype-3, 4.9% (n=7) were genotype-4, and 1.4% (n=2) were genotype-5. The treatment regimens of the patients were; paritaprevir + ritonavir + ombitasvir + dasabuvir in 54 (37.8%) patients, ledipasvir + sofosbuvir in 28 (19.6%) patients, glecaprevir + pibrentasvir in 23 (16.1%) patients, and paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin (RBV) in 15 (10.5%) patients. Dose reduction was implemented in 31 patients who received RBV treatment. Adverse events were observed in 49.7% (n=71) n of the study population. The rate of sustained viral response-12 (SVR12) was 100% in all treatment regimens.

Conclusion: Achieving a SVR12 in chronic HCV decreased all-cause mortality, whether liver-related or unrelated. Second-generation DAAs have been a beacon of hope for humanity in this regard.

Keywords: Sustained viral response, direct-acting agents, HCV, genotype, adverse events

ÖZ

Amaç: Direkt etkili antiviraller (DAA), yüksek etkinlikleri ve tolere edilebilirlikleri ile kronik hepatit C virüs (HCV) tedavisinde çığır açmıştır. Bu çalışmada, DAA tedavisi alan hastaların epidemiyolojik verileri ve tedavi sonu yanıtları analiz edilmiştir.

Gereç ve Yöntemler: HCV enfeksiyonu tanısı ile tedavi edilen 18 yaş üstü toplam 143 hasta retrospektif olarak incelendi. Komorbid hastalıklar, ko-enfeksiyon durumu (hepatit B virüsü ve insan bağışıklık yetmezlik virüsü-ko-enfeksiyonu), genotip dağılımı ve bulaşma yolları not edildi. Laboratuvar parametrelerindeki değişiklikler tedavi öncesi, tedavinin ilk ayı ve sonunda ve tedavi sonrası 12. haftada değerlendirildi.

Bulgular: Hastaların genotip dağılımları incelendiğinde hastaların %75,5'inin (n=108) genotip-1, %4,2'sinin (n=6) genotip-2, %12,6'sının (n=18) olduğu bulundu. Genotip-3, %4,9 (n=7) genotip-4 ve %1,4 (n=2) genotip-5 idi. Hastaların tedavi rejimleri; 54 hastada (%37,8) paritaprevir + ritonavir + ombitasvir + dasabuvir, 28 hastada (%19,6) ledipasvir + sofosbuvir, 23 hastada (%16,1) paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin (RBV) (%10,5) idi. RBV tedavisi alan 31 hastada doz azaltımı uygulandı. Yan etki çalışma popülasyonunun %49,7'sinde (n=71) gözlenmiştir. Tüm tedavi rejimlerinde kalıcı virolojik yanıt-12 (SVR12) oranı %100 idi.

Sonuç: Kronik HCV'de SVR12'nin elde edilmesi, karaciğerle ilişkili veya ilişkisiz tüm nedenlere bağlı ölümleri azaltmıştır. İkinci nesil DAA'lar bu konuda insanlık için bir umut ışığı olmuştur.

Anahtar Kelimeler: Kalıcı virolojik yanıt, direkt etkili antiviraller, HCV, genotip, yan etki

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Introduction

The prevalence of chronic hepatitis C virus (HCV) infection over the globe is between 1.2-1.7%. The prevalence of HCV in Turkey has been reported as 1-2%. The lack of an effective vaccine and serious consequences such as cirrhosis and hepatocellular cancer still poses an important research area worldwide (1,2).

While standard alpha interferon was used in the treatment of chronic HCV infection in the previous years, then the combination of pegylated interferons and ribavirin (RBV) has been used. These treatment options achieved 40-50% sustained viral response (SVR) (3,4). However interferon treatments have always caused compliance problems for patients since they were administered in the form of injections. In addition, flu-like symptoms, hemolytic anaemia and adverse psychiatric effects were other common side effects (4). This situation revealed the expectations of oral therapy in terms of better SVR rates, shorter duration of treatment and ease of use both in patients and clinicians.

The American Association for Liver Diseases Research and the American Infectious Diseases Society have stated in their HCV guidelines that direct-acting antiviral (DAAs) can be used in all chronic HCV patients who are likely to live longer than 12 months (5,6). The possibility of developing potential drug-related undesirable effects is also important for the sustainability of the treatment continuation. New treatment regimens (DAAs) present improved efficacy and a better safety profile (7).

Grade of liver fibrosis, decompensated cirrhosis, accompanying conditions (such as cryoglobulinemia, lymphoma) or special patient groups [human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection, hemodialysis, diabetes, pregnancy, drug addiction, liver transplant patients, etc.] are other factors that should be considered in the treatment process (3).

In this study, we aimed to present the epidemiological data and treatment outcomes of 143 patients who received DAAs.

Materials and Methods

A total of 143 patients, over 18 years of age, who were treated with the diagnosis of chronic HCV in the Infectious Diseases Outpatient Clinic of University of Health Sciences Turkey, Haseki Training and Research Hospital between 1 July 2016 and 1 September 2020, and who were admitted to their follow-up visits in the 12th week after the end of the treatment were analyzed retrospectively.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all participants. The study was approved by Ethics Committee University of Health Sciences Turkey, Haseki Training and research Hospital (approval number: 2020-180; date: 23.09.2020).

The comorbid diseases of all individuals (diabetes mellitus, hypertension, heart disease, chronic renal failure, thyroid disease, cirrhosis) have been examined. Additionaly, co-infection status (HBV and HIV co-infection) and transmission routes were noted. HCV genotype analyzes were conducted.

HCV-RNA, hemogram and biochemical parameters [urea, creatinine, aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase, total protein, albumin, total bilirubin, alpha-fetoprotein, prothrombin time, international normalized ratio) measured before treatment, at 4th week, end of treatment and 12th week after the end of treatment. The changes in the laboratory parameters of the patients as a result of the selected treatment were evaluated.

Statistical Analysis

Patient data collected within the scope of the study were analyzed with the IBM SPSS for Windows 23.0 (IBM Corp., Armonk, NY) package program. Frequency and percentage for categorical data, mean and standard deviation for continuous data were given as descriptive values.

For comparisons between groups, "Independent sample t-test" was used for two groups, and the "Pearson chi-square test" was used for the comparison of categorical variables. The results were considered statistically significant when the p-value was less than 0.05.

Results

A total of 143 patients have been enrolled in this retrospective analysis. The most prevalent HCV genotype was genotype 1 detected in 77.5% of the patients. The distribution of demographic and clinical findings of the patients was denoted in Table 1.

Patients with HBV co-infection consisted of 4.2% (n=6) of the individuals and 3 of these subjects were chronic HBV patients and 3 of them were inactive carriers. Additionally, 28 patients were (19.6%) anti-hepatitis B surface antigen (anti-HBs) (+) and were anti-hepatitis B core antigen (anti-HBc) immunoglobulin G (+). Three of our patients has been initiated chronic HBV treatment as they met the criteria and their medication still continued. Three of our patients did not receive any medication although they were HBsAg (+) and no reactivation developed after the end of treatment. HBV-DNA was negative in one patient at the end of treatment but became >2000 IU/mL in the follow-up however, AST and ALT values did not increase.

There were 4 patients (2.8%) with HIV co-infection. Treatment was changed in 2 patients due to drug interactions. As a treatment, 2 of our patients were taking tenofovir disoproxil fumarate + emtricitabine + dolutegravir, and one patient was taking tenofovir disoproxil fumarate + emtricitabine + lopinavir/ritonavir, and one patient was taking abacavir + lamivudine + dolutegravir. As hepatitis C treatment, 2 patients received sofosbuvir/ledipasvir (SOF/LDV), and one patient received glecaprevir/pibrentasvir (GLE/PIB), and one patient received SOF/velpatasvir treatment.

Cirrhosis has been observed in 5.6% (n=8) patients and all cases were compensated (Child-Pugh A).

Four patients with chronic renal failure who did not need dialysis, 1 received paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD) + RBV and 3 received GLE/PIB. There was no deterioration in urea-creatinine values during the treatment and they did not need dialysis.

Table 1. Distribution of demographic and clinical findings of the patients

Characteristics (n=143)	n (%) or median ± SD
Gender	
Female	82 (57.3)
Male	61 (42.7)
Age	53±15
Height	165.8±10.1
Weight	75.1±13.9
BMI	27.4±5.2
HBV coinfection	6 (4.2)
Inactive carrier	3 (50.0)
Chronic HBV	3 (50.0)
Anti-HBs (+), anti-HBc IgG (+)	28 (19.6)
Anti-HIV (+)	4 (2.8)
Cirrhosis	8 (5.6)
Compensated (Child-Pugh A)	8 (100.0)
Genotype	
1	108 (75.5)
1b + 4	2 (1.4)
2	6 (4.2)
3	18 (12.6)
4	7 (4.9)
5	2 (1.4)
Genotype-1 subgroup	
1a	18 (16.7)
1b	88 (81.5)
Not determined	2 (1.8)
Biopsy	75 (52.4)
Biopsy HAI	6.2±2.4
Biopsy fibrosis score	1.8±1.1
Known transmission cause	83 (58.0)
Transmission cause	
Surgery	19 (22.9)
Transfusion	17 (20.5)
Surgery + transfusion	10 (12)
Intravenous substance use	14 (16.9)
Medical intervention	10 (12)
Dental operation	6 (7.2)
Family spread	5 (6.0)
Sexual intercourse	2 (2.4)
Comorbidities	
Renal disease	13 (9.1)
Cardiac disease	18 (12.6)
Hypertension	37 (25.9)
Thyroid disease	13 (9.1)
Diabates mellitus	23 (16.1)

SD: Standard deviation, BMI: Body mass index, HBV: Hepatitis B virus, HBs: Hepatitis B surface antigen, IgG: Immunoglobulin G, HIV: Human immunodeficiency virus, HAI: Histological activity index

The distribution of laboratory parameters collected during and at the end of 12th week treatment period has been elaborated in Table 2.

The most common regimen used in treatment was PROD. The distribution of the treatment process was given in Table 3.

The rate of SVR12 was 100% in all treatment regimens.

Adverse effects were observed in 49.7% (n=71) of the 143 patients included in the evaluation. A total of 96 side effects were detected in 71 patients. A wide variety of these side effects were dermatologic (hair loss), gastrointestinal (diarrhoea, abdominal pain, distension) and muscle joint pain. Side effect distribution was shown in Table 4. Since the drug use was not the same in every patient the occurrence of side effects was also different. There was no statistically significant difference between the drugs in terms of side effects. A majority of our patients have been given PrOD and SOF/LDV treatment, side effects were mostly observed in these two groups.

Discussion

Viral hepatitis is an important public health problem all over the globe. HCV and chronic alcohol consumption are the most common causes of chronic liver disease in Western society while it is chronic viral hepatitis due to HBV and HCV in our country. Viral hepatitis viruses lead to increased morbidity and mortality by causing acute-chronic viral hepatitis, cirrhosis, liver failure and liver cancer (2).

PegIFN and RBV which were previously used in the treatment of HCV had low efficacy and high side effect profile. However, new treatment regimens (DAAs) present improved efficacy and a better safety profile (7). SVR rates have been reported to be over 90% in chronic HCV patients receiving DAA treatment (8). The rate of SVR12 was 100% in all treatment regimens and no recurrence was observed in our study.

In patients with chronic HCV genotype-1 and 4, Ombitasvir/paritaprevir/ritonavir ± dasabuvir ± RBV have been found to be well tolerated and highly effective in clinical trials (9,10). In a study conducted in chronic HCV genotype 1b treatment-naive and unresponsive non-cirrhotic patients in with PrOD SVR12 rates were 95.2% and 90%, respectively. In the same study, treatment-naive and treatment-experienced patients with cirrhosis SVR12 rates were 97.9% and 96.2%, respectively (9). In our study, we have achieved 100% SVR with ombitasvir/paritaprevir/ritonavir ± dasabuvir ± RBV.

In a study from Turkey, the overall SVR rate in genotype-1 patients was 96.4%, and the treatment SVR rate 98.2% in treatment with PrOD ± RBV while it was 96% in treatment with SOF + LDV ± RBV (11). Çakır (12) published that the rate of SVR24 was determined as 100% in HCV genotype-1a and genotype-4 patients who we were treated with PrOD ± RBV for 12 weeks. Ioannou et al. (13) found the rate of viral response as 92.8% in 13,974 patients with genotype-1 who were administered SOF/LDV or PrOD treatments. In this study, no significant difference was found between the treatment regimens. We have achieved 100% SVR with both PrOD ± RBV and SOF/LDV ± RBV in genotype 1 patients.

Table 2. Distribution of patients' laboratory values

Laboratory parameteters	Baseline (median ± SD)	First month (median ± SD)	Treatment end (median ± SD)	SVR12 (median ± SD)
HCV-RNA	7609577.6±12263951	0±0	0±0	0±0
AST	47.4±33.4	21.8±8	20.4±8.2	21.1±15.7
ALT	56.9±54	18.1±11.3	15.4±8.2	15.3±12.5
Albumin	4.2±0.4	4.2±0.4	4.2±0.4	4.2±0.3
Total bilirubin	0.7±0.4	0.9±0.6	0.7±0.5	0.8±1.8
INR	0.9±0.3	0.9±0.2	1±0.9	1±0.9
AFP	5±4.4	3.9±2.7	3.5±2.8	3.9±7.3
ALP	91.9±47.6	95.2±44.6	104.4±115.7	85.2±34.7
GGT	76.1±258.2	58.1±284.8	27.3±66.7	32±115.7
Urea	35.7±24.6	36.3±26.1	35.4±21.9	36.5±30.1
Creatinine	1.1±1.5	1.1±1.6	1.1±1.4	1.1±1.5
WBC	7.2±2.0	7.6±2.1	7.5±2.2	7.3±1.9
HCT	40.6±5.8	39.8±4.7	39.4±5.1	40.4±7.4
PLT	227.1±66.9	241.6±78.4	246.5±80.0	238.2±62.9
PT	12.1±3.1	11.8±2	11.8±1.1	11.9±1

SD: Standard deviation, HCV: Hepatitis C virus, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, INR: International normalized ratio, AFP: Alpha-fetoprotein, ALP: Alkaline phosphatase, GGT: Gamma-glutamil transferase, WBC: White blood cell, HCT: Hematocrit, PLT: Platelet, PT: Prothrombin time, SVR12: Sustained viral response-12

Table 3. Distribution of treatment and treatment processes

Characteristics (n=143)	n (%) or median ± SD
Previous treatment	22 (15.4)
Recurrence	13 (59.1)
Not responding to treatment	9 (40.9)
Previous treatment regimens	
PR	20 (90.9)
Telaprevir + PR	1 (4.5)
Sofosbuvir + ribavirin	1 (4.5)
Final treatment	
Paritaprevir + ritonavir + ombitasvir + dasabuvir	54 (37.8)
Ledipasvir + sofosbuvir	28 (19.6)
Glekaprevir + pibrentasvir	23 (16.1)
Paritaprevir + ritonavir + ombitasvir + dasabuvir + ribavirin	15 (10.5)
Sofosbuvir + ribavirin	8 (5.6)
Ledipasvir + sofosbuvir + ribavirin	7 (4.9)
Sofosbuvir + daclatasvir	3 (2.1)
Sofosbuvir + velpatasvir	3 (2.1)
Paritaprevir + ritonavir + ombitasvir + ribavirin	1 (0.7)
Sofosbuvir	1 (0.7)
Ribavirin dose reduction	3 (9.7)
Ribavirin early discontinuation	3 (9.7)
Study duration (12 weeks)	12.9±4.8
Side effects	71 (49.7)

SD: Standard deviation, PR: Pegylated interferon + ribavirin

In clinical trials the SVR12 was 95% with GLE/PIB, regardless of RBV coadministration, and was not affected by the previous treatment regimen or the presence of baseline resistance-associated substitutions. SVR12 rates of 100% and 94% have been achieved with no virological relapses. The GLE/PIB treatment is safe and well tolerated, regardless of treatment duration (12 or 16 weeks), and there were no adverse effects that led to study drug discontinuation (14). In our study, we have achieved 100% SVR with GLE/PIB.

Many studies have shown that IFN-free treatment regimens in HCV in chronic renal failure are effective and safe, regardless of Genotype, viral load, cirrhosis status, and whether RBV is used (15,16). Elbasvir-grazoprevir and PrOD are among the DAA treatment regimens that can be used in patients with advanced chronic renal failure (17). In a multicenter study evaluating the treatment of PrOD in patients with chronic renal failure, 90% of SVR-12 was achieved with 12 weeks of treatment in genotype-1, non-cirrhotic chronic HCV patients. The researchers did not observe any significant side effects during the treatment and concluded that PrOD treatment can be utilized safely in patients with stage 4 and 5 chronic renal failure without requiring dose adjustment (15). In our study CRF patients have been treated via PrOD or GLE/PIB and 100% SVR12 has been achieved and no significant side effects were observed during treatment.

Patients with HIV co-infection should also be emphasized in terms of the treatment they receive. Drug interactions should be kept in mind when using DAA as interactions with potential drugs may affect adherence to treatment. In our study, we had to implement amendments in the treatment regimens of patients with HIV co-infection due to drug interactions.

Tenofovir nephrotoxicity can develop in the use of SOF/LDV (5). In our study nephrotoxicity did not develop in 3 patients

Table 4. The side effects exposed during treatment

	Side effects n (%)	Details of side effect
1. Gastrointestinal	**36 (37.5)**	-
Change in appetite	6 (6.25)	-
Distension	6 (6.25)	-
Nausea	6 (6.25)	-
Diarrhoea	5 (5.2)	-
Abdominal pain	4 (4.16)	-
Constipation	2 (2.08)	-
Other	7 (7.2)	Belching (1), sternal burning/reflux (1), weight loss (2), reflux (1), diarrhea (1), weight gain (1)
2. Dermatological	**17 (17.7)**	-
Itching	7 (7.2)	-
Other	10 (10.4)	Hair loss (2), gingival itching (1), folliculitis (1), acne (3), dry skin (1), eczema (2)
3. Muscle-joint pain	**13 (13.5)**	-
4. CNS side effect	**7 (7.2)**	Changes in sleep patterns (3), dizziness (2), balance problem (1), forgetfulness (1)
5. Depression	**5 (7.2)**	-
6. Get Angry Quickly	**4 (4.1)**	-
7. Shortness of breath	**3 (3.1)**	-
8. Other	**11 (11.4)**	Palpitation (2), menstrual irregularity (1), increased need for suboxone (1), increased spontaneous bleeding (1), cough (2), sweating (2), urine redness (1), chills in the arm with fistula (1)
Total	**96**	-

with HBV-HCV co-infection who were treated with tenofovir disoproxil fumarate and 2 patients with HIV-HCV co-infection who were treated with tenofovir disoproxil fumarate + emtricitabine combination.

According to EASL chronic HCV Guideline (2018) it was stated as "Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post-anti-HCV therapy and be monitored monthly if HBV treatment is stopped (B1). In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly to detect possible reactivation (B1) (18). In our study, three of our patients did not receive any medication although they were HBsAg (+) and no reactivation developed after the end of treatment.

In a study from Turkey, the most common adverse events were pruritus (22.2%), fatigue (17%) and headache (19.8%) (11). In our study, the most common adverse events with a rate of 37% were gastrointestinal side effects (diarrhoea, abdominal pain, distension). We did not detect severe side effects and none of these had deteriorated the quality of life of the patients due to treatment. No hospitalisation occurred due to adverse events. We have observed laboratory parameter deviations in subjects using PrOD treatment however, the variables were statistically insignificant.

Study Limitations

The main limitation of this study could be attributed to its retrospective nature. Secondly, we had a relatively small sample size. The strength of this article lies beneath the fact that it merged epidemiological, biochemical and treatment-related parameters of a certain period.

Conclusion

Achieving a SVR in chronic HCV decreased all-cause mortality whether liver-related or unrelated. Second-generation DAAs have been a beacon of hope for humanity in this regard. DAAs have made a breakthrough in the treatment of chronic HCV with their high efficacy and tolerability. Time will elaborate on whether there will be a relapse after the follow-ups.

Ethics

Ethics Committee Approval: The study was approved by Ethics Committee University of Health Sciences Turkey, Haseki Training and research Hospital (approval number: 2020-180; date: 23.09.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.Z., Design: E.Z., Supervision: E.Z., Materials: E.Z., İ.Y.N., Data Collection or Processing: E.Z., İ.Y.N., Analysis or Interpretation: E.Z., İ.Y.N., Literature Search: E.Z., İ.Y.N., F.P., Writing: E.Z., F.P., Critical Review: E.Z., F.P.

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Research Article

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Investigation of the Effects of Total Oxidative Stress and Total Antioxidant Capacity on the Prognosis in Patients with Chronic Viral Hepatitis B

Kronik Viral Hepatit B Hastalarında Total Oksidatif Stres ve Toplam Antioksidan Kapasitenin Prognoza Etkilerinin Araştırılması

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ABSTRACT

Objectives: Experimental studies showed the role of oxidative stress in cell destruction and DNA damage in chronic viral hepatitis, In this study, oxidative stress was measured in various clinical forms of chronic hepatitis B (CHB) and the role of oxidative stress was investigated in the development of hepatitis clinic.

Materials and Methods: In total, 33 patients with inactive hepatitis B carrier (IHBC), 33 patients with active CHB infection, and 33 healthy adults were included in the study. Serum transaminases [alanine aminotransferase (ALT), aspartate aminotransferase, total antioxidant capacity, and total oxidative stress (TOS)] were measured and compared in the patient groups.

Results: In 99 patients were included in the study (56 men, 43 women). The mean age of patients in CHB was 33.21±10.20, in IHBC 36.73±11.54, and the control group 33±11.71. The mean ALT value was 40.93±28.28 U/L in the patients with CHB and 36.33±28.99 U/L in the patients with IHBC. The TOS value115.46±139.64 μm H_2O_2 equivalent/L in the CHB and 52.67±40.36-μm H_2O_2 equivalent/L in IHBC.

Conclusion: ALT and TOS levels were significantly higher in the CHB than in the other groups. The increased TOS levels in the CHB may be related to the activity of cell destruction in active cases.

Keywords: Hepatitis B virus, total oxidative stress, total antioxidant capacity, liver fibrosis

ÖZ

Amaç: Deneysel çalışmalar, kronik viral hepatitlerde hücre yıkımında ve DNA hasarında oksidatif stresin rolünü göstermiştir. Bu çalışmada, kronik hepatit B'nin (KHB) çeşitli klinik formlarında oksidatif stres ölçülmüş ve hepatit kliniğinin gelişiminde oksidatif stresin rolü araştırılmıştır.

Gereç ve Yöntemler: Çalışmaya toplam 33 inaktif hepatit B taşıyıcısı (İHBC), 33 aktif KHB enfeksiyonu hastası ve 33 sağlıklı yetişkin dahil edildi. Hasta gruplarında serum transaminazları [alanin aminotransferaz (ALT), aspartat aminotransferaz, toplam antioksidan kapasite ve toplam oksidatif stres (TOS) ölçüldü ve karşılaştırıldı.

Bulgular: Toplam 99 hasta (56 erkek, 43 kadın) çalışmaya dahil edildi. Hastaların yaş ortalaması KHB'de 33,21±10,20, İHBC'de 36,73±11,54 ve kontrol grubunda 33±11,71 idi. Ortalama ALT değeri KHB'li hastalarda 40,93±28,28 U/L, İHBC'li hastalarda 36,33±28,99 U/L idi. TOS değeri CHB'de 115,46±139,64 μm H_2O_2 eşdeğeri/L ve IHBC'de 52,67±40,36 μm H_2O_2 eşdeğeri/L bulundu.

Sonuç: ALT ve TOS seviyeleri KHB'de diğer gruplara göre anlamlı derecede yüksek seyretmektedir. KHB'deki artan TOS seviyeleri, aktif olgularda hücre yıkımının aktivitesi ile ilişkili olabilir.

Anahtar Kelimeler: Hepatit B virüs, toplam oksidatif stres, toplam antioksidan kapasite, karaciğer fibrozu

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Introduction

Hepatitis B virus (HBV) is one of the most important pathogens that lead to fibrosis, cirrhosis, and hepatocellular cancer through the damage it causes in the hepatic cells. Despite the efficient vaccine and the advanced diagnostic and treatment methods, 1.5 million people were newly infected with chronic hepatitis B (CHB) infection and 820,000 people are lost every year due to the complications of the HBV (1). However, the exact mechanisms for the pathogenesis of CHB have not been fully clarified.

In recent years, the relationship between oxidants and antioxidants has come into the spotlight and the imbalance among them was observed to play a greater role in cellular damage (2,3,4,5,6). As a part of the metabolic processes, the cells continuously produce free radicals and reactive oxygen species. These free radicals and reactive oxygen species are neutralized through the complex antioxidant system. Increasing oxidant levels or decreasing antioxidant levels disrupt this balance, this situation is called "oxidative stress" (7). The role of oxidative stress in cell destruction and in DNA and RNA damage in chronic viral hepatitis has been established in experimental studies (8). Free radicals show different chemical structures such as hydroxyl superoxide, nitric oxide, and lipid peroxide (9). This study aims to evaluate the total oxidative stress (TOS) and total antioxidant capacity (TAC) in the patients with different clinical forms of hepatitis B and the individuals in the healthy control group.

Materials and Methods

This prospective study was conducted between January 2012 and December 2013 on patients between the ages of 15-61 diagnosed with chronic viral hepatitis B. The patients were divided into three groups:

Group 1: Patients underwent a biopsy due to CHB;

Group 2: Inactive hepatitis B carriers (IHBC);

Group 3: Healthy controls.

Diagnostic criteria (10):

Group 1: CHB;

1. Hepatitis B surface antigen (HBsAg)-positive for more than 6 months,

2. Alanine aminotransferase (ALT) value greater than 1.5 times the normal value (normally, the ALT value is below 40 IU/mL),

3. HBV-DNA value ≥100,000 copies/mL (20,000 IU/mL) in those positive for the hepatitis B e antigen (HBeAg) (HBeAg-positive),

4. In those who are HBeAg-negative ≥10,000 copies/mL (2,000 IU/mL), and

5. Fibrosis ≥2 in the histopathological evaluation of the liver.

Group 2: IHBC;

1. HBsAg-positive,

2. Normal ALT values,

3. HBeAg-negative, and,

4. HBV-DNA ≤10,000 copies/mL (2,000 IU/mL)

The control group consisted of HBsAg-negative and anti-HBc-total negative patients. Patients with diabetes mellitus, liver cirrhosis, hypertension, coronary arterial disease, chronic obstructive pulmonary disease, malignancies, morbid obesity, liver and kidney failure, pregnant patients, those on corticosteroid treatment, and smokers were excluded from the study. Liver biopsy was performed in all patients with CHB and only the patient group that did not receive antiviral therapy was included in the study. The age, gender, HBsAg, HBeAg, anti-HBe, ALT, aspartate aminotransferase (AST), and HBV-DNA values of the patients were recorded. The fibrosis scores of the CHB patients who were applied biopsies were also recorded. The total oxidant status was determined using the automated measurement method developed by Erel (11). The results were expressed in terms of μm hydrogen peroxide equivalent per liter (μm H_2O_2 equivalent/L). The TAC was also determined using the automated method, developed by Erel (5). The results were expressed as micromol (μm) Trolox equivalent/L.

After the approval of the Dicle University Ethics Committee was obtained (approval number: 479, date: 28.03.2012), the TOS and TAC study was supported with the grant of the Dicle University Scientific Research Projects Coordinatorship. Informed consent was obtained.

Statistical Analysis

The obtained data were entered into the SPSS 15.0 statistics software. Categorical data were analyzed using the chi-square test. The normality of the distribution of the numeric data was tested through the Kolmogorov-Smirnov test. The normal data were analyzed with the help of the Student's t-test, while those outside the normal distribution were analyzed using the Mann-Whitney U test. Statistical significance was based on a value of $p<0.05$.

Results

A total of 99 patients divided into three groups of 33 patients were enrolled in the study. Among these patients, 56 (56.5%) were male, while 43 (43.5%) were female. No statistically significant difference in terms of mean age and sex was observed between the three groups (p=0.308, p=0.133, respectively). The characteristics (age, gender), ALT, TOS, and TAC values of the groups are presented in Table 1. While no significant difference in terms of the mean ALT values was observed between CHB and IHBC, the AST values were higher in CHB (p=0.020). When the mean TOS capacity was evaluated among the three groups, the highest level was observed in CHB. This difference was statistically significant (p=0.023). Only when CHB and IHBC were compared in terms of the TOS levels, the mean value in CHB was higher with a statistically significant result (p=0.017). No statistically significant relationship was observed among the mean TAC levels of the three groups (p=0.562). No relationship was observed between the fibrosis score, HBV-DNA, and the TOS and TAC values. No statistically significant relationship was evident between the HBV-DNA value and the TOS and TAC levels (Table 2).

Discussion

The infection caused by HBV manifests itself in various clinical forms from the asymptomatic form to fulminant hepatic failure. It is estimated that one-third of people with chronic HBV infection

Table 1. The clinical and demographic data of the study groups

	CHB (n=33)	IHBC (n=33)	Control group (n=33)	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	33.21±10.20	36.73±11.54	33.00±11.71	0.318
Gender (M/F)	21/12	21/12	14/19	0.133
TOS (μm H_2O_2 equivalents/L)	115.46±139.64	52.67±40.36	87.91±57.08	0.023[a]
TAC (μm Trolox equivalents/L)	1.47±0.24	1.46±0.20	1.42±0.18	0.562
ALT (U/L)	40.93±28.28	36.33±28.99	None	0.516
AST (U/L)	39.84±29.05	26.51±13.05	None	0.020*

CHB: Chronic hepatitis B, IHBC: Inactive hepatitis B carriers, TOS: Total oxidative stress, TAC: Total antioxidant capacity, ALT: Alanine transaminase, AST: Aspartate transaminase, [a]: There was a statistically significant difference between the CHB group and the other groups but no statistically significant difference between the IHBC group and the control group. *Statistically significant value (p<0.05)

Table 2. The correlation analysis of TAC, TOS with HBV-DNA and fibrosis score

	r (HBV-DNA)	p (HBV-DNA)	r (fibrosis score)	p (fibrosis score)
TOS	0.167	0.437	0.097	0.651
TAC	-0.189	0.377	0.294	0.162

TAC: Total antioxidant capacity, TOS: Total oxidative stress, HBV: Hepatitis B virus

developed liver cirrhosis or hepatocellular carcinoma as a result of long-term disease (12). Various studies have shown that TOS is increased in hepatitis B and hepatitis C infections, and liver disorders (13,14,15). When the generation of free radicals exceeds the antioxidant capacity, various metabolic and functional disorders may occur (16). An increase in oxidative stress leads to necrosis in the hepatocytes, paving the way for the development of fibrosis and cirrhosis in patients with untreated hepatitis C (17,18,19). In a study by Duygu et al. (20), the TOS value was observed to be higher in the groups with HBV infection compared to the HBV-free control group. In the same study, the TOS values in the patient group that have undergone biopsies after they were diagnosed with CHB were found to be higher than the IHBC patients. In another study comparing HBV positive and/or HCV positive, HBV-DNA and HCV-RNA negative individuals with the patients with proven chronic viral hepatitis, the TOS value was found to be significantly higher in the chronic viral hepatitis group (21). According to the results of our study, in line with other studies, the highest TOS value was observed in CHB. However, no statistically significant difference in terms of the TOS values was observed between IHBC and CHB.

TAC measurement is a method used to evaluate the scavenging capacity of free radicals and to estimate the antioxidant capacity *in vivo* (22). In a study comparing the TAC values, the TAC value in the healthy control group was found to be significantly higher compared to the CHB and IHBC groups (20). In the study by Sirmatel et al. (21), the TAC values were lower in the patients with HBV and HCV infections compared to the control group. A recent study revealed that a decrease in TAC and a high oxidative stress index may indicate an imbalance in redox status in HCV-infected patients (23). In our study, no significant result in TAC was observed among the three groups. The lack of difference in TAC levels between the groups can be partially explained by the homogeneity of the patients who underwent biopsy, the exclusion of cirrhotic patients, and the presence of moderate chronic active hepatitis in some patients. In the study by Duygu et al. (20), the relationship between the fibrosis score and the TOS and TAC values was evaluated and the results did not point to any association between the fibrosis score and the TOS and TAC scores. While the TOS score does not increase parallel to the fibrosis score, the TAC score was not observed to diminish either. Parallel to this study, also our study did not demonstrate a significant relationship between the fibrosis score and TOS and TAC values. In recent studies, TAC is a promising biomarker for evaluating the progression of liver fibrosis in patients with HBV, and this finding may indicate the involvement of TAC-composing factors in the pathogenesis of hepatic fibrosis in chronic HBV carriers (24).

Study Limitations

There are some limitations to our study. First, our study was limited to a single-center study, and we had a small number of patients. In addition, the patients were not grouped according to chronic HBV infection stages due to the small number of patients.

Conclusion

The high TOS capacity observed in our study is thought to be associated with HBV activity and disease progression. Further longitudinal and prospective studies are needed to elucidate the mechanisms of the pathophysiological role of TOS and TAC in CHB patients.

Ethics

Ethics Committee Approval: The study was approved by the Dicle University Clinical Research Board of Ethics (approval number: 479, date: 28.03.2012).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ç.M., Ö.D., S.C., İ.K., M.K.Ç., Concept: Ç.M., M.B., Ö.D., S.C., İ.K., M.K.Ç., Design: Ç.M., M.B., Ö.D., S.C., İ.K., M.K.Ç., Data Collection or Processing: Ö.D., İ.K., F.B.,

M.K.Ç., Analysis or Interpretation: Ç.M., M.B., Ö.D., F.B., M.K.Ç., Literature Search: M.B., Ö.D., Writing: M.B., Ö.D.,

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Research Article

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Anti-HDV Seroprevalence Among Patients with Chronic Hepatitis B Infection in Diyarbakır

Diyarbakır'da Kronik Hepatit B Enfeksiyonu Olan Hastalarda Anti-HDV Seroprevalansı

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ABSTRACT

Objectives: This study identifies the hepatitis delta virus (HDV) antibodies (anti-HDV) seroprevalence in patients with chronic hepatitis B (CHB) infection in a region highly endemic for HDV.

Materials and Methods: A total of 306 patients with CHB infection, who were followed up regularly between January 2016 and December 2019, were retrospectively analyzed. Demographic characteristics, hematological parameters, liver function tests, abdominal ultrasonography, hepatitis serologies, and liver biopsy results of the patients were analyzed through patient follow-up forms.

Results: Anti-HDV was positive in 43 (14.1%) of 306 patients, 129 (42.1%) of whom were female and had a mean age of 41.5±13.4 years. Alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and gamma-glutamil transferase levels of delta hepatitis (DH) patients were significantly higher than those of CHB patients (p=0.019, p<0.001; p=0.027; p=0.001, respectively), whereas albumin, white blood cell, and platelet levels were significantly lower (p<0.001; p=0.001; p<0.001, respectively). 55.8% of patients with DH were with the diagnosed with cirrhosis.

Conclusion: Anti-HDV was positive in 14.1% of patients diagnosed with CHB in the Diyarbakır region. The progression to liver cirrhosis and hepatocellular carcinoma is faster in DH; therefore, more efforts should be made to identify and treat this patient group.

Keywords: Anti-HDV, hepatitis B virus, hepatitis delta virus, seroprevalence

ÖZ

Amaç: Bu çalışmanın amacı hepatit delta virüsü (HDV) için yüksek oranda endemik olan bir bölgede kronik hepatit B (KHB) enfeksiyonu hastalarında HDV antikorları (anti-HDV) seroprevalansını belirlemektir.

Gereç ve Yöntemler: Ocak 2016-Aralık 2019 tarihleri arasında düzenli takipleri yapılan 306 KHB enfeksiyonu tanılı hasta retrospektif olarak analiz edildi. Hastaların demografik özellikleri, hematolojik parametreleri, karaciğer fonksiyon testleri, abdominal ultrasonografi raporları, hepatit serolojileri ve karaciğer biyopsi sonuçları hasta takip formları aracılığıyla incelendi.

Bulgular: Yüz yirmi dokuzu (%42,1) kadın ve yaş ortalaması 41,5±13,4 olan 306 hastanın 43'ünde (%14,1) anti-HDV pozitifti. Delta hepatiti (DH) hastalarının alanin aminotransferaz, aspartat aminotransferaz, alkalen fosfataz ve gama-glutamil transferaz seviyeleri KHB hastalarına göre anlamlı derecede yüksek (sırasıyla; p=0,019; p<0,001; p=0,027; p=0,001), albümin, beyaz kan hücresi ve trombosit değerleri ise anlamlı derecede düşük izlendi (sırasıyla; p<0,001; p=0,001; p<0,001). DH hastalarının %55,8'inde siroz tanısı mevcut idi.

Sonuç: Diyarbakır bölgesinde KHB tanılı hastaların %14,1'inde anti-HDV pozitif bulunmuştur. DH'de karaciğer sirozu ve hepatosellüler karsinomaya gidiş daha hızlı olduğundan, bu hasta grubunun tespiti ve tedavisi için daha fazla çaba sarf edilmelidir.

Anahtar Kelimeler: Anti-HDV, hepatit B virüs, hepatit delta virüs, seroprevalans

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Introduction

Hepatitis delta virus (HDV) is a small, defective RNA virus with a viroid structure. HDV can only spread to an individual with hepatitis B virus (HBV) by simultaneous transmission of two viruses (coinfection) or by the infection of an HBV carrier with HDV (superinfection) (1). Spontaneous recovery occurs in 95% of the patients with HBV/HDV coinfection. However, it may cause extensive hepatic necrosis in the remaining patients and lead to a presentation of fulminant hepatitis with high mortality rates (2). Superinfection of people with chronic hepatitis B (CHB) infection with HDV results in turning into chronic at a rate of 80%, which leads to accelerated progression to cirrhosis and an increased risk of hepatocellular carcinoma (HCC) compared to CHB infection alone (3). It is estimated that 0.16% of the general population, which approximately equals 12 million people, are anti-HDV positive worldwide. The prevalence of anti-HDV was reported to be 4.5% among all HBsAg-positive individuals and 16.4% among those presenting to hepatology clinics (4). In Turkey, the lowest prevalence of delta hepatitis (DH) in CHB patients is observed in the West with 4.8%, while the highest prevalence is observed in the Southeast with a rate of 27.1%. In recent years, there has been a decrease in DH in Turkey after the national HBV vaccination program; however, the prevalence is still high in the Southeastern and Eastern Anatolia Regions and continues to be an important health problem (5). The study aims to identify the anti-HDV seroprevalence in CHB patients in a region highly endemic for HDV.

Materials and Methods

Study Design

This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (approval number: 725, date: 26.03.2021).

This study is a retrospective analysis of medical data obtained from the Infectious Diseases Outpatient Clinic of Diyarbakır Bismil State Hospital. A total of 306 patients diagnosed with CHB infection, who were followed up regularly between January 2016 and December 2019, were included in the study. Demographic characteristics, hematological parameters, liver function tests, abdominal ultrasonography, hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HBe, anti-HDV immunoglobulin G, HBV-DNA, HDV-RNA, and liver biopsy results of the patients were analyzed through patient follow-up forms. Serological tests were performed using the macro-ELISA method (Architect i2000SR, Abbott Diagnostics, Chicago, IL, USA). Anti-HDV presence was analyzed using the Triturus (Triturus, Grifols, Spain) and the micro-ELISA (HDV Ab, Enzyme Immunoassay Test Kit, Delta Biologicals, Italy) systems according to the manufacturer's instructions. The presence of HBV-DNA and HDV-RNA was evaluated by real-time polymerase chain reaction (PCR) using the Rotor-Genee Q (QIAGEN, Germany) system and the HBV QS-RG PCR kit (Qiagen, Hilden, Germany) with a linear range of detection of 25.6-4.21x10^8 IU/mL.

Definitions

CHB infection was defined as the patient group known to be HBsAg positive for more than six months with serological and molecular test confirmation.

The diagnosis of liver cirrhosis was defined in patients who met at least one of the following items:

1. Hepatic surface irregularity, caudate lobe hypertrophy, splenomegaly, or hepatic parenchymal damage on ultrasonography,
2. Laboratory and histological analysis results,
3. Esophageal varices confirmed by endoscopy.

Patients with co-infection with hepatitis C virus and human immunodeficiency virus, or chronic liver diseases such as primary biliary cirrhosis, autoimmune hepatitis, and alcoholic hepatitis, and patients under the age of 16 were excluded from the study. Patients with acute hepatitis B, defined by the presence of HBsAg for less than six months and a clinical presentation compatible with recent HBV infection, were excluded from the study.

Statistical Analysis

Continuous variables were compared using the Independent samples t-test. Categorical variables were compared using the Pearson chi-square or the Fisher's exact test. All tests were performed using the SPSS for Windows version 18.0 software (SPSS Inc. Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

A total of 129 (42.1%) of the 306 patients included in the study were female and the mean age was 41.5±13.4 years. HBeAg was positive in 9.1% of the patients. 28.4% of the patients had undetectable HBV-DNA and 20.9% of HBsAg (+) patients were receiving oral antiviral therapy for HBV. HDV antibodies (anti-HDV+) were positive in 43 (14.1%) of the patients. HDV-RNA was above the detectable level in 17 (39.5%) of the anti-HDV (+) patients. Pegile interferon alfa 2 treatment was given to 19 (44.1%) of the anti-HDV positive patients for 48 months, and 4 (9.3%) for a total of 96 months. Liver transplantation was performed in 2 (4.6%) anti-HDV positive patients. The mean age of the anti-HDV (+) patients was significantly higher than that of the anti-HDV (-) patients (p<0.001). Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamil transferase (GGT) levels in anti-HDV (+) patients were significantly higher than those of anti-HDV (-) patients based on the analysis of the biochemical data (p=0.019; p<0.001; p=0.027; p=0.001, respectively). The anti-HDV (+) patients had significantly lower albumin, white blood cell count (WBC), and platelet levels compared to the anti-HDV (-) patients (p<0.001; p=0.001; p<0.001, respectively). While more than half of the anti-HDV (+) patients were diagnosed with liver cirrhosis, this rate was very low in the anti-HDV (-) patient group (55.8% vs 1.9%, p<0.001). The distribution of demographic, biochemical, and hematological characteristics of the study participants according to the groups is shown in Table 1.

Discussion

It is estimated that more than 15 million of the 350 million CHB carriers worldwide are exposed to HDV (6). Similar to HBV, HDV is transmitted parenterally through exposure to infected blood or body fluids. Therefore, transmission rates are high in intravenous drug users (7). There is evidence of sexual transmission, and people with high-risk sexual activity are at greater risk for infection (8). Intrafamilial transmission, known as non-specific parenteral transmission, is common in areas with high HDV prevalence. On the other hand, perinatal transmission of HDV is rare. Despite the antiviral therapies used in HDV treatment, these patients are subject to increased liver decompensation, which leads to faster progression to cirrhosis and death, compared to those with HBV infection alone (9). In a viral hepatitis prevalence study in which a large population was screened in Turkey, a middle-endemic country for HBV, anti-HDV positivity was found in 2.8% of the patients with HBsAg positivity (10). The eastern and southeastern parts of Turkey are especially the regions with the highest prevalence of DH. The prevalence of DH in the east and southeast of the country has been associated with the low socioeconomic status of these regions which represent the poorest regions of Turkey (5).

In the present study, anti-HDV positivity was identified in 14.1% of HBsAg (+) patients. More than half of the DH patients (55.8%) were diagnosed with cirrhosis. In a meta-analysis study in which studies conducted in Turkey between 1995 and 2004 were evaluated, anti-HDV seropositivity in patients diagnosed with CHB was reported to be the lowest in the western region with a rate of 5% and the highest in the southeast region with a rate of 27%. In the same study, anti-HDV seropositivities in patients with cirrhosis caused by hepatitis B were at a rate of 20% in the western region and 46% in the southeast region (5). In studies conducted after 2010, anti-HDV positivity in HBsAg (+) patients has been reported to be the lowest in the Western regions, within a range of 1.4-4.1% (11,12,13,14). The rate was within the range of 0.9-4.2% in studies conducted in the middle Anatolia regions (15,16,17). As in previous years, the highest rates have been observed in the East (8.8-15.2%) and Southeast (3.2-27.8%) regions in studies conducted after 2010 (18,19,20,21,22,23,24). Recent studies in Turkey are summarized in Table 2.

In the present study, ALT, AST, ALP, and GGT levels of the DH patients were significantly higher than those of the CHB patients ($p=0.019$; $p<0.001$; $p=0.027$; $p=0.001$, respectively), while albumin, WBC, and platelet levels were significantly lower ($p<0.001$; $p=0.001$; $p<0.001$, respectively). The presence of cirrhosis in 55.8% of the DH patients suggests the laboratory changes that occurred. Studies have shown that DH patients have significantly higher ALT levels and histological activity compared to CHB patients who are not infected with HDV (25). In a recent meta-analysis, it was shown that DH progresses to cirrhosis within a mean of five years and HCC within a mean of 10 years (26).

Study Limitations

There are some limitations to the present study. It was single-centered, retrospective, and had a relatively small sample size. Moreover, sequential HDV-RNA monitoring could not be performed in some of the patients.

Conclusion

In the present study, the anti-HDV seroprevalence of the patients with CHB infection was identified above the Turkey average and close to the average of the data reported from the Eastern and Southeastern regions with a rate of 14.1%. Agents

Table 1. Clinical, demographic features, and laboratory data of the participants

	Anti-HDV positive	Anti-HDV negative	p-value
Patient count, n (%)	43 (14.1)	263 (85.9)	
Age, years, mean ± SD	51.7±11.3	39.9±12.9	<0.001
Sex, female n (%)	17 (39.5)	112 (42.6)	0.834
ALT (U/L)	50.7±32.2	37.0±35.9	0.019
AST (U/L)	50.2±28.4	29.0±16.1	<0.001
ALP (U/L)	105.8±47.8	87.2±45.4	0.027
GGT (U/L)	68.4±69.2	24.2±18.9	0.001
Albumin (g/dL)	3.86±0.59	4.39±0.40	<0.001
Total bilirubin (mg/dL)	0.80±0.57	0.67±0.47	0.091
Creatinine (mg/dL)	0.82±0.14	0.86±0.16	0.154
White blood count (mm^3)	6375±1841	7450±2019	0.001
Hemoglobin (g/dL)	14.6±1.8	14.8±1.8	0.620
Platelet (mm^3)	150198±56492	211630±59039	<0.001
INR	1.14±0.13	1.08±0.69	0.609
AFP	8.21±21.15	7.18±20.13	0.778
Liver cirrhosis n (%)	24 (55.8)	5 (1.9)	<0.001
CTP score	5.3±0.9	5.1±0.3	0.054

HDV: Hepatitis delta virus, SD: Standard deviation, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma-glutamil transferase, INR: International normalized ratio, AFP: Alpha-fetoprotein, CTP: Child-Turcotte-Pugh

Table 2. Anti-HDV positivity in patients with chronic hepatitis B in Turkey

Region	Study period	Researcher	Anti-HDV (+)
West Turkey			
İstanbul	2015-2017	Yolcu et al. (14)	4.1%
İstanbul	2015-2019	Ergen et al. (11)	2.9%
İzmir	2016-2018	Kaya et al. (13)	2.8%
Sakarya	2015-2018	Aydemir et al. (12)	1.4%
Central Turkey			
Ankara	2010-2013	Gürkan et al. (15)	4.2%
Ankara	2012-2014	Yozgat et al. (17)	3.0%
Eskişehir	2012-2013	Korkmaz et al. (16)	0.9%
East Turkey			
Elazığ	2017-2019	Eser-Karlıdağ (20)	8.8%
Malatya	2012	Duman et al. (19)	15%
Van	2012-2014	Dulger et al. (18)	15.2%
Southeast Turkey			
Adıyaman	2010-2012	Kölgelier et al. (23)	3.2%
Diyarbakır	2012-2017	Ayaz and Sarı (21)	4.4%
Siirt	2017-2018	Bal (22)	27.8%
Şanlıurfa	2011-2012	Uyanıkoğlu et al. (24)	5.0%

HDV: Hepatitis delta virus

that can be used in the treatment of DH are limited, and response rates are very low; therefore, more efforts should be made to minimize the proportion of undiagnosed or not regularly followed-up CHB patients. In addition, HBV vaccination should be applied effectively not only in childhood but also in all risk groups in endemic regions.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Gazi Yaşargil Training and Research Hospital (approval number: 725, date: 26.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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