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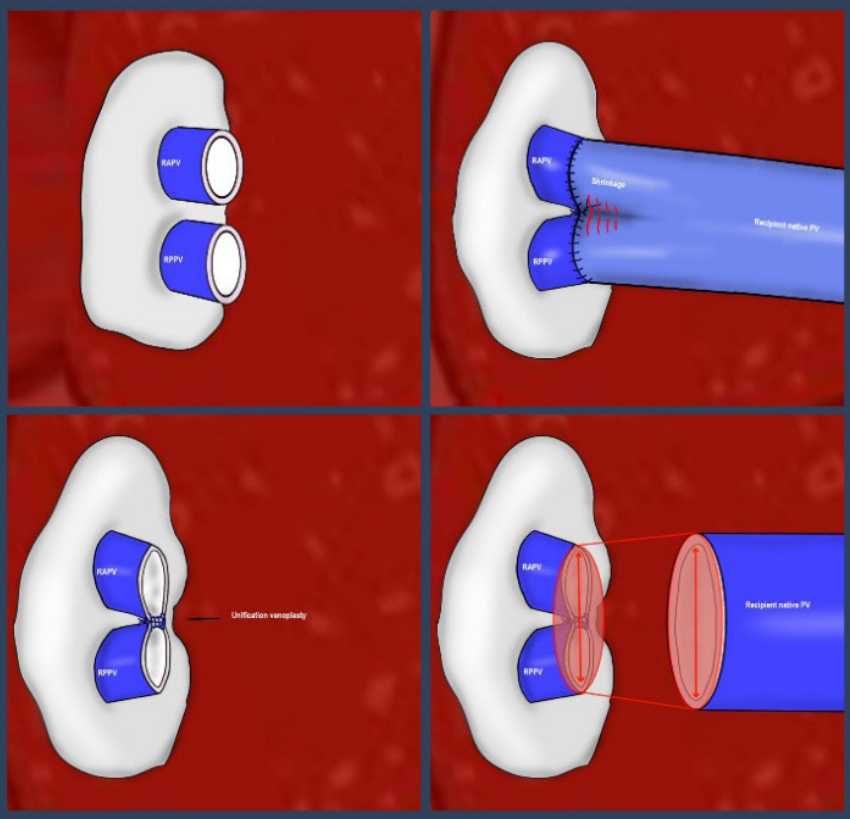
The Official Journal of the Inonu Liver Transplantation Institute

Journal of Inonu Liver Transplantation Institute



Are In Situ Double Portal Vein Anastomosis or Unification ideal for Anomalous Portal Vein Reconstruction in Right Lobe Living Donor Liver Transplantation?

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Aim and Scope: The Journal of Inonu Liver Transplantation Institute is a peer-reviewed open-access e-only publication in the field of liver transplantation publishing research articles on clinical, experimental liver transplantation, combined liver and other organ transplantation, and liver diseases. The journal welcomes original research articles, reviews, meta-analyses, case reports, and letters.
Average Duration of the First Review Round: 2 months
Type of Publications: Research Article, Review Article, Meta-Analyses, Case Report, Letter to the Editor
Language of Publication: English
Frequency: 3 issues per year
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JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

Aim and Scope

Aim

The Journal of Inonu Liver Transplantation Institute is a peer-reviewed open-access e-only publication in the field of liver transplantation publishing research articles on clinical, experimental liver transplantation, combined liver and other organ transplantation, and liver diseases. The journal welcomes original research articles, reviews, meta-analyses, case reports, and letters.

Overview

Journal of Inonu Liver Transplant Institute has been founded and established by Inonu Liver Transplant Institute in order to form a source of high-quality research in diseases and therapy of the liver and biliary tract. Both clinicians and basic science researchers are the target population of our journal.

Scope

Hepatobiliary disorders are a complex spectrum of diseases, usually requiring a multi-disciplinary approach that involves interventional radiologists, hepatologists, oncologists, hepatobiliary-transplant surgeons and translational researchers. The Journal of Inonu Liver Transplant Institute (JILTI) is internationally peer reviewed and provides a source for articles on prevention, diagnosis and cutting-edge therapy of hepatobiliary diseases and cancers which also includes liver transplantation, complex hepatobiliary surgical procedures, medical and immune therapies. In accordance with our aims, basic and translational research as applied to these diseases have utmost importance for our journal.

Keywords: Hepatobiliary diseases and cancers, liver surgery, liver transplantation, advanced therapy of hepatobiliary diseases, basic and translational research on hepatobiliary diseases.

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Ethical Responsibilities and Policies

Fee - Charges

The Journal of Inonu Liver Transplantation Institute (The Journal) assesses NO submission fee, publication fee (article processing charges - APC), or page charges.

Publication Ethics

The Journal applies standards throughout the publication process to further our goal of sharing high-quality, objective, reliable, and useful information. We implement these processes to ensure appropriate support for our authors and their institutions, as well as our readers. It is crucial that all of the stakeholders in the process (authors, readers and researchers, publishers, reviewers, and editors) comply with ethical principles.
The Journal is an open access publication and follows the guidelines and policies published by the Committee on Publication Ethics (COPE) (https://publicationethics.org). We expect all participants to observe the ethical responsibilities presented below.

Author's Responsibilities

- Studies submitted for publication must be original works of the author. References to other studies must be cited and/or quoted completely and accurately;
- Only those who provide a substantial intellectual contribution to the content of the work may be cited as an author. Other contributors may be recognized with acknowledgements at the conclusion of the article;
- Competing interests or relationships that may constitute a conflict of interest must be declared and explained in all studies submitted for publication;
- Authors must be able to provide documentation showing that they have the right to use the data analyzed, the necessary permissions related to the research, and any appropriate consent;
- Raw data used in the article must be available and may be requested from the author(s) within the framework of the evaluation process;
- In the event the author(s) notice an error at any point in the publication process or after publication, they have the obligation to inform the journal editor or publisher and cooperate in appropriate corrective action;
- Authors may not submit their article for publication to more than one journal simultaneously. Each application must be initiated following the completion of any previous effort. The Journal will not accept previously published articles;
- Changes in authorship designation (such as adding authors, changing the printed order of the authors, removing an author) once the evaluation process has begun will not be accepted in order to protect all parties involved.

Editor's Role and Responsibilities

General Duties

The editor is responsible for everything published in the journal. In the context of this responsibility, editors have the following duties and obligations:

- Endeavor to meet the needs of readers and authors;
- Maintain continuous development to improve the quality of the journal;
- Consistently work to ensure quality;
- Support freedom of thought;
- Ensure academic integrity;
- Prevent business needs from compromising intellectual and ethical standards;
- Demonstrate clarity and transparency with any necessary corrections or explanations.

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The editor is to make publication decisions based on expectations of suitable and desirable material. Studies accepted for publication must be original contributions that benefit the reader, researcher, practitioner, and the literature. In addition, editors are obliged to take into account feedback from readers, researchers, and practitioners, and to provide an informative response. Readers will also be informed of any funding provided to support published research.

Author Relationship

- The decision to accept an article is to be based on the importance, original value, validity, and clarity of expression of the work, and the goals and objectives of the journal;
- Studies accepted for evaluation and publication will not be withdrawn unless serious problems are identified;
- The editor will not disregard positive reviewer comments unless there is a serious problem with the study;
- New editors will not change publishing decisions made by previous editor(s) unless there is a serious problem;
- A description of the submission and evaluation process is publicly available;
- Authors are provided with descriptive and informative feedback.

Reviewer Relationship

Reviewers are to be selected according to the subject of the study;
Information and guidance for the evaluation phase is provided;
Any conflicts of interest between authors and reviewers will be disclosed and managed appropriately;
Reviewer identity is to be kept confidential to preserve a blind review process;
Reviewers are to evaluate the study using unbiased, scientific, and constructive comments. Unkind or unscientific commentary will not be permitted;
Reviewers will be evaluated using criteria such as timely response and quality of observations;
The pool of reviewers is to be assessed and supplemented regularly to ensure a broad scope of expertise.

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The editor works with the members of the editorial board to ensure that they are familiar with journal policies and developments in regular meetings and announcements, and will provide training for new members and assistance to board members during their tenure in their role as a supporter of the journal.

- Editorial board members must be qualified and able to contribute to the journal;
- Members of the editorial board must evaluate studies impartially and independently;
- Editorial board members with the appropriate expertise will be given the opportunity to evaluate suitable articles;
- The editor will maintain regular contact with the editorial board and hold regular meetings regarding the development of editorial policies and other aspects of journal management.

Relations with the Owner of the Journal and the Publisher

The relationship between the editors and the publisher/journal owner is based on the principle of editorial independence and stipulated by contract.

Editorial and Blind Review Processes

The editor will apply the publicly defined publication policies created and enforced to ensure a timely and impartial evaluation process for all submissions.

Quality Assurance

The editor is responsible for confirming that the The Journal publishing policies and standards are upheld for all articles.

Protection of Personal Data

The editor is obliged to ensure the protection of personal data related to subjects or images included in published work. Explicit documented consent of the individuals referenced in the research is required before the study will be accepted. The editors is also responsible for protecting the individual data of authors, reviewers, and readers.

Ethics Committee, Human and Animal Rights

The editor is required to ensure that human and animal rights were protected in the studies submitted for publication.

Measures Against Potential Misconduct

The editor must take action against any allegations of possible misconduct. In addition to conducting a rigorous and objective investigation of complaints, the editor is expected to share the findings and conclusions.

Maintaining Academic Publication Integrity

The editor is expected to ensure that any errors, inconsistencies, or misleading statements are corrected quickly and appropriately acknowledged.

Protection of Intellectual Property Rights

The editor is obliged to protect intellectual property and to defend the rights of the journal and author(s). In addition, the editor is to take the necessary measures to prevent any violation of the intellectual property rights of others in journal publications.

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- Constructive criticism is to be encouraged;
- Authors will be given the opportunity to reply to criticism;
- Negative results will not be a reason for submission denial.

Complaints

Editors are to respond to all complaints in a timely and comprehensive manner.

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Political or commercial factors will not affect editorial decisions.

Conflicts of Interest

The editor is required to ensure that any conflicts of interest between authors, reviewers, or other editors are disclosed and managed appropriately to provide an independent and impartial process.

Reviewer's Ethical Responsibilities

Peer review of research embodies the scientific method, subjecting the work to the rigorous scrutiny of knowledgeable colleagues. The rigor of the review process directly affects the quality of the literature; it provides confidence in an objective and independent evaluation of the published work. The Journal uses a double-blind review process. All comments and the evaluation are transmitted through the journal management system. Reviewers should:

- Only agree to evaluate studies related to their specialty;
- Return reviews within the designated timeframe;
- Evaluate with impartiality. Nationality, gender, religious beliefs, political beliefs, commercial concerns, or other considerations must not influence the evaluation;
- Refuse to review any work with a potential conflict of interest and inform the journal editor;
- Maintain confidentiality of all information. Only the final published version may be used for any purpose;
- Use thoughtful and constructive language. Hostile or derogatory comments are not acceptable;
- Report any potentially unethical behavior or content to kare@karepb.com via e-mail.

JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

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Information for the Authors

THE JOURNAL

The Journal of Inonu Liver Transplantation Institute (The Journal) is an international, scientific, open access periodical published in accordance with independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Inonu Liver Transplantation Institute, and it is published in April, August and December, three times a year. The publication language of the journal is English.

The Journal aims to contribute to international literature by publishing high-quality manuscripts in the field of diseases and therapy of the liver and biliary tract. The journal's target audience includes academics and expert physicians working in transplantation surgery specialists.

REVIEW PROCESS

Manuscripts submitted to the Journal will undergo a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their field in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation process of manuscripts submitted by editors or by the editorial board members of the journal. The editor-in-chief is the final authority in the decision-making process for all submissions.

Reviews are typically completed within one month of submission to the journal. Authors will be sent constructive reviewer comments intended to be useful. In general, the instructions, objections, and requests made by the reviewers should be followed. The revised manuscript should clearly and precisely indicate every step taken in accordance with the reviewers' notes. A list of responses and the corrections made to each comment should be provided.

AUTHORSHIP

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for their own work, authors should have confidence in the integrity of the contributions of their co-authors and each author should be able to identify which co-authors are responsible for other parts of the work.

All of those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged on the title page of the manuscript.

The Journal requires that corresponding authors submit a signed and scanned version of the authorship contribution form (available for download through www.jilti.org) during the initial submission process in order to appropriately indicate and observe authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that they accept all responsibility for authorship during the submission and review stages of the manuscript.

ORCID ID

The Open Researcher and Contributor ID (ORCID) number of each author must be submitted when creating an account for correspondence. To obtain an ORCID number, please visit https://orcid.org/

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MANUSCRIPT PREPARATION

Manuscripts should be prepared in accordance with the ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2015 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for randomized research studies, the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for observational original research studies, the Standards for Reporting Diagnostic Accuracy (STARD) guidelines, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines for experimental animal studies, and the Transparent Reporting of Evaluations with Non-randomised Designs (TREND) guidelines for non-randomized behavioral and public health evaluations.

Manuscripts may only be submitted through the journal's online manuscript submission and evaluation system, http://jag.journalagent.com/jilti/ Manuscripts submitted via any other medium will not be evaluated.

Manuscripts will first be submitted to a technical evaluation process in which the editorial staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the author with requests for technical correction.

The quality and clarity of the language used in a manuscript is very important. The editors may request that authors have the manuscript professionally edited if the language of the submission does not conform to the journal standards. The Journal uses American English. Please submit text of a quality ready for publication. Information about language editing and copyediting services pre- and post-submission may contact Kare Publishing at kare@karepb.com. Please refer to specific formatting requirements noted in the submission checklist and elsewhere in this document.

MANUSCRIPT TYPES

Original Article: This is the most valued type of article, since it provides new information based on original research. The main text of an original article should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Original articles are limited to 3500 words and 30 references.

Editorial comment: Editorial comments provide a brief critical commentary offered by reviewers with experience and standing in the topic of a research article previously published in the journal. The authors are selected and invited by the journal to provide the benefit of their expertise. The submission should not include an abstract, keywords, tables, figures, and images. The word count is limited to 1200 and 15 references may be included.

Review article: Two kinds of review are accepted for publication in the Journal: narrative review and systematic review. Reviews of relevant topics not recently discussed in this format that will be helpful to readers are welcomed.

Case report: There is limited space for case reports and therefore the journal selects reports of rare cases or conditions that reflect challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not in the literature, or present something otherwise particularly interesting and educative. The abstract with structured of background, case and conclusion, is limited to 150 words and the report must include the subheadings of introduction, case report, and discussion, which includes a conclusion. A case report is limited to 1300 words and 15 references.

Image: Original, high-quality clinical or laboratory images will be considered for publication. If a photo of an identifiable patient is used, a consent form for its use must be completed and signed by the patient and enclosed with the submission. All printed information that might identify the patient or the authors' institution (including, but not limited to the hospital or patient name, date, or place) should be removed from images. The submission should have no more than 3 authors, the case description is limited to a maximum of 200 words, the discussion section may contain no more than 200 words, and only 3 references and 3 figures are permitted.

Letter to the editor: This type of manuscript discusses important observations, overlooked aspects, or details lacking in a previously published article. Noteworthy articles on subjects within the scope of the journal, particularly educative cases, may also be submitted in the form of a "Letter to the editor." No abstract, keywords, tables, figures, images, or other media should be included. The article that is the subject of commentary must be properly cited within the manuscript. The text should be unstructured and is limited to 500 words. No more than 5 references will be accepted.

Table 1. Limitations for each manuscript type.

Type of manuscript	Wordlimit	Abstract word limit	Referencelimit	Table limit	Figure limit
Original Article	3500	350 (Structured)	40	6	6
Review Article	5000	350	50	6	10
Meta analysis	5000	350	50	6	10
Caser Report	1500	200	20	No tables	5
Letter to the Editor	1000	No abstract	10	No tables	1

Title page: A separate title page should be submitted with all submissions and this page should include:

The full title of the manuscript as well as a short title (running head) of no more than 50 characters

Name, affiliation, ORCID ID number, and highest academic degree of the author(s)

Funding and other material support

Name, address, phone number(s), fax number, and email address of the corresponding author

Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria

Manuscripts that have been presented orally or as a poster should include the name, date and place of the event

Abstract: An English-language abstract is required with all submissions except editorial comments, images, and letters to the editor. Systematic reviews and original articles should contain a structured abstract of maximum 250 words with the subheadings of objective, methods, results, and conclusion.

Keywords: Each submission must be accompanied by a minimum of three and a maximum of six keywords for subject indexing included at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database (https://www.nlm.nih.gov/mesh/MBrowser.html).

Tables: Tables should be uploaded as separate files and not embedded in the main text. They should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the table with footnotes, even if they are defined within the main text. Tables should be created using the "insert table" command of the word processing software and they should be designed for easy reading. Data presented in tables should not be a repetition of the data presented within the main text but should support the main text.

Figures and figure legends: Figures, graphics, and photographs should be submitted as separate files in TIFF or JPEG format through the article submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be

merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legend. Like the rest of the submission, the figures should be blind. Any information within the images that may identify an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100x100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition. Units should be prepared in accordance with the International System of Units (SI). When a drug, device, hardware, or software program, or other product is mentioned within the main text, the name of the product, the manufacturer/copyright holder of the product (not simply the vendor), and city and the country of the company (including the state, if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric Co., Boston, MA, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References: The editorial team may request that the authors cite related recently published articles (preferably within the last 10 years) in their manuscripts, with the exception of historical papers.

If an ahead-of-print publication is cited, the digital object identifier (DOI) number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in the Index Medicus /MEDLINE/ PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numerals in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal article: van Erk MD, Dam-Vervloet AJ, de Boer FA, Boomsma MF, van Straaten H, Bosschaart N. How skin anatomy influences transcutaneous bilirubin determinations: an in vitro evaluation. Pediatr Res 2019;86:471-7.

Epub ahead-of-print article: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead-of-print].

Manuscript published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

Book section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a single author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or technical report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

REVISIONS

When submitting a revised version of a paper (include a clean copy and a highlighted copy), the author must submit a detailed response to the reviewers that replies to each issue raised by the reviewers and indicates where changes can be found (each reviewer's comment, followed by the author's reply and line number where changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be withdrawn. If the submitting author(s) believe that additional time is required, they should request this extension within the initial 30-day period.

Accepted manuscripts are copy edited for grammar, punctuation, format, and clarity. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in the scheduled issue. A PDF proof of the manuscript is sent to the corresponding author and their publication approval is requested within 2 days of receipt of the proof.

PUBLICATION PROCESS

Accepted manuscripts will be made available and citable online as rapidly as possible. The stages of publication are as follows;

Uncorrected publication: A PDF of the final, accepted (but unedited and uncorrected) paper will be published online on the journal web page under the "Accepted Articles" section. A DOI will be assigned to the article at this stage.

Ahead-of-print publication: After copy editing, typesetting, and review of the resulting proof, the final corrected version will be added online in the "Ahead-of-Print" section.

Final publication: The final corrected version will appear in an issue of the journal and added to the journal website. To ensure rapid publication, we ask authors to provide your publication approval during the proofreading process as quickly as possible, and return corrections within 48 hours of receiving the proof.

SUBMISSION CHECKLIST

Please use this list and the following explanations to prepare your manuscript and perform a final check before submission to ensure a timely review.

Formatting of text

- Text should be written in 12-point Times New Roman font
- Main headings and subheadings should be in 12-point and bold font
- Type a single space at the end of each sentence
- Do not use bold face for emphasis within the text
- Numbers one to ten are written out in words unless they are used as a unit of measurement, except in figures and tables
- Use a single hard return to separate paragraphs. Do not use tabs or indents to start a paragraph
- Do not use software options for hyphenation, headers, or footers
- Use page numbering
- Use line numbers
- Use US English

Ensure that the following items are present:

- **Cover letter**
- **Title page including:**
  - Article type
  - Article title
  - Running title
  - All author names and affiliations
  - One author has been designated as the corresponding author with contact details
    - Full postal address, phone number(s), and email address
- Acknowledge
- Manuscripts that have been presented orally or as a poster must include the name of the event, the date, and the location
- State financial or other support for the study
- Word count
  - Abstract word count
  - Text word count
- **Main text of the manuscript must include:**
  - Article title
  - Abstract
  - Keywords
  - Text with required subheadings
  - References (ensure written according to journal rules)
  - Figures and tables
- Numbered according to text citation
- Descriptive legends/titles and abbreviations
- Ensure all figure and table citations in the text match the files provided
- **Figures:** to be submitted separately.
- **Tables:** to be submitted separately
- **Ensure that the following forms have been properly completed and submitted:**
- ICMJE Potential Conflict of Interest Disclosure Form (completed by all contributing authors), AND
- Copyright Transfer Form, AND
- Author Contributions Form

These forms are available for download at www.jilti.org

- **Further review**
  - Check the statistical analysis
  - Use the US English spell check and grammar check software functions
  - Check that all references cited in the text are correctly listed in the reference list
  - Permission has been obtained for use of copyrighted material from other sources (including the Internet)
  - All abbreviations have been identified
  - All figures and tables are correctly labeled
  - Journal policies detailed in this guide have been followed.

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Review

Liver Transplantation Management from Anti HBc Positive Donors to HBV Negative Recipients in Liver Transplantation

Yilmaz Bilgic

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Abstract

Anti HBc + people are in the marginal donor group. It is considered as a donor source, especially in places where Hepatitis B is endemic. In endemic areas, 21.4% of donors are HBcAb positive. In regions where HBV is not endemic, it is 4.75%-7%. Anti-HBc is a 'non-neutralizing' antibody that does not provide immune protection. In other words, it is 'serological scar', that is the evidence of previous exposure to HBV). De novo hepatitis may develop in liver transplants from anti-HBc positive donors. The most important factors for de novo hepatitis are the presence or absence of anti-HBc and anti-HBs positivity. If both antibodies are positive, the risk of denovo hepatitis is least and if both antibodies are negative, it is highest. High genetic barrier antivirals alone are recommended for the treatment and prophylaxis of developing de novo hepatitis. Hepatitis B immune globulin has no place in de novo treatment and prevention.

Keywords: Anti HBc positise donors, liver transplantation, HBV negative recipient

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Isolated anti-HBc positivity can be seen in the following situations:[1,2]

- False positivity (1-2%) caused by substances in the IgM structure that disappear as a result of the use of reducing substances such as dithiothreitol, cysteine, sodium metasulphite, or due to diagnostic systems,
- In acute infections, the window period in which HBsAg disappears but anti-HBs has not yet formed,
- Chronic infections in which HBsAg is undetectable,
- A defect in the humoral response to HBV antigens or the inability to produce anti-HBs, which is especially common in diabetics and kidney patients,
- Anti-HBs disappears over time,
- Viral infections which share antigenic determinants with HBcAg (such as HCV),
- Infections caused by mutant strains,
- Passive transfer of anti-HBc from mother to baby or from person to person as a result of blood transfusion.

Anti-HBc+ status can be seen both after acute infection and chronic infection.[3]

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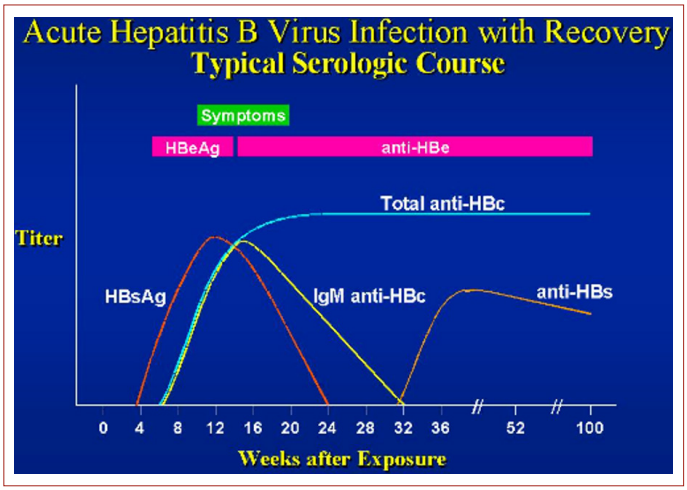

Figure 1. Acute infection.

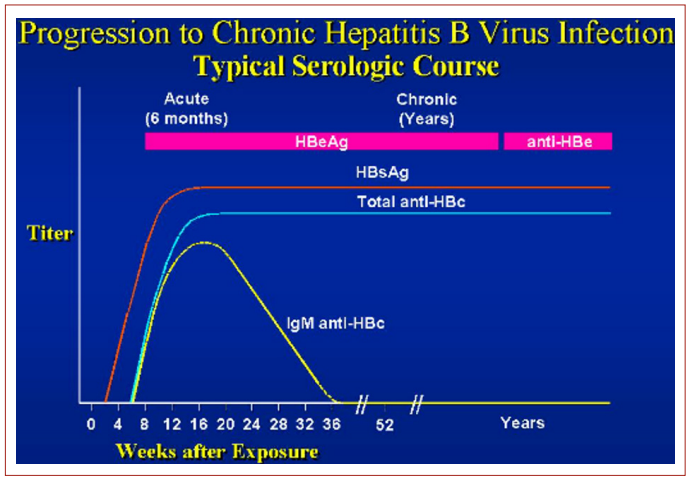

Figure 2. Chronic infection.

Stage 5: HBsAg Negative Phase[4]

In cases where HBsAg is negative, HBV DNA is positive in serum or liver parenchyma.

- HBsAg negative, anti HBc positive, anti HBs positive or negative in serum
- It is also called occult HBV infection.
- ALT levels are within normal limits and HBV DNA is undetectable.

Table 1. Incidence of de novo hepatitis B infection by recipient antibody status in patients receiving HBcAb- positive graft

	HBcAb (+) HBsAb (+) (n=24)	HBcAb (+) HBsAb (-) (n=6)	HBcAb (-) HBsAb (+) (n=6)	HBcAb (-) HBsAb (-) (n=4)	Total (n=40)
Recurrence	1 (4.2)	1 (16.7)	1 (16.7)	2 (50.0)	5 (12.5)
Nonrecurrence	23 (95.8)	5 (83.3)	5 (83.3)	2 (50.0)	35 (87.5)

Values are presented as number (%); HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody.

Table 2. Risk factors for de novo hepatitis B infection in recipients of HBcAb- positive graft

Veriable	Total (n=40)	Nonrecurrence (n=35)	Recurrence (n=5)	p
Donor				
Age	40.10±11.44	39.56±11.86	43.80±7.98	0.446
Male sex	28 (70.0)	26 (74.3)	2 (40.0)	0.125
HBsAb (+)	36 (90.0)	31 (88.6)	5 (100)	0.655
Recipient				
Age	50.12±10.68	51.37±10.49	41.40±8.14	0.049
Male sex	16 (40.0)	12 (34.3)	4 (80.0)	0.418
Alcohol: HCV: others	18 : 5 : 17	15 : 4 : 16	3 : 1 : 1	0.790
MELD	13.94±8.53	14.12±7.94	12.25±3.40	0.794
HBcAb (+)	30 (75.0)	28 (80.0)	2 (40.0)	0.096
HBsAb (+)	30 (75.0)	28 (80.0)	2 (40.0)	0.096
LDLT	30 (75.0)	26 (74.3)	4 (80.0)	0.633
Operative time (min)	1,093.6±446.7	1,114.8±237.6	1,080.0±423.6	0.806
Blood transfusion (unit)	6.9±4.4	9.6±5.1	4.3±5.1	0.106
Mortality	1 (2.5)	1 (2.9)	0 (0)	0.663
Survival time (mo)	43.73±35.03	40.19±32.37	66.4±46.75	0.121

Values are presented as mean±standard deviation or number (%); HBcAb: hepatitis B core antibody; HBsAb: hepatitis B surface antibody; hepatitis B surface antibody; BMI: body mass index; MELD: model for end- stage liver disease; LDLT: living donor liver transplantation.

- HBV DNA (ccc DNA) is frequently detected in the liver.
- If HBsAg loss occurred before the development of cirrhosis, the risk for cirrhosis, decompensation and HCC development is low.
- If cirrhosis developed before HBsAg loss, the risk of developing HCC remains the same.
- Immunosuppression may cause HBV reactivation in these patients.

Accurate measurement of ccc DNA can be achieved through droplet digital PCR (ddPCR) assays using hepatocyte samples obtained via liver biopsy. A new biomarker for Ccc DNA can be detected in serum HBV RNA, especially under NA treatment. In virally suppressed patients with low HBV DNA, HBV RNA level is an important marker to show ccc DNA level.[5]

This large cohort study described the long-term results of HBIG monotherapy preventing DNHB infection following liver transplantation using Anti-HBc antibody+ liver grafts in an area where hepatitis B virus is endemic. There is no advantage over monotherapy. Anti-HBc antibody negative recipients were more likely to develop new hepatitis B virus infection than Anti-HBc antibody positive recipients. High MELD score was significantly associated with DNHB virus infection.[6]

Between 2000 and 2010, 71 anti-HBs antibody negative adult patients who received anti-HBc antibody positive grafts. Patients were divided into 3 groups: Group 1, good responders to active vaccination, patients with anti-HBs titer >1000 IU/L before transplantation and who didn't required prophylaxis after transplant (n=24); group 2, pretransplant active vaccinated patients but the level of anti-HBs antibody titer less than 1000 IU/L at transplantation time, who were administered lamivudine prophylaxis after transplantation at least 2 years, and who responded well to post-transplant active vaccination by maintaining their anti-HBs titers at > 100 IU/L (n=30); and group 3, patients with post-transplant anti-HBs<100 IU/L despite active vaccination who continued lamivudine lifelong (n=17). DNHB incidence was 17.6% and all DNHB occurred in group 3 patients with posttransplant level of anti-HBs <100 IU/L. No DNHB was occurred in patients with post-transplant anti-HBs levels >100 IU/L (p=0.001). Anti-HBs level >1000 IU/L before transplantation was significantly associated with early achievement and sustained post-transplantation level of anti-HBs >100 IU/L (p<0.001). Prevention of DNHB in LDLT patients can be achieved by active immunization in adults when the level of anti-HBs is kept above 100 IU/L after transplantation by active vaccination.[7]

Table 3. Characteristics of liver transplantation recipients who developed de novo hepatitis B infection, and treatment outcomes

No	Age	Sex	Diagnosis	At recurrence					Treatment			After treatment				
				ALT	HBsAg	HBsAb	HBeAb	DNA	DFS	Treatment	Duration (mo)	ALT	HBsAg	HBsAb	HBeAb	DNA
1	37	F	Wilson	23	74.10	-	957.7	1,091,234,112	119	No treatment	29	32	95,200	-	>4,000	1,038,348,586
2	46	M	Alcohol	33	72.90	-	77.3	28,279,990	28	Entecavir	71	53	311.3	-	-	-
3	43	M	Toxic	98	74.06	-	163.73	59,383	35	Entecavir HBIG	31	39	54.16	-	7.24	-
4	30	M	HCV	120	728.7	-	-	103,143,448	7	Entecavir HBIG	5	38	+	-	-	-
5	51	M	Alc	36	1.44	-	-	-	9	Entecavir	20	25	1,033	-	>4,000	-

HBcAb: hepatitis B surface antibody; DFS: disease- free survival; Wilson: Wilson disease; Toxic: toxic hepatitis; HBIG: hepatitis B immunoglobulin.

Table 4. Classification of De Novo HBV Infection Risk in Liver Transplants from Anti-HBc Positive Donors According to Hepatitis B Marker and Treatment Status of the Recipient.[10]

	Anti-HBc – Anti-HBs - Anti-HBc – Anti-HBs -	Anti-HBc + Anti-HBs - Anti-HBc + Anti-HBs -	Anti-HBc + Anti-HBs + Anti-HBc + Anti-HBs +	Anti-HBc – Anti-HBs + Anti-HBc – Anti-HBs +
In Those Not Receiving Prophylactic Treatment	>%40	%13	%2	%10
In Those Receiving Prophylactic Treatment	%12 High risk	%12 Moderate Risk	%12 Low Risk	%12 Moderate Risk

In a systematic review by Cholongitas et al on recipients of anti-HBc antibody positive liver grafts concluded that the highest risk rate of DNHI was among the recipients without HBV infection by 47.8%. In contrast, recipients with natural immunity had the lowest risk rate of DNHI by 1.4%–4.0%.[8]

In another article investigating the risk of developing DNHB virus infection in patients who received a graft from a donor with anti-HBc antibody positive the incidence of de novu hepatitis B was evaluated according to the anti-HBc and anti-HBs positivity or negativity of the recipient. De novo hepatitis developed in one of them. While the most risky group was the group in which both antibodies were negative, the risk was found to be lowest in the group in which both antibodies were positive. When the risk groups of patients who developed de novo hepatitis were examined, age, anti-HBc positivity and anti-Hbs positivity were found to be significant. Antivirals were started in patients who developed de novo hepatitis B. It was observed that HBsAg turned negative in all patients who developed de novo hepatitis after treatment.[9]

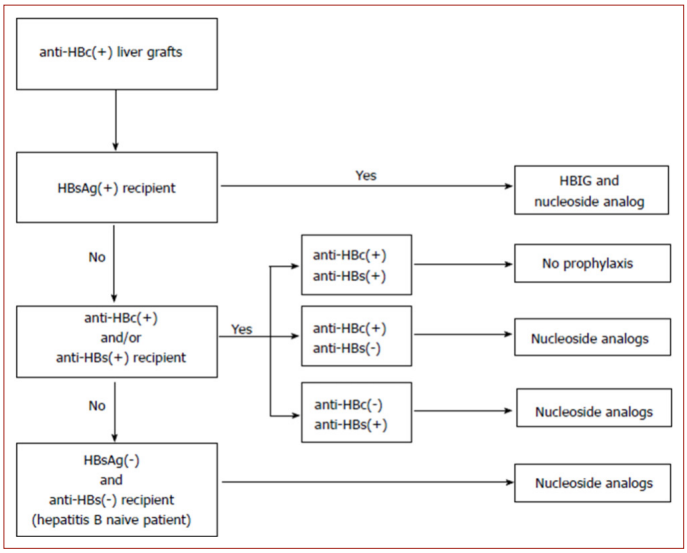

Figure 3. Treatment recommendations for recipients of anti-HBc positive donors.[8]

Treatment of de Novo Hepatitis;[8]

Cholongitas et al. In HBsAg negative recipients, de novo infection rates were determined as 2.6% in lamivudine only, 2.8% in combination of lamivudine and HBIG, and 19% in HBIG monoprophylaxis. In other words, NA treatment revealed that the rate of de novo hepatitis was significantly reduced. This study showed that treatment with NA is effective in preventing de novo hepatitis.

- HBIG+LAM combination compared to LAM monotherapy in HBV DNA(-) patients receiving HBcAb(+) liver grafts;
- LAM monotherapy has the same efficacy as HBIG+LAM combination therapy
- Entecavir and tenofovir monotherapy is safer
- Therefore, we recommend that clinicians administer nucleoside(t)ide analogs with lower resistance profiles to recipients of HBcAb(+) liver allografts without additional HBIG therapy.
- AASLD and EASL recommend monotherapy.

The role of Immunosuppressants used in the Development of de Novo Hepatitis

The immunosuppressive regimen using mTOR inhibitors after liver transplantation has been shown to generally reactivate HBV infection, as well as viral infections such as HCV, cytomegalovirus (CMV), HIV-1, human papillomavirus (HPV), and Epstein Barr.[11]

Survival in de Novo Hepatitis

The recipient survival at 5 years in patients who received a graft from a donor with Anti-HBc antibody positive was 97.5% while in patients with Anti-HBc abtibody negative was 89.7%. It shows that the survival rate does not differ significantly depending on the anti-HBc antibody status of the donor.[7]

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Original Research

Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation

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Abstract

Objectives: Hepatitis B virus (HBV), one of the biggest health problems of the world and our country, still constitutes the largest cause of liver failure and liver transplantation in the world. Here, we will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data.

Methods: İnönü University Liver Transplant Institute Patients who underwent liver transplantation due to any reason related to HBV were included in the study. Patients who underwent liver transplantation due to liver diseases caused by HBV in our institute between 2009 and 2023 were included in the study. . A total of 3679 patients underwent liver transplantation between 2002 and 2024. Of these patients, 1275 patients were operated on with the diagnosis of HBV. When 530 patients whose data were not available and 49 patients who were retransplanted were excluded from the study, a total of 695 patients were included in the study.

Results: Treatment is given in combination with antiviral and HBIG. It is available in centers where powerful antivirals are used alone. Although the approaches of the centers vary, patients who have had a liver transplant due to HBV definitely need postoperative medical treatment to prevent HBV recurrence.

Conclusion: Patients who have undergone liver transplantation due to HBV must have their Hbs-ag level checked when they are discharged from the hospital. Informing the patient about HBV recurrence and medical treatment provides a more meticulous medical treatment.

Keywords: Hepatitis B, Recuurence, Liver transplantation

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Hepatitis B virus (HBV), one of the biggest health problems of the world and our country, still constitutes the largest cause of liver failure and liver transplantation in the world. Here, we will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations. Hepatitis B virus (HBV) is a double-stranded DNA virus with a diameter of 42 nm. It has a spherical appearance. The outermost sheath is HBsAg, which is the surface antigen. Under the HBsAg sheath is the HBcAg core antigen. In the innermost part, there is the genomic structure consisting of DNA. In the inner part is HBeAg, which is the internal coated antigen.[1] Serological tests used in diagnosis; HBsAg, Anti HBc Total, Anti HBcIgM, Anti HBs, HBeAg, Anti HBe, HBV DNA. HBsAg, It is the first indicator . It is the surface antigen of the virus. It is the first antigen to appear in acute infections. It reaches a detectable level 1-2 weeks before symptoms. Positivity

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continues for 2-12 weeks. Positivity exceeding 6 months indicates chronicity. HBeAg, It is the internal antigen located at the core of the virus. It is found in dissolved form in the blood. It becomes positive with HBsAg. It becomes negative before HBsAg. It indicates that there is a high level of virus in the blood. It shows that the person is highly contagious. AntiHBs, It is the antibody against HBsAg. HBsAg becomes positive 2-3 months after it becomes negative. It is permanent for a lifetime. Indicates previous infection. It is also positive in vaccinated people. Anti-HBs positivity alone does not always mean that there is an infection. It indicates that the person is immune to hepatitis B infection. AntiHBc Total, It is an antibody against the hepatitis B core antigen. It generally consists of IgG. It becomes positive with clinical findings. Positivity continues throughout life. The positivity of this antibody indicates that the person has encountered the exact virus particle. It is positive in acute infections, chronic infections and carriers. HBV DNA It is the best indicator of the presence of the virus. Allows tracking of active replication. It is safer than HBeAg. It is important in monitoring the treatment. It allows determination of viral load.HBV Genotypes, Genotype A,B,C,D,E,F,G Genotype D is common in our country.

Regardless of the situation of a person who has encountered HBV, the disease rates that this HBV will cause in the person are as follows. After HBV is detected in the blood, a 90% recovery rate is observed. 1% has fulminant hepatitis and the remaining 9% remains HBs-Ag positive. 50% of this 9% rate recovers within 6 months. The remaining 50% progresses as asymptomatic carrier, chronic resistant carrier, and chronic active hepatitis, which in the future will emerge as a liver transplant candidate in the form of cirrhosis or hepatocellular cancer (HCC) (Fig. 1, Table 1).[2]

In the 1980s, cirrhosis due to HBV was considered a relative contraindication for liver transplantation.[5] Because without antiviral prophylaxis, the recurrence rate of HBV after liver transplantation was close to 100% and the mortality rate in the first year after transplantation was approximately 50%. With the discovery of hepatitis B immunoglobulin (HBIG), a polyclonal antibody developed against HBV surface antigen, in the early 1990s, HBV recurrence after liver transplantation decreased significantly and survival increased.[6] HBIG has a polycolonal immunoglobulin G (IgG) structure and is in the IgG subclass. Its distribution is very close to the rates in human plasma. HBIG has been shown to neutralize circulating virions, facilitate the lysis of infected hepatocytes through antibody-dependent cellular cytotoxicity, and block HBV receptors on hapatocytes. HBIG half-life is on average 22 days. The dose and frequency of HBIG use after liver transplantation, the method of application and the duration of application vary from center to center.[7] Both high and low risk groups have been defined in terms of HBV recurrence. The groups are as follows. High Risk Groups for HBV Recurrence; Pre-Transplant Hbv DNA + • Pre-Transplant Hbe-ag + • Presence of HCC , Low compliance with antiviral treatment • Resistance to antiviral treatment• Concomitant HIV or HDV infection[8,9] Low Risk Group for HBV Recurrence, Pre-Transplant HBV DNA negativity • Pre-Transplant Hbe-ag negativity • No HCC• High compli-

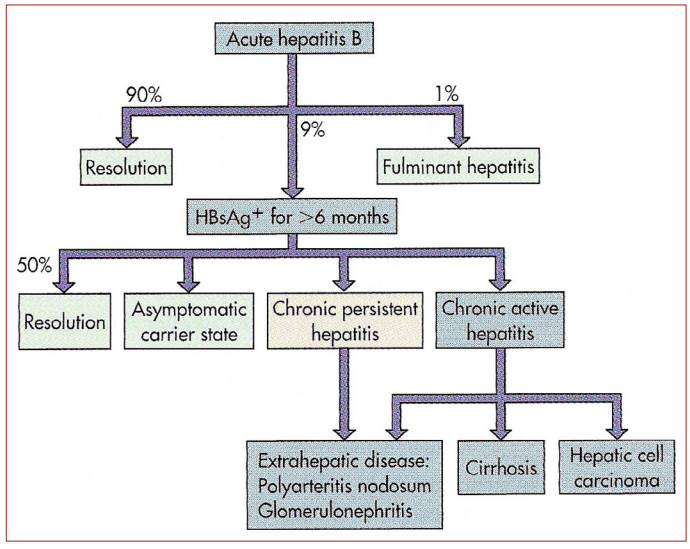

Figure 1. A patient exposed to HBV.

Table 1. Laboratory findings can be used to determine whether the patient has encountered HBV, early HBV infection, acute HBV infection, chronic HBV infection, acute HBV infection window period, previous HBV infection, and HBV vaccine response.[3,4]

HBs Ag	Hbe Ag	Anti HBe	AntiHBc IgM	Anti HBc	Anti HBs	Comment
-	-	-	-	-	-	Not exposed to HBV.
+	+/-	-	-	-	-	* Early HBV infection?
+	+/-	+/-	+	+	-	Acute HBV infection
+	+/-	+/-	-	+	-	Chronic HBV infection
-	-	+/-	+	+	-	* Acute HBV infection (window period)
-	-	-	-	+	-	AntiHBc positivity only
-	-	+/-	-	+	+	Previous HBV infection
-	-	-	-	-	+	HBV vaccine response

ance with antiviral treatment• Lack of resistance to antiviral treatment• No accompanying HIV or HDV infection.[8,9]

In a center where more than 300 liver transplants are performed annually, HBV constitutes the largest part of the indications for liver transplantation. More than 3000 liver transplants have been performed so far. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations.

Methods

İnönü University Liver Transplant Institute Patients who underwent liver transplantation due to any reason related to HBV were included in the study.

Patients who underwent liver transplantation due to liver diseases caused by HBV in our institute between 2009 and 2023 were included in the study. Demographic data of the patients, Meld score, operation date, preop eliza tests (hbs-ag. hbe-ag,hbc-ag, anti-hbc, anti-hbs delta ag, delta ab, hbv dna, hdvrna), postop 1. Monthly Hbs-ag level and follow-up Hbs-ag levels were examined. A total of 3679 patients underwent liver transplantation between 2002 and 2024. Of these patients, 1275 patients were operated on with the diagnosis of HBV. When 530 patients whose data were not available and 49 patients who were retransplanted were excluded from the study, a total of 695 patients were included in the study. Of these patients, no HBV recurrence was observed in 599 patients. HBV recurrence was observed in 96 of these patients (13.8%).

Table 2. Demographic Data of Patients, 74% of the patients were male and 26% were female. Their average age is 64, their average MELD score is 16, and their average follow-up period is 65 months.

Variables	n	%
Gender (female/male)	178/517	25.6/74.4
	Mean±SS	**Median**
Age (Years)	53.45±15.08	58
Tracking Period (Months)	81.17±52.02	65
MELD Score	18.52±4.969	16

Findings

Laboratory findings can be used to determine whether the patient has encountered HBV, early HBV infection, acute HBV infection, chronic HBV infection, acute HBV infection window period, previous HBV infection, and HBV vaccine response.[3,4]

When the Hbs-ag levels of the patients are examined at the first month after surgery, Hepatitis B recurrence is observed in a total of 112 patients (16.1%) and when the Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence (Tables 1-5).

Discussion

In a study, subcutaneous HBIG was given to patients who had completed 1 year after liver transplantation, with an anti-HBS titer of >150 Iu/L. After 48 weeks, the average anti-HBs titer was found to be 232 Iu/L, and no HBV recurrence was observed in any of the patients.[10]

In our clinic, HBIG treatment is given for life. In the unhepatic phase, HBIG is given for 7 days postoperatively and every month, depending on the AntiHbs level. Anti-HBS level is tried to be kept above 100 IU/L. The HBV recurrence rate seen in our clinic shows that patients are not fully compliant with medical treatment and that patients must receive postoperative education.

In another study involving 176 patients, the combination of HBIG and potent antivirals was targeted to have an anti-HBS titer of 100-250 Iu/l in the post-transplant period. It was reported that only 2 patients developed relapse during an average follow-up of 43 months and one of these patients did not use the treatment.[11]

Table 3. We see that there is no significant difference in the demographic and follow-up period data of the two groups with and without HBV recurrence.

	HBSAG			
	Negative, n (%)		**Positive (Relapse), n (%)**	
Gender				
Female	157 (26.48)		19 (19.79)	
Male	436 (73.52)		77 (80.21)	
	Mean±SS	**Median (Min-Max)**	**Mean±SS**	**Median**
Age	53.55±14.73	58 (5-83)	53.14±16.53	58
Tracking Period (Months)	79.61±52.04	64 (5-177)	89.28±50.98	75.5
MELD	18.57±5.02	16 (15-40)	18.1±4.58	16

Table 4. When the Hbs-ag levels of the patients are examined at the first month after surgery, Hepatitis B recurrence is observed in a total of 112 patients (16.1%) and when the Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence

Variables	n	(%)
Diagnosis		
HBV	454	65.3
HBV+HCC	151	21.7
HBV+HDV	61	8.8
HBV+HDV+HCC	24	3.5
HBV+HCV	3	0.4
HBV+HDV+HCV+HCC	1	0.1
HBV+HCV+HCC	1	0.1
HBSAG 1st month after liver transplantation		
Negative	583	83.9
Positive	112	16.1
Last chech HBSAG		
Negative	599	86.2
Positive	96	13.8

Treatment is given in combination with antiviral and HBIG. It is available in centers where powerful antivirals are used alone. Although the approaches of the centers vary, patients who have had a liver transplant due to HBV definitely need postoperative medical treatment to prevent HBV recurrence.

In another study where HBIG + Antiviral treatment was used, the anti-HBS level was 500 IU/L for the first 6 months and 100 IU/L for the follow-up, and no recurrence was observed during an average follow-up of 25 months.[12]

Anti-HBS level differences may be required in the follow-up of high-risk and low-risk groups. However, monitoring this requires detailed information about the patient discharged from the hospital.

In a study conducted by Fung et al., a 91% HBsAg negativity rate was reported at the end of 10 years with antiviral monotherapy in liver transplant patients with chronic hepatitis B who were previously resistant to Lamivudine.[13,14]

Combination therapy is recommended in our clinic. Comparative studies are needed in our high-volume center.

In the same study, while 72% of the patients had positive HBV DNA before surgery, HBV DNA was found to be negative in 91% of the patients at the end of the first year, and this rate was found to be 100% in the 5th and 8th years.[15]

When the effect of high-risk patient group on postoperative HBV recurrence was examined, it was seen that noncompliance with medical treatment was effective.

Despite all these findings, it has been reported that the use of HBIG has additional contributions such as reducing rejection and HCC recurrence rates after liver transplantation.[16]

Table 5. HBIG treatment algorithm, In the high risk group, 10,000 IU per day in the anhepatic phase, 2000 IU HBIG per day for the next week, and 2000 IU per day for 14 days if AntiHBS is <100 IU/L. In the low risk group, 5000 IU per day in the anhepatic phase, 500 IU HBIG per day for the next week, and 2000 IU per day for 14 days if AntiHbs is <100 Iu/l. Monthly anti-HBS levels are tried to be kept above 100 for life.

	High risk	Low risk
Anhepatic phase	10000 ıu	5000
First 7 days	2000	500
14 days	2000	500
Long term	2000	2000

If the anti-HBS level is < 100 IU/L in the first 7 days, the treatment is completed in 14 days.

Conclusion

Patients who have undergone liver transplantation due to HBV must have their Hbs-ag level checked when they are discharged from the hospital. Informing the patient about HBV recurrence and medical treatment provides a more meticulous medical treatment. In particular, antiviral treatment and access to HBIG should be provided, and a prospective study should be started in our liver transplantation institute to investigate HBV recurrence. The shortcomings of the study are that it is a retrospective study, not all patient data can be accessed in the study (Hospital automation system change), and the HBIG doses taken by the patient cannot be determined.

Disclosures

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Original Research

Liver Transplantation for Cryptogenic Cirrhosis: Where we are

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Abstract

Objectives: This study aimed to compare clinical and immunological features between patients undergoing liver transplantation with cryptogenic cirrhosis and those with determined etiologies.

Methods: Patients who underwent liver transplantation at our institute between March 2019 and March 2020 were retrospectively analyzed. Data including demographics, laboratory results, and post-transplant outcomes were collected from a prospectively maintained database. Immunoglobulin levels, autoantibodies, and pathological findings were evaluated.

Results: Of 201 patients, 24.4% had cryptogenic cirrhosis. These patients were older (mean age 54.8 years) and had higher BMI (mean 27.3) compared to those with determined etiologies. Immunological biomarkers did not significantly differ between groups. Autoimmune hepatitis was the most common diagnosis upon pathological examination of cryptogenic cases.

Conclusion: Immunological biomarkers did not differentiate cryptogenic cirrhosis from other etiologies in liver transplant patients. Higher BMI was associated with cryptogenic cirrhosis. Pathological examination frequently revealed autoimmune hepatitis in cryptogenic cases.

Keywords: Autoimmune hepatitis, cryptogenic cirrhosis, liver transplantation

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Liver transplantation (LT) represents a critical therapeutic intervention for individuals suffering from end-stage liver diseases, offering a chance of survival and improved quality of life. Among the diverse etiologies leading to irreversible liver damage, cryptogenic cirrhosis (CryC) has long been recognized as a significant indication for LT. CryC delineates a perplexing scenario where liver cirrhosis manifests without a clear underlying cause, despite exhaustive diagnostic endeavors. This diagnostic ambiguity poses challenges in both understanding the disease's pathophysiology and devising optimal treatment strategies. However, recent advancements in diagnostic modalities have heralded a notable decline in CryC prevalence, concurrent with the burgeoning recognition of nonalcoholic steatohepatitis (NASH) as a major etiological factor necessitating LT. This paradigmatic shift in disease landscape underscores the need for a comprehensive reevaluation of the clinical and immunological characteristics exhibited by LT recipients, particularly comparing those with CryC to individuals with identifiable etiologies.[1]

While CryC has historically accounted for a substantial proportion of LT cases, its declining prevalence raises intriguing questions regarding its underlying pathogenesis, clinical course, and outcomes post-transplantation. Under-

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standing these nuances is imperative not only for enhancing diagnostic accuracy but also for refining therapeutic interventions tailored to the specific needs of CryC patients. Moreover, the emergence of NASH as a prevalent indication for LT underscores the dynamic nature of liver disease epidemiology and necessitates a recalibration of clinical approaches to optimize patient care.[2-5]

Against this backdrop, this study endeavors to delve into the comparative analysis of clinical and immunological features exhibited by LT recipients with CryC versus those with determined etiologies. By scrutinizing demographic characteristics, comorbidities, liver function tests, and immunological markers, we aim to elucidate the distinct phenotypic profiles of these patient cohorts. Such insights hold immense potential for guiding clinical decision-making, prognostication, and therapeutic interventions in the context of LT for CryC. Moreover, a deeper understanding of the immunological underpinnings of CryC may pave the way for the development of targeted immunomodulatory therapies aimed at ameliorating disease progression and enhancing transplant outcomes.[2-5]

Through this comprehensive investigation, we aspire to contribute to the burgeoning body of knowledge surrounding CryC and its implications for LT, thereby advancing the frontiers of liver disease management and transplantation medicine. Ultimately, our overarching goal is to improve patient outcomes and enhance the efficacy of LT in addressing the diverse spectrum of liver pathologies encountered in clinical practice.

Methods

Study Population

All patients who underwent liver transplantation (LT) at our Liver transplantation Institute between March 2019 and March 2020 were considered for inclusion in this retrospective study. Patients were retrospectively identified from a prospectively maintained database. The diagnosis of cryptogenic cirrhosis (CryC) was established based on the exclusion of all other potential causes of liver disease according to standard criteria.

Exclusion Criteria

Patients were excluded from the study if they were under the age of 18 years or if they were lost to follow-up during the study period.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of Inonu University, and informed consent was obtained from all participants.no 2021/2571.

Data Collection

Clinical, demographic, and laboratory data were collected from patient records. This included age, gender, body mass index (BMI), graft source (living donor transplants), Model for End-Stage Liver Disease (MELD) scores, liver function tests, and immunological markers such as immunoglobulin levels (IgG1, IgG2, IgG3, Anti-gliadin IgA) and levels of autoantibodies (ANA, ASMA, anti-dsDNA). Additionally, post-transplant pathological findings and early survival data were investigated.

Statistical Analysis

Continuous variables were expressed as means and standard deviations, while categorical variables were presented as frequencies and percentages. Student's t-test was used to compare continuous variables, while Chi-square or Fisher's exact test was employed for dichotomous variables. All statistical analyses were conducted using SPSS version 20 software. p-values < 0.05 were considered statistically significant (IBM Corp. 1989, 2013. U.S. Government Users Restricted Rights - Use, duplication or disclosure restricted by GSA ADP Schedule Contract with IBM Corp.)

Results

During the study period, a total of 341 patients underwent LT. Among them, 140 patients were excluded from the study due to predefined exclusion criteria. Therefore, the final study cohort consisted of 201 patients, among whom 67% (n=132) were male, and the mean age was 49.9±13 years.

Preoperatively, 63 patients (31.3%) were initially diagnosed with cryptogenic cirrhosis (CryC). However, pathological examination revealed the etiology of cirrhosis in 14 of these cases. Consequently, a total of 49 patients (24.4%) were classified into the cryptogenic group (Table 1). The distribution of underlying diagnoses among the 201 patients who underwent LT is presented in Table 2.

Table 1. Pathological findings of the patients who were initially diagnosed as CryC

Findings	n (%)
No specific feature	42 (66.7)
HCC(incidental)	7 (11.1)
Autoimmune Hepatitis	5 (7.9)
NASH	3 (4.8)
Veno-occlusive Disease	3 (4.8)
Wilson Disease	2 (3.2)
Viral Hepatitis	1 (1.6)

CryC: Cryptogenic Cirrhosis; HCC: Hepatocelluler Carcinoma; NASH: Non Alcholic Steato Hepatitis.

Table 2. The frequencies of underlying diagnoses in 201 patients underwent LT.

Diagnosis	n (%)
Cryptogenic Cirrhosis	49 (24.4)
HBV	38 (18.9)
HCC	27 (13.4)
Autoimmune Hepatitis	17 (8.5)
Veno-occlusive disease	13 (6.5)
Alcoholic Cirrhosis	11 (5.5)
Wilson Disease	8 (4)
HBV+HDV	7 (3.5)
NASH	7 (3.5)
HCV	5 (2.5)
Primary Biliary Cirrhosis	5 (2.5)
Primary Sclerosing Cholangitis	5 (2.5)
Cystic Liver Disease (Ech. alveolaris)	4 (2)
Hemochromatosis	2 (1)
Epitel Hemanjioendotelioma	1 (0.5)
Toxic Hepatitis	1 (0.5)

CryC: Cryptogenic Cirrhosis; HCC: Hepatocelluler Carcinoma; NASH: Non-Alcoholic Steato Hepatitis; HBV: Hepatitis B; HCV Hepatitis C; HDV: Hepatitis D.

Comparison of demographic, clinical, and biochemical characteristics between the groups is summarized in Table 3. Patients with cryptogenic cirrhosis were found to be significantly older than those with other etiologies (54.8±10.2 vs. 48.3±13.5, p=0.002) and had a higher body mass index (BMI) (27.3±4.4 vs. 25.7±4.7, p=0.045). However, other parameters such as gender distribution, liver function tests, and immunological markers were similar between the groups.

Discussion

Cryptogenic cirrhosis (CryC) remains a significant indication for liver transplantation (LT) worldwide, albeit with varying prevalence rates across different regions. Our study adds to the growing body of literature on CryC by providing insights into its clinical, pathological, and prognostic characteristics within our patient cohort. Despite efforts to ascertain the etiology of liver cirrhosis, a considerable proportion of patients are diagnosed with CryC, highlighting the complexity of liver disease diagnosis and management.

The prevalence of CryC among LT recipients in our study cohort was notably higher (24.4%) than previously reported rates in Western countries (4–10%). This discrepancy may be attributed to several factors, including referral patterns, diagnostic practices, and regional variations in the epidemiology of liver diseases. Notably, our center serves as a tertiary referral center for complicated liver diseases in our region, receiving referrals from both within the country and neighboring countries. Consequently, we often encounter patients with advanced decompensated liver

Table 3. Demographic. clinical and biochemical characteristics of the groups

Parameters	Patients with Cryptogenic Cirrhosis (n=49)	Patients with Determined Etiologies (n=152)	p
Age	54.83±10.18	48.28±13.47	0.002
Gender (M/F)	30/19	102/50	0.451
BMI (kg/m2)	27.25±4.38	25.70±4.70	0.045
MELDNa	14.54±5.39	15.67±13.74	0.573
Early Mortality (%)	7 (14.29)	17 (11.18)	0.560
IgG1	13.79±4.40	14.90±7.04	0.319
IgG2	6.24±2.87	5.97±11.58	0.872
IgG3	0.98±0.55	1.14±1.68	0.534
IgG4	1.49±1.48	1.24±1.93	0.411
AntiGliadin IGA	19.51±17.49	22.41±36.15	0.693
AMA(Negative/Positive) (1/100 titer)	2/21	67/8	0.655
ASMA(Negative/Positive) (1/100 titer)	1/10	7/49	0.521
ANA (1/100 titer)	0.75±1.36	0.47±0.29	0.307
dsDNA			
<10	38 (77.55%)	131 (86.18%)	0.350
10-15	4 (8.16%)	7 (4.61%)	
>15	7 (14.28%)	14 (9.21%)	

IgG: Immunglobulin G; ANA: Anti-nükleer antikorlar; ASMA :Anti Smooth Muscle Antikor; AMA: Anti mitokondriyal Antikor; BMI: Body mass Index; MELD: The Model for End-Stage Liver Disease.

disease and high Model for End-Stage Liver Disease (MELD) scores, contributing to the higher prevalence of CryC in our cohort.

Comparisons with other studies from different geographic regions reveal substantial variability in CryC prevalence and clinical characteristics. For instance, Siriwardana et al. reported CryC as the leading indication for LT (58%) in Sri Lanka, with a predominantly male population and a mean age of 51 years. This highlights the diverse epidemiological patterns of liver diseases worldwide, influenced by factors such as environmental exposures, genetic predispositions, and healthcare infrastructure.[6]

In our study, despite extensive pre-transplant workup including viral profiles, immunoglobulin levels, autoantibody profiles, and specific markers for liver diseases, a definitive etiology could not be established in a significant proportion of CryC patients. This underscores the diagnostic challenge posed by CryC and the limitations of current diagnostic modalities in elucidating its underlying cause. Consistent with previous studies, we observed that a subset of patients initially diagnosed with CryC had identifiable etiologies upon pathological examination post-transplantation.[7] Ayata et al. similarly found that detailed clinicopathological correlation revealed specific diagnoses in the majority of cases initially labeled as CryC, including nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, and alcohol-related liver disease.[8]

Interestingly, despite the higher mean BMI observed in CryC patients in our cohort, histological examination revealed features of NASH in only a minority of cases. This suggests that CryC may not always be synonymous with NASH and underscores the importance of histopathological evaluation in establishing the etiology of liver cirrhosis.

Moreover, the presence of incidental hepatocellular carcinoma (HCC) in a subset of CryC patients raises concerns regarding surveillance and management strategies in this population. Thuluvath et al. demonstrated a higher prevalence of HCC in NASH cirrhosis compared to CryC in a large cohort analysis, highlighting the need for vigilant surveillance protocols in patients with CryC, especially considering the rising incidence of NASH-related HCC.[9]

The perioperative outcomes of CryC patients undergoing LT have been a subject of debate, with some studies reporting higher mortality rates compared to patients with other etiologies. Alamo et al. and Masior et al. reported higher perioperative mortality rates in CryC patients, attributing this to the advanced stage of liver disease and associated comorbidities.[10,11] However, in our study, we did not observe a significant difference in perioperative mortality between CryC and other etiologies. This suggests that meticulous patient selection, perioperative management, and advances in surgical techniques may have contributed to improved outcomes in CryC patients undergoing LT at our center.

Nevertheless, several limitations of our study warrant consideration. Regional differences in liver disease epidemiology and referral patterns may limit the generalizability of our findings to other populations. Additionally, the retrospective nature of the study and the relatively small sample size may have introduced selection bias and limited statistical power. Furthermore, the study was conducted during the COVID-19 pandemic, which may have impacted transplant practices and outcomes.

Conclusion

In conclusion, our study provides valuable insights into the clinical characteristics, diagnostic challenges, and outcomes of CryC patients undergoing LT. Despite regional variations in CryC prevalence and etiology, histopathological evaluation remains crucial in elucidating the underlying cause of liver cirrhosis in these patients. Future research endeavors should focus on refining diagnostic algorithms, exploring novel biomarkers, and elucidating the pathophysiological mechanisms underlying CryC to improve patient outcomes and optimize transplant allocation strategies.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of Inonu University, and informed consent was obtained from all participants.no 2021/2571.

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Authorship Contributions: Concept – A.B., M.K., M.Z.O., S.Y.; Design – A.B., M.K., M.Z.O., S.Y., Supervision – A.B., M.K., M.Z.O., V.I., S.Y.,; Materials A.B., M.K., M.Z.O., D.Y.B.; V.I., Data collection &/or processing – A.B., M.K., M.Z.O., D.Y.B.; V.I., Analysis and/or interpretation – A.B., M.K., M.Z.O., V.I., S.Y; Literature search – A.B., M.K., M.Z.O., D.Y.B.; V.I., Writing – A.B., M.K., M.Z.O., Critical review – A.B., M.K., M.Z.O., D.Y.B.; V.I., S.Y.

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Original Research

Effect of Bile on Fatty Liver and Metabolism in Rats

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Abstract

Objectives: Non-alcoholic fatty liver disease (NAFLD) is a range of liver disorders ranging from accumulation of fat in the liver (steatosis) to non-alcoholic steatohepatitis (necrosis and inflammation), eventually progressing in some individuals to fibrosis, cirrhosis, and liver failure, respectively.

Methods: The bile taken from the gallbladder, which was removed as a specimen from donor hepatectomy and living donor liver transplantation (LDLT) performed at Liver Transplantation Institute, was delivered daily to İnönü University Experimental Animal Production and Research Center under suitable conditions for use in the project. Monthly weights of all rats included in the study and the amount of bile consumed by rats in separate cages in the bile group were recorded.

Results: When the change in rat weights according to months was analyzed in the three groups 1st month, 2nd month, and 3rd month are made separately, the comparisons between the groups. Statistically significant differences were detected in the first month ($p<0.001$) and in the 3rd month ($p=0.001$).

Conclusion: This study aimed to determine whether bile contributes to the reduction of fatty liver. It was aimed to observe the effect of human bile fluid by giving it to study animals. In this study, by comparing the rats to which we gave bile by creating fatty liver, with the group with fatty liver damage and the control group, it was shown that bile improved fatty liver. In addition, it has been determined that bile has significant effects on routinely used laboratory tests such as ALT, ALP, cholesterol, triglyceride, HDL, and VLDL. When the results are evaluated, they make important contributions to the question of whether bile can be used by exogenous administration in the human body.

Keywords: Bile, bile acid, fatty liver

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Hepatitis Non-alcoholic fatty liver disease (NAFLD) is a group of liver diseases that includes steatosis, or the buildup of fat in the liver, and non-alcoholic steatohepatitis, or the inflammation and necrosis of the liver. In certain cases, NAFLD eventually progresses to cirrhosis, fibrosis, and liver failure.[1] A significant contributor to liver-related morbidity and death, nonalcoholic fatty liver disease (NAFLD) is being recognized as a hepatic manifestation of

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metabolic syndrome due to its prevalence linked to obesity, diabetes, and insulin resistance.[2,3]

Cirrhosis, cancer, and liver failure are all related to non-alcoholic fatty liver disease (NAFLD).[4] The prevalence of fatty liver disease is rising as a result of industrial food consumption, malnourishment, and alcohol usage. According to recent research, between 80 and 100 million Americans, or 30 to 40% of the country's population, suffer from NAFLD.[5] NAFLD is the primary cause of liver transplants globally, comes at a high financial cost, and lowers quality of life.[6] Because of this, research using animal experimental models to treat and prevent fatty liver has started to rise.[7,8]

Lipid droplets build up in the cytoplasm of hepatocytes, which results in fatty liver. Fatty liver is defined as having more than 5% of its weight in lipids and more than 2% of triglycerides (TG).[9]

Hepatosteatosis is categorized as mild, moderate, or severe based on factors such as lobular and portal inflammation, hepatocyte ballooning, and steatosis. A liver biopsy is the most accurate way to grade, diagnose, and determine the prognosis of steatohepatitis; thus, those who are at risk of liver disease should have a liver biopsy.

The liver produces bile, which is involved in the breakdown and assimilation of lipids. With an osmolality of 300 mOsm/kg, it is the physiological secretion of the liver that is comparable to plasma. Because it comprises bilirubin, salts attached to bile acids, phospholipids, cholesterol, proteins, electrolytes, bile dye, water, and several metabolites, it is the physiological secretion of the liver. The removal of metabolites—such as cholesterol and bilirubin—from the body that is produced as a result of the breakdown of blood products is another purpose of bile. Along with penicillin, sulfate, glucuronide, glutathione molecules, metals including copper and zinc, prostaglandins, fat-soluble vitamins, adrenal cortical hormones, and other steroid hormones are also expelled with bile.[10,11]

The liver produces bile, which is involved in the breakdown and assimilation of lipids. With an osmolality of 300 mOsm/kg, it is the physiological secretion of the liver that is comparable to plasma. Because it comprises bilirubin, salts attached to bile acids, phospholipids, cholesterol, proteins, electrolytes, bile dye, water, and several metabolites, it is the physiological secretion of the liver. The removal of metabolites—such as cholesterol and bilirubin—from the body that is produced as a result of the breakdown of blood products is another purpose of bile. Along with penicillin, sulfate, glucuronide, glutathione molecules, metals including copper and zinc, prostaglandins, fat-soluble vitamins, adrenal cortical hormones, and other steroid hormones are also expelled with bile.[12]

The gut is affected by bile salts in two significant ways. It first influences the separation of fat globules into minute pieces by lowering the surface tension on the oil particles. Second, bile salts combine with micelles, which are tiny lipid complexes. They return to the intestinal content after aiding in the transfer of lipids. Bile salts are critical for the absorption of fat-soluble vitamins because of their impact on fat absorption. By stool, 40% of lipids are lost in the absence of bile salts.[13,14]

Hepatic cholesterol metabolism produces bile acid amphipathic (i.e., containing both hydrophobic and hydrophilic) steroids, which are crucial for preserving energy balance. Despite their historical use as detergents in lipid emulsification, digestion, and absorption, fatty acids were discovered at the start of the twenty-first century to be ligands for the nuclear farnesoid X receptor (FXR), which regulates their synthesis.[15]

The body needs certain metals, including iron, zinc, copper, and selenium, for various metabolic processes. In different disorders, the number of atoms in the liver increases and decreases. Exposure to hazardous heavy metals like lead, mercury, manganese, zinc, nickel, chromium, and zinc rises with industrialization.[16]

An average of 250–300 living donor liver transplants are carried out each year at the İnönü University Liver Transplantation Institute. This high-volume transplant clinic provides bile. By giving the bile from the gallbladder specimen removed from donor hepatectomy and living donor liver transplantation performed in our center for living donor liver transplantation to rats that develop fatty liver, the study aims to determine the effects of the bile on fatty liver and metabolism. It was looked into whether bile could slow the progression of nonalcoholic fatty liver disease (NAFLD) by enhancing hepatic lipid metabolism and decreasing fat buildup. Rat liver biopsies were performed to assess the extent of hepatosteatosis. Additionally, blood analyses were used in the laboratory to study the follow-up parameters of hepatosteatosis.

Methods

The İnönü University Faculty of Medicine Animal Studies Local Ethics Committee was contacted before the commencement of the studies, and clearance was obtained (approved number: 2021/8-9/11732). The study was carried out in January 2023 and February 2022. The İnönü University Scientific Research Projects Coordination Unit provided financial assistance for the study (project approval number: TSA-2022-2734).

While the power analysis of the study was 0.05, the power of the test (1-beta) was 0.80, the effect size was 0.90 and the

alternative hypothesis (H1) was two-sided, the minimum sample size required to find a significant difference using this test was 25 in each group. It was calculated that there should be 75 rats in total.

75 Wistar albino female rats, three months old and weighing 200–300 g, were bred by İnönü University Experimental Animal Production and Research Center and utilized in the research. 75 Wistar albino female rats were randomly assigned to three groups (n=25) as part of the project's scope.

The same number of rats that developed hepatosteatosis after being fed a high-fat diet (ARD-24, Diets D12451, Ankara, Turkey) with 45% of the food content being fat after 12 weeks were produced as the harm group and 25 rats fed a normal diet were established as the control group.

By including 20 milliliters of bile fluid per day into the dietary regimen, a bile group was established to assess the impact of bile on hepatosteatosis and metabolism.

Rats were kept in living quarters with regulated temperature (22±1°C) and humidity (55±5%) with a 12:12 h light/dark cycle. The rats were fed normal pellet feed measuring 8 mm, and they had unlimited access to water. The study groups are summarized in Table 1.

Under appropriate conditions, the gallbladder's bile—which was removed as a specimen from the Liver Transplantation Institute's donor hepatectomy and living donor liver transplantation (LDLT)—was sent every day to the İnönü University Experimental Animal Production and Research Center for use in the project. All of the study's rats' monthly weights were noted, as was the quantity of bile eaten by the rats in the bile group who were housed in different cages.

Measurements were made of the following: high-density lipoprotein (HDL) from intracardiac blood samples taken at the end of the third month; triglyceride; aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Lactate Dehydrogenase (LDH), cholesterol, total bilirubin, Alkaline Phosphatase (ALP), Gamma Glutamyl Transferase (GGT), and very low-density lipoprotein (VLDL). In the biochemistry lab of İnönü University Turgut Özal Medical Center, measurements were taken on several instruments.

Table 1. Summary of Study Groups

Study groups	Group Name	Explanation
1. Group	Control group (n=25)	8 mm standard pellet feed was used for 12 weeks and access to drinking water was provided *ad libitum*.
2. Group	Damage group (n=25)	Rats were fed with 45% high-fat feed for 12 weeks and had access to drinking water *ad libitum*.
3. Group	Bile group (n=25)	Rats were fed with 45% high-fat feed for 12 weeks, and access to bile fluid was provided *ad libitum*. The bile fluids of the cages were renewed every other day.

As part of the experiment, rats were put to death intraperitoneally with 300 mg/kg of ketamine and 25 mg/kg of xylazine to identify fatty liver. The pathology department then assessed the level of hepatosteatosis in the liver tissues that were removed.

The livers of the rats were fixed in 10% formaldehyde solution, embedded in paraffin, sectioned at 4-5 µm thickness by a microtome and stained with routine hematoxylin-eosin (HE) for microscopic examination. The morphological evaluation was made under a light microscope (Olympus BX51).

The percentage of hepatocytes (0% to 100%) with macro- or micro-vesicular fat was used to semi-quantitatively quantify the liver steatosis. The proportion of fat in the hepatocytes was expressed as a score between 0 and 4 (0): less than 5%, 1: 5–15%, 2: 16–25, 3: 26–35, and 4: more than 35% steatosis.

The following elements are present in liver tissue: sodium (Na23), potassium (K39), vanadium (V51), copper (Cu65), zinc (Zn66), rubidium (Rb85), and molybdenum (Mo98), lithium (Li7), magnesium (Mg24), and aluminum. Atomic weights of iron (Fe57), nickel (Ni60), calcium (Ca44), chromium (Cr52), manganese (Mn55), selenium (Se78), and aluminum (Al27) were noted. Measurements were conducted at the İnönü University Faculty of Engineering's Chemical Engineering laboratory.

The Shapiro-Wilk test was used to determine if the quantitative data in the research were appropriate for a normal distribution. The summary of non-normally distributed data was represented by the median (minimum-maximum), whereas the summary of normally distributed data was mean±standard deviation. The Kruskal Wallis test, One-Way Analysis of Variance, and One-Way Analysis of Variance in Repeated Measurements were employed in statistical studies when needed. The Kruskal Wallis test in multiple comparisons was conducted using the Mann-Whitney U test with Bonferroni correction, the One-Way Analysis of Variance in Repeated Measurements was conducted using the dependent sample t-test with Bonferroni correction, and the Tukey test was utilized for the one-way analysis of variance. A p-value of less than 0.05 was deemed statistically significant in the statistical analysis used. Every analysis was carried out with IBM.

Results

When the change in rat weights according to months was analyzed in the three groups 1st month, 2nd month, and 3rd month are made separately, the comparisons between the groups. Statistically significant differences were detected in the first month ($p<0.001$) and in the 3rd month ($p=0.001$) (Table 2).

The total amount of bile consumed in 24 hours by 5 rats in each cage in the Bile group fed with bile is given in Table 3. When the control group fed normally, the damage group fed a high-fat diet, and the group given bile along with a high-fat diet were compared in terms of the percentage of fatty liver, a statistically significant difference was detected ($p<0.001$) (Table 4).

Upon evaluating the laboratory tests, statistically significant changes were found in the levels of ALT, cholesterol, ALP, and HDL between the groups that were fed a normal control, the damage group that was fed a high-fat diet, and the group that received bile fluid in addition to a high-fat diet ($p<0.001$). Triglycerides, VLDL levels, and a high-fat meal were supplied to the harm group, the control group, and the group that also received bile.

Statistically significant differences were found ($p=0.015$) when the values were compared. There was no statistically significant difference seen ($p=0.504$) between the direct bilirubin values of the control group, which was fed normally, the harm group, which was fed a high-fat diet, and the group that received bile in addition to a high-fat diet. Upon comparing the AST readings of the normal control group, the high-fat diet-eating damage group, and the group that consumed bile in addition to a high-fat diet, no statistically significant difference was seen ($p=0.113$). Upon comparing the LDH levels of the normal control group, the high-fat diet group that underwent damage, and the group that combined a high-fat diet with bile, no statistically significant difference was seen ($p=0.928$).

There was no discernible statistical difference in the total bilirubin values of the groups that were fed normally as the control, the harm group that followed a high-fat diet, and the group that took bile in addition to the high-fat diet ($p=0.227$). Upon comparing the GGT values of the control group, the high-fat diet group that received damage, and the group that received bile in addition to a high-fat diet, no statistically significant variation was seen ($p=0.354$) (Table 5).

Table 2. Analysis table of rat weights according to months in terms of groups

Variable **	Group*			p***
	Control	Damage	Bile	
Beginning	188.92[a,b]±7.182	163.16[b]±11.123	173.8±9.161	<0.001
1. Month	252.24[a,b]±12.451	225.16±21.005	228.708±19.767	<0.001
2. Month	275.44[a,b]±15.387	250.8±24.157	251.583c±23.063	<0.001
3. Month	282.087[a,b]±15.951	255.391±27.696	262.545±24.114	0.001

*: [a]: Different according to damage group, [b]: Different according to bile group; **: Variables are summarized as 'mean±standard deviation'; ***: One-Way Analysis of Variance.

Table 3. Amount of bile fluid drunk in cages in the bile group

Variable*	Group**					p***
	1. Cage	2. Cage	3. Cage	4. Cage	5. Cage	
Amount of Bile Fluid Consumed (mL)	132 (50-199)	133d (40-261)	134d (45-226)	137d (47-221)	127 (37-195)	0.00674

*: Variables are summarized as 'median (min.-max.)'; **: d: It differs depending on the cage 5; ***: Kruskal Wallis test.

Table 4. Analysis table regarding the percentage values of fatty liver in terms of groups

Variable*	Group**			p***
	Control	Damage	Bile	
Percentage	0[a,b] (0-0)	10[b] (0-35)	0 (0-20)	<0.001

*: Variables are summarized as 'median (min.-max.)'; **: a: It differs according to the damage group, b: It differs according to the bile group; ***: Kruskal Wallis test.

Table 5. Serum biochemistry parameters

Variables	Groups					
	Control		Damage		Bile	
	Mean±SD	Median±Min.-Max.	Mean±SD	Median±Min.-Max.	Mean±SD	Median±Min.-Max.	p
Direct Bilirubin (mg/dL)	0.03±0.02	-	0.04±0.01	-	0.04±0.02	-	0.504**
AST (U/L)	149.57±37.88	-	140.53±47.4	-	124.06±25.74	-	0.113**
ALT (U/L)	54.35[a,b]±15.7	-	33.53±6.44	-	29.78±7.05	-	<0.001**
LDH (U/L)	957.61±407.59	-	974.95±330.27	-	1000.61±301.8	-	0.928**
Cholesterol (mg/dL)	62.96[a,b]±13.65	-	74.47±7.98	-	80.78±10.97	-	<0.001**
Total Bilirubin (mg/dL)	-	0.2 (0.1-0.2)	-	0.1 (0.1-0.2)	-	0.2 (0.01-0.2)	0.227***
ALP (U/L)	-	90[a,b] (33-143)	-	136 (102-259)	-	124.5 (77-237)	<0.001***
GGT (IU/L)	-	0 (0-5)	-	0 (0-5)	-	0.5 (0-5)	0.354***
HDL (mg/dL)	-	40[a,b] (28-69)	-	52 (40-63)	-	54.5 (45-67)	<0.001***
Triglyceride (mg/dL)	-	91[a,b] (60-249)	-	113 (83-253)	-	134.5 (17-201)	0.015***
VLDL (mg/dL)	-	18.2[a,b] (12-49.8)	-	22.6 (16.6-50.6)	-	26.9 (3.4-40.2)	0.015***

AST: Aspartate Aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; GGT: Gamma-glutamyl transferase; HDL: High density lipoprotein; VLDL: Very low density lipoprotein; **: One-way analysis of variance; ***:Kruskal Wallis test.

When the levels of atoms in the liver tissue are examined across the groups, the concentrations of molybdenum (Mo98), copper (Cu65), zinc (Zn66), sodium (Na23), potassium (K39), vanadium (V51), and rubidium (Rb85) differ statistically significantly. (p is less than 0.0550). In terms of ppb atoms, there is statistical significance between groups for lithium (Li7), magnesium (Mg24), aluminum (Al27), calcium (Ca44), chromium (Cr52), manganese (Mn55), iron (Fe57), nickel (Ni60), and selenium (Se78). No discernible change has occurred. (p>0.05) (Table 6).

Discussion

This study aimed to investigate the potential role of bile in the decrease of fatty liver. The purpose of administering human bile fluid to study animals was to see what effects it might have.

The liver secretes bile, which travels via the bile duct system and into the duodenum. Following cholecystokinin activation, some bile enters the gastrointestinal system where it is concentrated before being distributed during digestion. In particular, bile plays a role in the digestion of fat. Additionally, it is a crucial and exclusive method for excreting copper, bilirubin, and cholesterol. enters the intestine: bile, immunoglobulins, bile acids, etc.[17]

When the groups in our study were compared, total bilirubin readings did not change, despite differences in the levels of copper in the liver, cholesterol, HDL, triglyceride, and VLDL.

Up to 90% of NAFLD cases show an asymptomatic rise of ALT and AST values when other liver disease causes are ruled out, according to research by Pouwels et al.[18] In NAFLD patients, ALT rises to occur more frequently than AST elevations. Compared to ordinary steatosis, NASH typically has higher ALT levels. Levels of albumin, bilirubin, and ALP may also be raised. No change in AST levels was identified, even though ALT levels were shown to be different in our investigation, which is consistent with the conclusion in this review.

The distribution of components in the liver tissue for each of the three groups—control, injury, and bile—displays variations when Table 5 is studied. In all three groups, the elements Li, Na, Mg, Al, K, Ca, Mn, Fe, and Zn have a very homogenous distribution. Except for Al and Li, these elements are crucial to human existence. Nonetheless, it is noted that the damage group and bile group exhibit noticeably higher accumulations of metals such as nickel, copper, chromium, selenium, vanadium, rubidium, and molybdenum in comparison to the control group. This is to be expected given the significance of liver tissue to the body.

Lithium, salt, iron, and nickel levels in liver tissue drop in the

Table 6. Analysis table regarding the amounts of atoms in liver tissue in terms of groups

Variable*	Group**			p***
	Damage group	Control groub	Bile groub	
Lİ7 ppb	34.375 (3.85-71)	58.775 (34.375-89.3)	22.15 (3.85-77.1)	0.21793
NA23 ppm	512.619 (463.918-564.87)	537.213[b] (489.264-555.724)	456.601 (413.521-495.886)	0.04372
MG24 ppm	218.779 (200.157-226.721)	226.05 (193.015-228492)	228.043 (223.307-231.825)	0.08982
AL27 ppb	409.175 (225.1-648.275)	468.95 (155.775-1231.6)	538.3 (117.5-1289)	0.81058
K39 ppm	2199.806[a,b] (1977.853-2240.771)	2546.138 (2198.558-2569.618)	2349.414 (2299.303-2459.962)	0.02065
CA44 ppm	39.956 (32.282-61.829)	40.862 (39.835-47.267)	44.186 (36.149-57.056)	0.78432
V51 ppb	140.95[a] (84.75-229.025)	69.575[b] (44.7-112.575)	173.55 (116.4-219)	0.01674
CR52 ppb	279.35 (191.85-448.925)	354.1 (297.6-507.25)	390.575 (310.35-428.875)	0.20488
MN55 ppb	2375.225 (1949.025-2769.05)	2427.575 (2205.75-2727.925)	2754.1 (2609.525-3288.75)	0.06654
FE57 ppm	287.226 (129.296-300.063)	288.599 (247.101-384.551)	207.335 (182.735-224.054)	0.07502
Nİ60 ppb	33.275 (12.3-40.25)	5.3 (0-40.25)	19.3 (0-68.225)	0.41066
CU65 ppb	2907.825[ab] (2526.325-3282.275)	4031.15 (3020.875-4299.625)	3833.35 (3211.625-3925.175)	0.02086
ZN66 ppm	21.259[ab] (19.675-22.127)	24.661 (20.326-25.228)	23.827 (22.427-25.461)	0.03579
SE78 ppb	216.2 (0-684.65)	937.9 (399.375-1679.675)	496.975 (0-1022.675)	0.10791
RB85 ppb	1657.75[ab] (1538.675-1834.7)	10957.33[b] (10509.95-11504.85)	2061.725 (1716.725-2121.8)	0.00306
MO98 ppb	566.7[ab] (408.725-573.725)	829.6[b] (647.45-935.3)	668.5 (636.525-766.8)	0.00443

*: Variables are summarized as 'median (min.-max.)', **: [a]: Different from the control group, [b]: Different from the bile group., ***: Kruskal Wallis test.

bile-fed group while other elements rise. The body's requirements, intake, and tissue buildup can be used to explain these findings. That is, if it is required in other bodily areas, it is used up and does not build up; if it is not required, it builds up in the liver. This perspective is supported by the elevated concentrations of all harmful components in the liver.

It is possible to say that bile plays a role in the liver's buildup of inorganic substances from nutrient-rich food, particularly harmful substances.[19] According to research by Ashley et al., there is a reciprocal association between hepatic lipid accumulation and fibrosis. In this study, there was a substantial difference in the end-of-study weights of the groups fed a high-fat diet and those fed a regular diet. Despite having a shorter research time, there was a noticeable difference between the three groups' monthly weights, particularly in the third month, when the comparison was made.

According to Donkers et al.,[20] bile acid intake may be a novel strategy for treating hepatosteatosis and obesity by lowering intestinal fat absorption and boosting energy at the same time. Fatty acid absorption and de novo lipogenesis both influence the lipid buildup in the liver that is brought on by a high-fat diet. Hyperglycemia and insulin resistance are linked to obesity and high-fat diets.[19] There is compelling evidence that the pathophysiology of extreme obesity, insulin resistance, non-alcoholic fatty liver disease (NAFLD), dyslipidemia, and type 2 diabetes is shared. This is due to aberrant fatty acid metabolism and signaling.[16]

Metabolic implications of fatty liver are a global health concern. Bile acids are involved in the metabolism of fat and energy. The liver produces primary bile acids, which the intestinal bacteria transforms into secondary bile acids. Both animal models of non-alcoholic steatohepatosis (NASH) and fatty liver disease have been the subject of substantial research on bile acid receptors and their agonists. Bile acid receptor agonists have been shown in clinical studies to offer promise in the treatment of NASH.[21] At the moment, research on the benefits of natural products and herbal extracts on non-alcoholic fatty liver disease (NAFLD) is becoming more and more popular. Several of these studies have been done on a variety of herbal items that have strong anti-NAFLD properties.[22,23]

With a high incidence and prevalence across all age and gender categories, nonalcoholic fatty liver disease has emerged as the leading cause of chronic liver disease in both industrialized and developing nations. NAFLD impacts several organ systems outside of the liver in addition to being linked to mortality or morbidity related to the liver. The most prevalent conditions are type 2 diabetes, chronic renal disease, and cardiovascular illnesses.[24]

Cachexia can be affected by exogenous administration of artificial bile acids (ursodeoxycholic acid).[25] A medication called ursodeoxycholic acid is used to treat and control cholestatic liver disease. It affects the liver by several intricate and synergistic processes, including modifications to the bile acid pool, cytoprotection, immunomodulation,

and choleretic action.[26] Yet, there isn't presently a nonalcoholic steatohepatitis (NAFLD) medication that has been licensed by the Food and Drug Administration (FDA).[27]

Despite the identification of several chemical processes, routes, and histological mechanisms associated with fatty liver, no effective therapeutic approach is now in common use. Strategies for weight loss and dietary cholesterol reduction are still employed in the battle against fatty liver. We believe that larger-scale animal studies and later human studies will provide additional insight into the advantages of actual bile fluid, given the areas in which physicians employ fake bile acids.

In this study, it was demonstrated that bile improved fatty liver by comparing the rats to which we provided bile by inducing fatty liver, with the group with fatty liver damage and the control group. Additionally, it has been found that bile significantly affects commonly used laboratory tests including HDL, VLDL, ALT, ALP, cholesterol, and triglycerides. When the data are analyzed, they significantly advance the debate over whether the human body can utilize bile that has been administered externally.

Conclusions

In our investigation, bile acid generated by the human body was utilized in place of synthetic bile acid. The results of this investigation will significantly advance our knowledge of bile's impacts.

Our research revealed that giving bile to rats with high-fat diet-induced NAFLD enhanced liver function, raised hepatic antioxidant activity, and decreased blood levels of lipid profiles. In rats with nonalcoholic fatty liver disease (NAFLD), bile therapy reduced lobular inflammation, liver steatosis, and ballooning, according to pathological examination.

Important findings from this study suggest that bile may be a novel therapeutic agent for lowering body weight, liver fat mass, and body fat percentage. To fully understand the impact of bile on human metabolism, more research is required.

Disclosures

Ethics Committee Approval: The İnönü University Faculty of Medicine Animal Studies Local Ethics Committee was contacted before the commencement of the studies, and clearance was obtained (approved number: 2021/8-9/11732). The study was carried out in January 2023 and February 2022. The İnönü University Scientific Research Projects Coordination Unit provided financial assistance for the study (project approval number: TSA-2022-2734).

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Case Report

Nodular Hyperplasia Mimicking Colon Cancer Liver Metastasis

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Abstract

Oxaliplatin-based chemotherapy protocols have improved survival in colorectal cancer as an adjuvant treatment. Nevertheless, sinusoidal obstruction syndrome (SOS) may occur during oxaliplatin therapy. Liver lesions related to sinusoidal obstruction syndrome can mimick liver metastasis. A 35-year-old female patient who has a history of right hemicolectomy due to colon adenocarcinoma 10 years ago, received 9 cycles of 500 mg capecitabine and 100 mg oxaliplatin as an adjuvant chemotherapy. Suspicious nodules were diagnosed at the liver during magnetic resonance imaging (MRI) which was performed 10 years after right hemicolectomy. Surgical intervention was performed. Focal nodular hyperplasia was diagnosed for all the liver lesions after pathological evaluation. Patients with colorectal cancer who received oxaliplatin based chemotherapy with the new onset liver lesions should be examined carefully. Not only radiological evaluation but also core needle biopsy should be used for misdiagnosis and preventing overtreatment.

Keywords: Chemotherapy, liver, metastasis

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Oxaliplatin-based chemotherapy protocols have improved survival in colorectal cancer as an adjuvant treatment.[1,2] Nevertheless, sinusoidal obstruction syndrome (SOS) which includes pathologic changes at the liver such as sinusoidal dilatation, peliosis and nodular hyperplasia may occur during oxaliplatin therapy.[3] Liver lesions related to sinusoidal obstruction syndrome can mimick liver metastasis on radiologic images.[4] These lesions can be misdiagnosed and overtreated as metastatic liver disease. We would like to report a 35 years old lady who seems to have metastatic liver disease due to colon cancer after adjuvant chemotherapy, but the final diagnosis of her liver lesions are focal nodular hyperplasia which were confirmed on pathology.

Case Report

A 35-year-old female patient had a nonspecific bellyache. She has a history of right hemicolectomy due to colon adenocarcinoma 10 years ago. Also, she had received 9 cycles of 500 mg capecitabine and 100 mg oxaliplatin as an adjuvant chemotherapy. Routine physical examination for the patient has been performed. There was no pathological sign. Laboratory test results were in normal range except AFP level (21.30 ng/ml) and CA 125 level (42 u/ml). CEA level was in normal range. Suspicious nodules were diagnosed at the liver during magnetic resonance imaging (MRI) which was performed 10 years after right hemicolectomy (Fig. 1). Differential diagnosis of these liver nodules couldn't be clarified if they were malignant or benign le-

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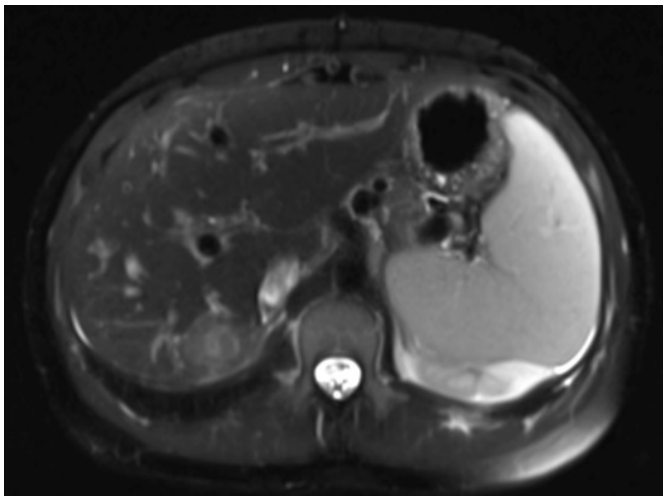

Figure 1. Axial MRI images shows a 3.6 cm mass lesion in segment 6-7 with heterogenous contrast enhancement.

sions, so surgical intervention was planned. There were 4 lesions in the liver. Metastasectomies with intact surgical margins were performed for both of the lesions (Figs. 2 and 3). Patient was discharged 5 days after surgery without any complication. Focal nodular hyperplasia was diagnosed for all the liver lesions after pathological evaluation.

Discussion

Oxaliplatin-based chemotherapy as an adjuvant therapy is routinely used for patients with colorectal cancer.[5,6] SOS, has some manifestations such as sinusoidal dilatation, peliosis and nodular regenerative hyperplasia as a side effect of oxaliplatin.[7,8] Deleve et al. showed that the pathologic process is initiated in the liver sinusoidal cells so it is called as sinusoidal obstructive syndrome in 1999.[9] The injury of sinusoidal endothelial cells causes the sinusoidal wall disjunction.[10,11] Extravasation of the foating red blood cells into the space of Disse through the opened gaps (peliosis) which starts the depositon of collagens, exposes perisinusoidal fibrosis. This is the main reason of sinusoidal outlet obstruction. The pathologic process is usually widespread and involves all the liver, but sometimes focal areas on non-tumoral liver tissue can be affected which may be misdiagnosed as metastatic liver disease.[12]

These focally affected liver lesions can be misdiagnosed as metastasis.[13] Generally the affected areas of liver can be visualised as heterogeneous echotexture lesions on the ultrasonography, on the other hand they are examined as hypodense lesions on multiphase CT scans. Also heterogeneous enhancement may be seen in some cases.[3] On

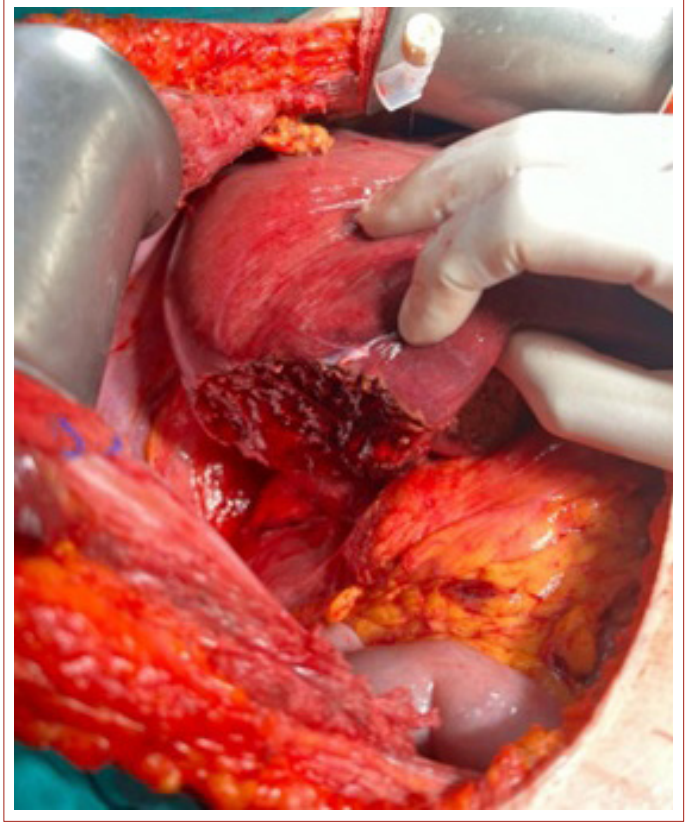

Figure 2. Metastasectomy from segment 6 and 7.

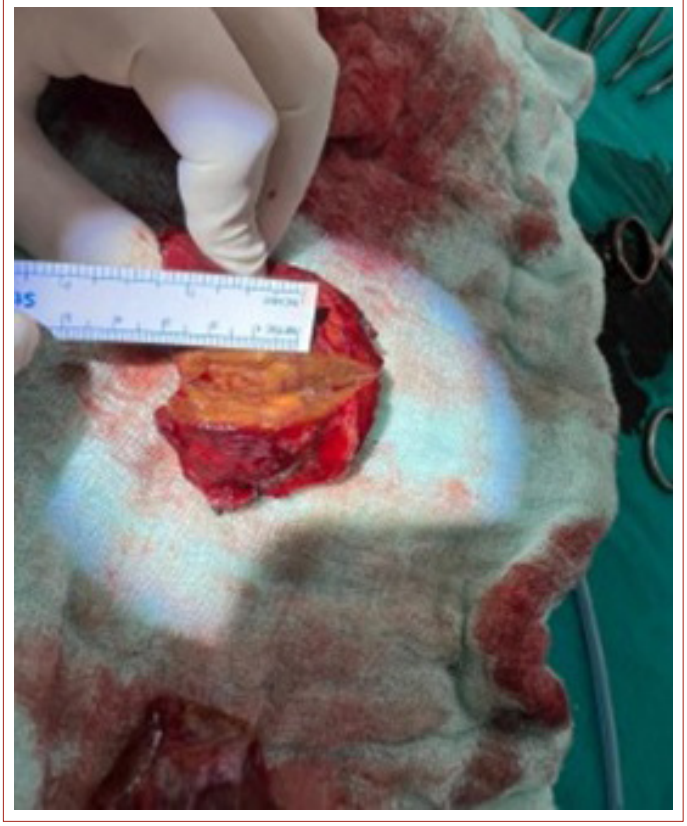

Figure 3. Metastasectomy from segment 6 and 7.

T1-weighted portal phase MRI these lesions can be visualised as hypo and iso-intense on pre-contrast phase with no enhancement. And also they can be examined as hyper intense on T2-weighted MRI.[14] Pathologically proven chemotherapy-induced focal sinusoidal injury and metastatic liver lesions were compared in a study using liver MRI (with liver specific contrast agents). They reported specific findings of focal SOS such as non-spherical shape, ill-defined margin and intermingled signal intensity pattern. When they compare these lesions to metastatic liver lesions they found that ninety percent of the metastatic lesions had peripheral rim enhancement on arterial and portal phase.[14] There were four lesions visualised at our patient's MRI. The largest one was approximately 3,5 cm at segment 6-7, one of them was 1.2 cm in largest diameter at segment 4 and other two lesions were almost 1 cm in diameter subcapsular localization at segment 2 and 3. Both of them had heterogenous contrast enhancement.

Colorectal liver metastasis can be diagnosed with various imaging modalities. After the comparison of these tools they found that sensitivity of MRI is better than CT (91% vs 82%) and PET CT (91% vs 60%) in all patients.[15] In recent metaanalysis MRI has been found as the most sensitive imaging modality to identify colorectal liver metastasis.[16,17]

Carsino embryonic antigen (CEA) is an important tool in confirming tumour burden and response to adjuvant therapy. In a recent study it is reported that CEA levels of<1.97 ng/ml after chemotherapy may be the evidence of pathologic response with a sensitivity of 73.6%, a specifity of 75% and accuracy of 74.6%.[18] CEA level of our patient was stabile and in normal range during the follow up period. Only the AFP level and CA125 level was slightly high.

Because of the needle tract seeding and bleeding risk core needle biopsy for resectable colorectal liver metastases is quited.[19] If there is a situation like atypical imaging or suspicious diagnosis, preoperative biopsy can be performed with multidisciplinary discussions. In our daily practice we do not prefer to perform liver biopsy for resectable colorectal liver mestases. We generally prefer to remove these contrast enhanced liver lesions surgically if they have the history of colon adenocancer.

Conclusion

Patients with colorectal cancer who received oxaliplatin based chemotherapy with the new onset liver lesions should be examined carefully. Not only radiological evaluation but also core needle biopsy should be used for misdiagnosis and preventing overtreatment.

Disclosures

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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Case Report

Major Liver Resection for Advanced Alveolar Echinococcosis: An alternative to Liver Transplantation

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Abstract

Alveolar Echinococcosis (AE) is a zoonotic infestation with aggressive behavior1. Most patients are asymptomatic in the early period, and therefore they are often detected incidentally during radiological examinations performed for other reasons.[1] AE is considered a tumor-like disease because the disease grows in the liver by invading the surrounding tissue and metastasizes to distant organs in some patients.[2] Therefore, resection is recommended in surgical treatment according to oncological principles, that is, with clean surgical margins.[3] The present report aims to present our approach to a patient diagnosed with alveolar echinococcosis, which occupied the right lobe of the liver and included the part of the left hepatic vein flowing into the IVC, was prepared for liver transplantation and was saved from liver transplantation by liver resection.

Keywords: Alveolar Echinococcosis, hepatectomy, liver transplantation, resection

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Alveolar Echinococcosis (AE) is a zoonotic invasion that progresses slowly, has aggressive behavior, and is difficult to treat due to its tendency to infiltrate tissue. Most patients are asymptomatic in the early stages, and therefore they are often detected incidentally during radiological examinations performed for other reasons.[1] AE considered a tumor-like disease because the disease grows in the liver by invading surrounding tissue and occasionally, metastasizes to distant organs.[2] The disease is usually fatal due to complications caused by metastatic lesions or liver failure caused by the primary lesion. For this reason, resection with clean surgical margins is recommended in surgical treatment according to oncological principles.[3] Depending on the localization of the disease in the liver, one or more of the options of non-anatomical hepatectomy, segmentectomy, partial hepatectomy and liver transplantation can be performed.[3] We present a patient who was planned for liver transplantation with a diagnosis of AE, was taken into surgery after donor preparation, underwent resection (ICG test for parenchymal adequacy), and did not need liver transplantation with vascular reconstruction in the remnant liver tissue.

Case Report

A 33-year-old male patient weighing 76 kg was admitted to our center with complaints of abdominal swelling and jaundice. Contrast-enhanced abdominal and thoraxic tomography revealed an alveolar echinococcus compatible

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lesion (200 mm x 110 mm x 100 mm) (Fig. 1a, b), which completely included the right and middle hepatic veins of the liver, partially surrounded the left hepatic vein without invading and had no extrahepatic spread. At the multidisciplinary council, it was decided to radiologically embolize the right portal vein to increase the size of the left lobe of the liver and to take the patient into surgery for resection three weeks later, after the living liver donor candidate was prepared (for emergency liver transplantation). In the CT scan taken 3 weeks after selective right portal vein embolization performed by interventional radiology (Fig. 2), the left lobe liver volume increased from 570 grams to 660 grams, and there was a 15.9% volume increase. ICG extraction test was performed (Fig. 3) and the R-value was below 15 and the PDR value was above 18. During parenchymal transection, the left hepatic vein was observed to be in close contact with the lesion. Two vascular clamps were placed on the part of the left hepatic vein opening to the inferior vena cava and on the part remaining within the intact parenchyma, and the surrounding left hepatic vein was removed en bloc together with the tumoral-like lesion. Then, left hepatic vein reconstruction was performed using a polyethylene terephthalate (Dacron) vascular graft (Fig. 3). Perioperative doppler ultrasonography confirmed that reconstructed left hepatic vein flow was normal. The patient was given low molecular weight heparin in the early postoperative period. When the patient was discharged, albendazole (15 mg/kg/day) and coumadin (INR: 1.5-2 for 6 months) were prescribed. The patient was given albendazole treatment for 2 years and it was confirmed by radiological instruments that there was no disease recurrence (Fig. 4).

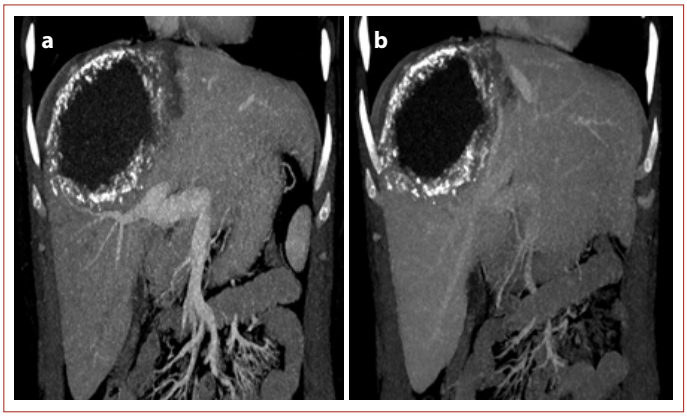

Figure 1. (a, b) Preoperative dynamic CT image of.

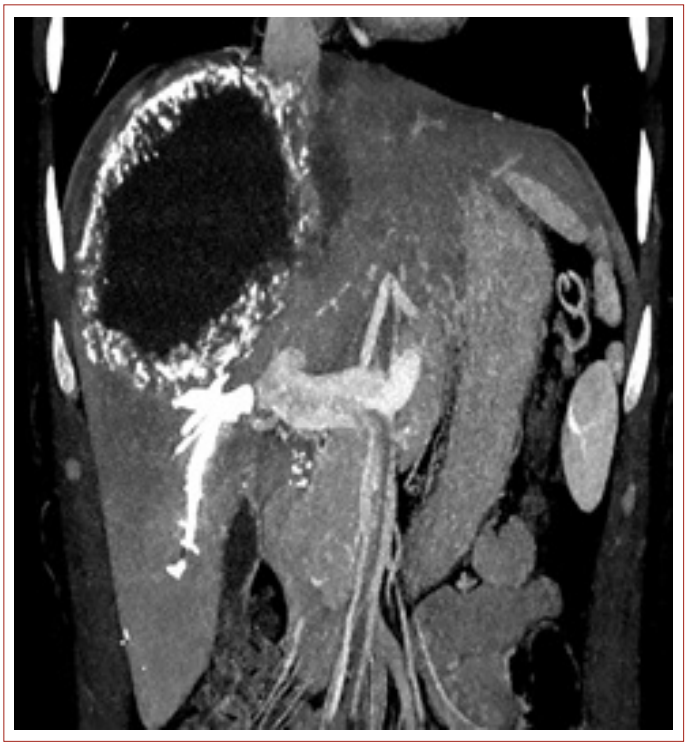

Figure 2. Dynamic CT image of the liver after embolization of the portal vein.

Discussion

If AE cannot be resected with a clean surgical margin and without causing hepatic failure due to a zoonotic infection, hilar involvement, or involvement of both liver lobes, the only treatment option is LT.[5] Liver transplantation was planned for our patient. Hepatic AE occupied the right lobe of the liver and invaded the left hepatic vein where it com-

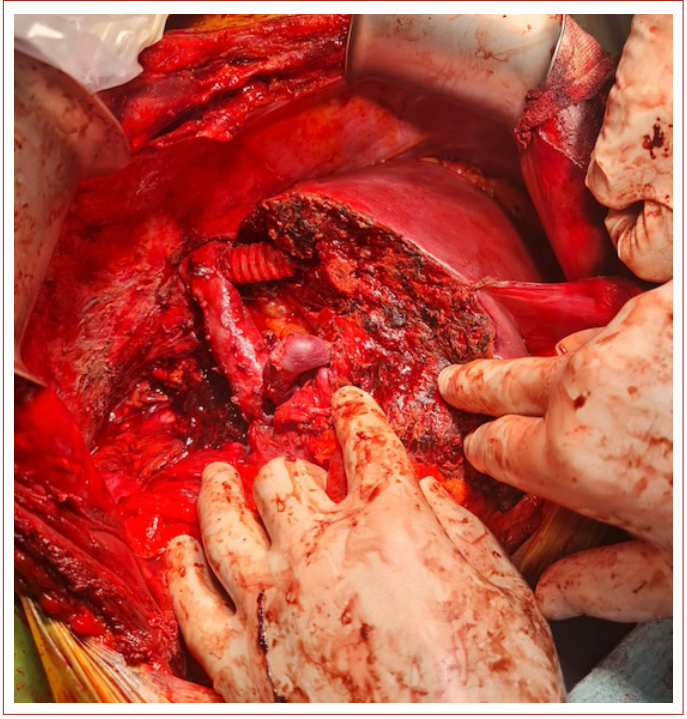

Figure 3. Reconstructed image of the left hepatic vein with synthetic graft.

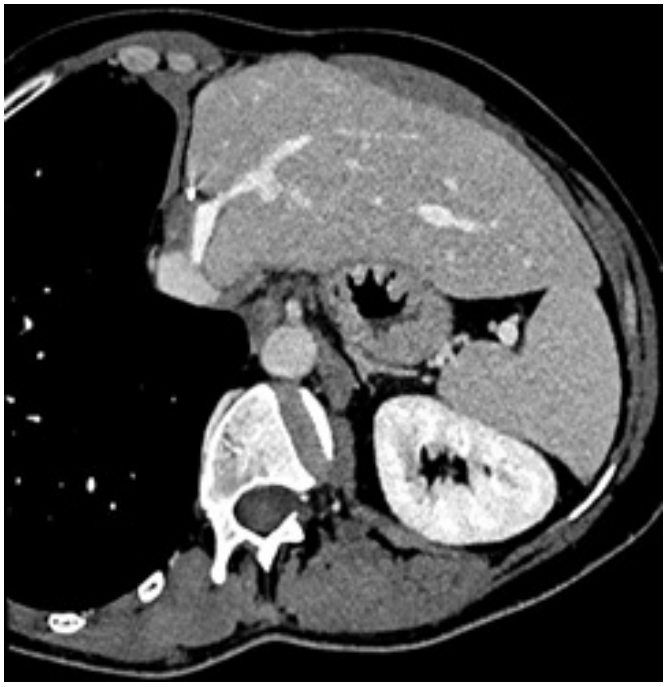

Figure 4. Dynamic CT image of the reconstructed left hepatic vein at 6 months.

mences with the VCI. There was no lesion in the left lobe of the liver parenchyma. Hepatic vein flow was achieved by right hepatectomy and partial left HV resection and reconstruction with a synthetic vascular graft. We were able to resect the lesion and therefore, we did not perform liver transplantation for the patient. As a medical treatment for AE patients, benzimidazole derivatives such as mebendazole and albendazole have a 55-97% success rate due to their parasitostatic rather than parasiticidal effect.[4]

In conclusion, the surgical treatment of AE disease varies depending on the stage of the disease, the number and size of the lesions, the relationship of the lesion with the hilar structures and inferior vena cava, and ultimately the experience of the center. In treatment, resection with clean surgical margins, long-term anthelmintic treatment, and close follow-up are essential.

Disclosures

Informed consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.K., S.Y., S.A.,B.I.; Design – C.K., S.Y., S.A.,B.I.; Supervision – C.K., S.Y., S.A.,B.I.; Materials C.K., S.Y., S.A.,B.I.; Data collection &/or processing – C.K., S.Y., S.A.,B.I.; Analysis and/or interpretation – C.K., S.Y., S.A. ; Literature search – C.K., S.Y., S.A. ; Writing – C.K., S.Y., S.A.; Critical review – C.K., S.Y., S.A.,

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Letter to the Editor

Are In Situ Double Portal Vein Anastomosis or Unification ideal for Anomalous Portal Vein Reconstruction in Right Lobe Living Donor Liver Transplantation?

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Liver Transplantation Institute, Inonu University Faculty of Medicine, Malatya, Türkiye

Please cite this article as "Usta S, Akbulut S, Yilmaz S. Are In Situ Double Portal Vein Anastomosis or Unification ideal for Anomalous Portal Vein Reconstruction in Right Lobe Living Donor Liver Transplantation? J Inonu Liver Transpl Inst 2024;2(1):31–33".

Dear Editor;

We read with great interest the article by Shehta et al.[1] regarding "Feasibility and outcomes of living-donor liver transplantation utilizing the right hemi-liver graft with portal vein anatomical variations". We would like to express the following thoughts regarding this article:

1. According to the Cheng classification,[2] in type 2 anomalous portal venous branching, unification and anastomosis with the recipient portal vein are a process that is extremely prone to stenosis or thrombus. If unification is performed, the posterior and anterior sectoral branches of the right portal vein should be positioned as top and bottom (Fig. 1a and 1b). Then the corner sutures should be placed at both ends of the venoplasted suture line (Fig. 2a and 2b). In an anastomosis performed in this way, adaptation will be difficult and it will be possible for one or both of the portal vein branches of the right lobe to narrow. Even if the corner sutures are placed not on the venoplasty line, but at the point opposite it, adaptation problems will occur during anastomosis (Fig. 2c). There will be shrinkage in the recipient vena porta (Fig. 2d). In addition, during unification, forcing both portal vein lumens of the right lobe to come closer together will result in narrowing of both lumens.
2. In autologous Y graft anastomosis, the recipient's portal vein remains clamped for a long time. In those who do not have adequate portosystemic shunt, problems such as edema in the intestines, hemodynamic instability and failure to close the abdomen are likely. Therefore, our recommendation is the use of homologous portal vein Y graft. Since our institute is a high-volume transplant center, in total hepatectomy, the portal vein is cut from its distal end branches before the portal vein anastomosis and the recipient portal vein is cut to obtain the Y portal vein graft. Y portal vein is kept in cryopreservation and is used the next right lobe LDLT with anomalous portal venous branching. Authors, in their own studies[1] and in another study[3], mention a 5.8 – 6.3% incidence of portal vein thrombosis, especially in the right lobe posterior portal vein, with autologous Y grafting. This is due to malalignment between the Y portal vein graft and the recipient's sectorial portal vein branches. In addition to the article we have previously published[4], we are preparing homologous Y portal vein graft use in more than 50 cases

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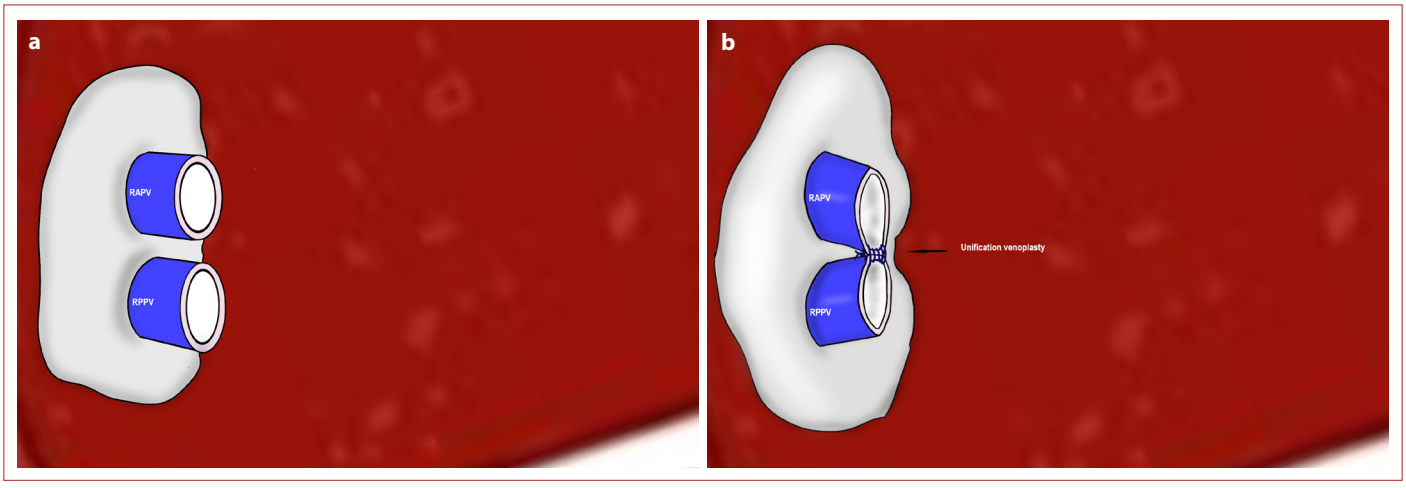

Figure 1. (a) Anterior and posterior sectorial portal vein branches of the right lobe of the liver. **(b)** Unification anterior and posterior sectorial portal vein branches of the right lobe of the liver.

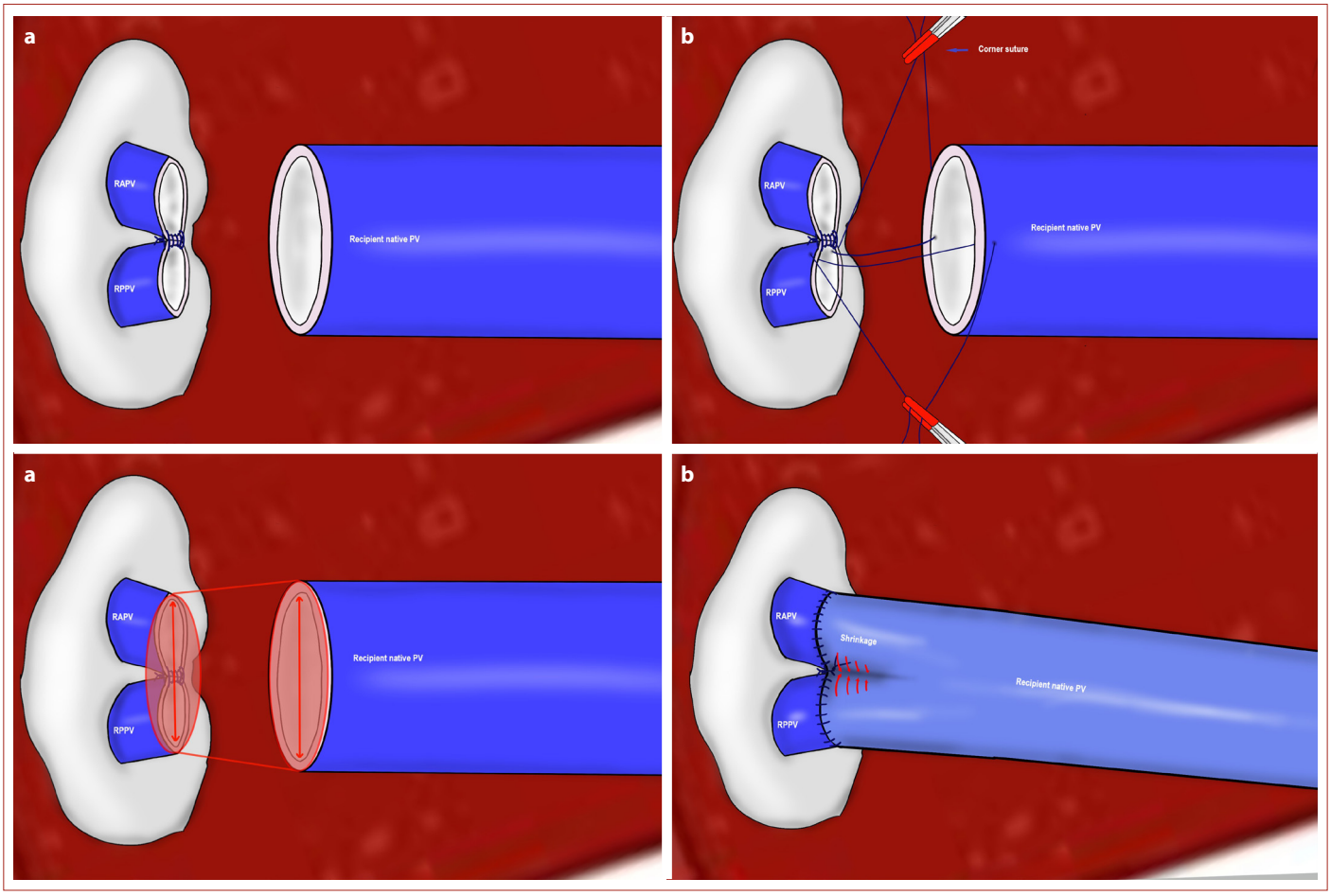

Figure 2. (a) Unified portal vein branches before anastomosis with the recipient portal vein. **(b)** The corner sutures were be placed at both ends of the venoplasted suture line and to the recipient portal vein. **(c)** Even if the corner sutures are placed not on the venoplasty line, but at the point opposite it, adaptation problems will occur during anastomosis. **(d)** There will be shrinkage in the recipient vena porta after the anastomosis.

of anomalous portal venous branching in right lobe living donor liver transplantation and its excellent results. In this study, we especially will focus on very important tips regarding alignment.

3. The authors have presented the feasibility of double portal vein anostomoses. Double portal vein anostomoses can be performed with right and left portal veins or right anterior and right posterior portal veins of the

recipient. But, double portal vein anostomoses may also result in portal vein thrombosis because of an angulation of the main portal vein axis. Moreover, in cases where GRWR <1 %, double portal vein anostomoses are prone to portal vein thrombosis due to rapid regeneration causing progressive malalignment.[4] Angulations are inevitable in dual anastomosis due to length or shortness. The authors have never mentioned which landmarks they technically met.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Financial Support: This study was not supported.

Data Availability: Not applicable.

Authorship Contributions: Concept – S.U., S.A., S.Y.; Design – S.U., S.A., S.Y.; Analysis and/or interpretation – S.A., S.Y.; Critical review – S.A., S.Y.

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Inonu University Liver Transplant Institute

Liver Transplantation and Hepatitis B Symposium

1 March 2024

From the Symposium President

Dear Participants,

Before the use of antiviral prophylaxis and hepatitis B immune globulin, posttransplantation recurrence of hepatitis B virus infection was almost universal and was commonly associated with accelerated hepatitis B virus-related graft injury leading to graft failure and death.

Many studies showed that the application of hepatitis B immune globulin and antiviral drugs is effective to prevent hepatitis B reinfection after liver transplantation. However, there are still many controversial issues regarding hepatitis B immune globulin prophylaxis, including dosage and time. In the meeting, an attempt was made to find answers to the controversial issues in hepatitis B immune globuline treatment.

The president of the Symposium

Prof. Burak ISIK, MD, FACS

Director of Inonu University

Liver Transplant Institute

Organizing Committee of the Symposium
Session Chairs
Burak ISIK
Cemalettin KOC
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Ahmet Sami AKBULUT
Murat HARPUTLUOGLU
Murat YAVUZ
Kemal Baris SARICI
Ersoy KEKILLI

Symposium program

1 March 2024

Session I

Chairperson: Prof. Burak Isik; MD and Prof. Cemalettin Koc; MD

Yilmaz Bilgic

14.00-14.20 Liver transplantation management from Anti HBc positive donors to HBV negative recipients in Liver Transplantation

Deniz Yavuz Baskiran

14.30- 14.50 Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation

Ahmet Sami Akbulut

15.00- 15.20 Protocols with and without Hepatitis B immunoglobulin following Liver Transplantation

15.30 - 15.40 Tea/Coffee Break

Session II

Chairperson: Prof. Dincer Ozgor; MD and Prof. Fatih Ozdemir; MD

Murat Harputluoglu

15.40 - 16.00 Approach to patients whose Hepatitis B surface antigen does not become negative and have early hepatitis B virus recurrence after liver transplantation

Murat Yavuz

16.10 - 16.30 Effectiveness, Patient Contentment, and Safety Profile of Subcutaneous Hepatitis B Immunoglobulin Therapy Following Liver Transplantation

Kemal Baris Sarici

16.40 - 17.00 HBV Prophylaxis After Liver Transplantation in HCC

17.40 CLOSING REMARKS

Liver transplantation management from Anti HBc positive donors to HBV negative recipients in Liver Transplantation

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Abstract

Anti HBc + people are in the marginal donor group. It is considered as a donor source, especially in places where Hepatitis B is endemic. In endemic areas, 21.4% of donors are HBcAb positive. In regions where HBV is not endemic, it is 4.75%-7%. De novo hepatitis may develop in liver transplants from anti-HBc+ donors. The most important factors for de novo hepatitis are the presence or absence of anti-HBc and anti-HBs positivity. If both antibodies are positive, the risk of denovo hepatitis is least and if both antibodies are negative, it is highest. High genetic barrier antivirals alone are recommended for the treatment and prophylaxis of developing de novo hepatitis. Hepatitis B immune globulin has no place in de novo treatment and prevention.

Introduction

Anti-HBc positivity can be explained by more than one scenario. Anti-HBc is a 'non-neutralizing' antibody that does not provide immune protection. In other words, it is a 'serological scar' (i.e. evidence of previous exposure to HBV). Anti-HBc+ status can be seen both after acute infection and chronic infection.[1]

This large cohort study described the long-term results of HBIG monotherapy preventing de novo HBV infection after LT using HBcAb positive liver grafts in an area where HBV is endemic. There is no advantage over monotherapy. HBcAb-negative recipients were more likely to develop new HBV infection than HBcAb-positive recipients. A high MELD score was significantly associated with de novo HBV infection.[2]

Between 2000 and 2010, 71 anti-HBs negative adult patients who received anti-HBc+ grafts were vaccinated against hepatitis B virus to ensure that Anti-HBs was >1000 IU/L before transplantation and >100 IU/L after transplantation. The cohort was divided into 3 groups: patients who did not need post-transplantation prophylaxis, patients with pre-transplant anti-HBs titer >1000 IU/L (group 1, n=24), patients with pre-transplant anti-HBs titer <1000 IU/L and anti-HBs administered. Patients who received post-transplant lamivudine prophylaxis and responded appropriately to post-transplant vaccination by maintaining anti-HBs titers >100 IU/L (group 2, n=30) and low titer non-responders (anti-HBs titer <100 IU/L despite vaccination) to lamivudine patient continued indefinitely (group 3, n=17). All DNHB occurred in group 3 patients with posttransplant anti-HBs levels <100 IU/L; The incidence rate was 17.6% compared to 0% in patients with post-transplant anti-HBs levels >100 IU/L (p=0.001). A pretransplantation anti-HBs level >1000 IU/L was significantly associated with early access and a persistent posttransplantation anti-HBs level of >100 IU/L (p<0.001). Active immunization is effective in preventing DNHB in adult LDLT if the post-transplant anti-HBs level is kept above 100 IU/L by vaccination.[3]

In another article investigating the risk of De novo hepatitis B virus infection developing after liver transplantation using a hepatitis B core antibody positive graft, the incidence of de novu hepatitis B was evaluated according to the anti-HBc and anti-HBs positivity or negativity of the recipient. De novo hepatitis developed in one of them. While the most risky group was the group in which both antibodies were negative, the risk was found to be lowest in the group in which both antibodies were positive. When the risk groups of patients who developed de novo hepatitis were examined, age, anti-HBc positivity and anti-Hbs positivity were found to be significant. Antivirals were started in patients who developed de novo hepatitis B. It was observed that HBsAg turned negative in all patients who developed de novo hepatitis after treatment.[4]

Treatment of de novo hepatitis;[5]

- HBIG+LAM combination compared to LAM monotherapy in HBV DNA(-) patients receiving HBcAb(+) liver grafts;
- LAM monotherapy has the same efficacy as HBIG+LAM combination therapy
- Entecavir and tenofovir monotherapy is safer.
- Therefore, we recommend that clinicians administer nucleoside(t)ide analogs with lower resistance profiles to recipients of HBcAb(+) liver allografts without additional HBIG therapy.
- AASLD and EASL recommend monotherapy.

The role of immunosuppressants used in the development of de novo hepatitis

The immunosuppressive regimen using mTOR inhibitors after liver transplantation has been shown to generally reactivate HBV infection, as well as viral infections such as HCV, cytomegalovirus (CMV), HIV-1, human papillomavirus (HPV), and Epstein Barr.[6]

Survival in de novo hepatitis

The 5-year survival rate for recipients of HBcAb-positive grafts was 97.5% and 89.7% for recipients of HBcAb-negative grafts. It shows that the survival rate does not differ significantly depending on the HBcAb status of the donor.[3]

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Inonu University Experience in Hepatitis B Recurrence After Liver Transplantation

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Abstract

We will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations.

Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence.

In our clinic , HBIG treatment is given for life. In the unhepatic phase, HBIG is given for 7 days postoperatively and every month, depending on the AntiHbs level. Anti-HBS level is tried to be kept above 100 IU/L. The HBV recurrence rate seen in our clinic shows that patients are not fully compliant with medical treatment and that patients must receive postoperative education. In particular, antiviral treatment and access to HBIG should be provided, and a prospective study should be started in our liver transplantation institute to investigate HBV recurrence.

Introduction

Hepatitis B virus (HBV), one of the biggest health problems of the world and our country, still constitutes the largest cause of liver failure and liver transplantation in the world. Here, we will introduce the HBV virus closely and share the health problems of HBV in the world and in our country in the literature data. We will evaluate patients who underwent liver transplantation due to HBV at İnönü University Liver Transplant Institute in terms of HBV recurrence, our results and recommendations.

HBV Epidemiology

In the 1980s, cirrhosis due to HBV was considered a relative contraindication for liver transplantation.[1] Because without antiviral prophylaxis, the recurrence rate of HBV after liver transplantation was close to 100% and the mortality rate in the first year after transplantation was approximately 50%. With the discovery of hepatitis B immunoglobulin (HBIG), a polyclonal antibody developed against HBV surface antigen, in the early 1990s, HBV recurrence after liver transplantation decreased significantly and survival increased.[2] HBIG has a polycolonal immunoglobulin G (IgG) structure and is in the IgG subclass. Its distribution is very close to the rates in human plasma.

High Risk Groups for HBV Recurrence;[8,9]

- Pre-Transplant Hbv DNA +
- Pre-Transplant Hbe-ag
- Presence of HCC
- Low compliance with antiviral treatment
- Resistance to antiviral treatment
- Concomitant HIV or HDV infection

Low Risk Group for HBV Recurrence[8,9]

- Pre-Transplant HBV DNA negativity
- Pre-Transplant Hbe-ag negativity
- No HCC
- High compliance with antiviral treatment
- Lack of resistance to antiviral treatment
- No accompanying HIV or HDV infection

Material Method

İnönü University Liver Transplant Institute Patients who underwent liver transplantation due to any reason related to HBV were included in the study.

Patients who underwent liver transplantation due to liver diseases caused by HBV in our institute between 2009 and 2023 were included in the study, A total of 3679 patients underwent liver transplantation between 2002 and 2024. Of these patients, 1275 patients were operated on with the diagnosis of HBV. When 530 patients whose data were not available and 49 patients who were retransplanted were excluded from the study, a total of 695 patients were included in the study. Of these patients, no HBV recurrence was observed in 599 patients. HBV recurrence was observed in 96 of these patients (13.8%).

Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence.

Findings

Hepatitis B recurrence is observed in a total of 112 patients (16.1%) and when the Hbs-ag levels after the long follow-up are examined, 96 patients (13.8%) are observed to have Hepatitis B recurrence.

Variables		n	(%)
DIAGNOSIS	HBV	454	65.3
	HBV+HCC	151	21.7
	HBV+HDV	61	8.8
	HBV+HDV+HCC	24	3.5
	HBV+HCV	3	0.4
	HBV+HDV+HCV+HCC	1	0.1
	HBV+HCV+HCC	1	0.1
HBSAG 1st month after liver transplantation	Negative	583	83.9
	Positive	112	16.1
Last check HBSAG	Negative	599	86.2
	Positive	96	13.8

Discussion

In a study, subcutaneous HBIG was given to patients who had completed 1 year after liver transplantation, with an anti-HBS titer of >150 Iu/L. After 48 weeks, the average anti-HBs titer was found to be 232 Iu/L, and no HBV recurrence was observed in any of the patients.[3]

In our clinic, HBIG treatment is given for life. In the unhepatic phase, HBIG is given for 7 days postoperatively and every month, depending on the AntiHbs level. Anti-HBS level is tried to be kept above 100 IU/L. The HBV recurrence rate seen in our clinic shows that patients are not fully compliant with medical treatment and that patients must receive postoperative education.

In another study involving 176 patients, the combination of HBIG and potent antivirals was targeted to have an anti-HBS titer of 100-250 Iu/l in the post-transplant period. It was reported that only 2 patients developed relapse during an average follow-up of 43 months and one of these patients did not use the treatment.[11th]

Treatment is given in combination with antiviral and HBIG. It is available in centers where powerful antivirals are used alone. Although the approaches of the centers vary, patients who have had a liver transplant due to HBV definitely need postoperative medical treatment to prevent HBV recurrence.

Anti-HBS level differences may be required in the follow-up of high-risk and low-risk groups. However, monitoring this requires detailed information about the patient discharged from the hospital.

When the effect of high-risk patient group on postoperative HBV recurrence was examined, it was seen that noncompliance with medical treatment was effective.

Despite all these findings, it has been reported that the use of HBIG has additional contributions such as reducing rejection and HCC recurrence rates after liver transplantation.[4]

Conclusion and Recommendations

Patients who have undergone liver transplantation due to HBV must have their Hbs-ag level checked when they are discharged from the hospital. Informing the patient about HBV recurrence and medical treatment provides a more meticulous medical treatment. In particular, antiviral treatment and access to HBIG should be provided, and a prospective study should be started in our liver transplantation institute to investigate HBV recurrence. The shortcomings of the study are that it is a retrospective study, not all patient data can be accessed in the study (Hospital automation system change), and the HBIG doses taken by the patient cannot be determined.

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Protocols with and without Hepatitis B immunoglobulin following Liver Transplantation

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Abstract

Hepatitis B Virus (HBV) is the most frequent etiology of liver failure requiring liver transplantation. The crucial point of liver transplantation for HBV-related liver disease is the prevention of HBV relapse in the postoperative period. Current evidence suggests combining Hepatitis B Immunoglobulin (HIBIG) and nucleotide/nucleoside analogs. The decision to start HIBIG therapy and its duration is controversial. However, studies suggest that it should be tailored according to individual patients. Generally, HIBIG monotherapy is not recommended. Short-term HIBIG in combination with antiviral agents followed by monotherapy with newer and potent antiviral agents is recommended in low—risk patient groups. On the other hand, long-term HIBIG with nucleotide/nucleoside analogs is effective in the prevention of post-transplant HBV relapses.

Key words: Hepatitis B virus; Liver Transplantation; Hepatitis B immunoglobulin

Introduction

Liver transplantation for Hepatitis B virus (HBV)-related to end-stage liver disease is a rapidly developing topic. Prevention of relapse of Hepatitis B virus following liver transplantation is critical. Before the development of effective antiviral treatment HBV recurrence rates were 100% and the 2-years survival rates were nearly 50%. Together with the current antiviral therapies combined with Hepatitis B Immunoglobulin (HIBIG), the survival rates rose above 75% and the relapse rates dropped below 10%. For these reasons, the combination of HIBIG with nucleoside (lamivudine, entecavir, and telbivudine) and nucleotide (tenofovir and adefovir) analogs is the standard treatment protocols for prevention of HBV relapse in the post-transplant period. These protocols can prevent the relapse of HBV in more than 90% of the recipients in the post-transplant period. Entecavir, Tenofovir disoproxil, and tenofovir alafenamide are antiviral agents with a high potency. These antiviral therapies should be continued indefinitely in the post-transplant period regardless of the Hepatitis B envelope antigen (HBeAg) and HBV DNA status of the patient.

HBV recurrence in the post-transplant period can be defined as relapse of HBsAg positivity and/or HBV-DNA positivity or the presence of specific histopathological changes. The risk factors for HBV recurrence are summarized in Table 1.

There are many protocols combining HIBIG and antiviral treatments. However, the data in the literature regarding the use of a combination of HIBIG and antivirals are still controversial. For example, many protocols include HIBIG in the treatment. Some of them use high or low-dose HIBIG, some use HIBIG for a limited period and some use HIBIG as monotherapy. However, with the development of high-potency antiviral agents, protocols combining HIBIG and antivirals are preferred.

The current Regulations for Health Care Applications state that the reimbursement of HIBIG therapy is indicated under the following conditions; i) during the unhepatic phase of the liver transplantation, 10.000

Table 1. Summary of the risk factors for HBV recurrence in the post-transplant period.

The Risk Factors for HBV Recurrence
The presence of high concentrations of HBV DNA in the pretransplant period
HBeAg positivity
History of resistance to antiviral treatments
Presence of HCC at the time of liver transplantation
HCC recurrence
History of chemotherapy for HCC
Treatment non-compliance of the patient
Presence of coinfection with either HDV or HIV

HDV: Hepatitis D; HIV: Human immunodeficiency virus; HCC: Hepatocellular carcinoma; HBeAg: Hepatitis B envelope antigen; DNA: Deoxyribonucleic acid.

IU HIBIG in high-risk patients and 5000 IU HIBIG in low-risk patients are reimbursed, ii) following the liver transplantation, 2000 IU/day of HIBIG for postoperative first 7 days are reimbursed. At the end of the period, if the HBSag is negative or anti-HBS antibodies are >100 IU/l, maintenance therapy 2000 IU HIBIG /month is performed, iii) if HBSAg is still positive or anti-HBs antibody titers are < 100 IU/l, another week of daily 2000 IU HIBIG therapy is indicated and at the end of these 14 days, maintenance therapy of monthly 2000 IU HIBIG is performed, iv) Every prescription of HIBIG (ether therapy or maintenance)should include the up-to-date HBV DNA or HBsAg concentrations, v) if the results of the HBV DNA or HBsAg concentrations are positive, then the HIBIG therapy is discontinued, vi) The HIBIG therapy is continued up to 1 year following liver transplantation in low-risk patients and it is continued for 10 years following transplantation in high-risk patients who have HCC. HIBIG can be continued for 5 years following the transplant procedure in other high-risk patients, vii) patients who are coinfected with delta hepatitis virus (HDV) and human immunodeficiency virus (HIV) are entitled to lifelong HIBIG treatment.

Acute Liver Failure and Liver Transplantation Special Interest Group have prepared detailed recommendations for post-transplant HIBIG treatment and are summarized in Table 2.[1]

The Protocol for HIBIG Maintenance Treatment of Inonu University Liver Transplant Institute

We taper the dose according to the anti-HBs antibody titers. The monthly dose of the HIBIG can be waived if anti-HBs titers are > 100 IU/l. If the anti-HBs titers were between 50-100 IU/l, 500 IU HIBIG is recommended. If antibody titers are below 50 IU/l, 1000IU HIBIG is recommended.

Literature Review on this Issue

We have performed a literature review regarding the protocols of post-transplant HBV therapies to prevent HBV relapse. The data regarding the subject seems controversial in terms of the use and duration of the treatment of HIBIG. Buti et al.[2] reported that the short course of Lamivudine and HIBIG was as effective as a combination of HIBIG and Lamivudine for the first 18 months. Another study showed the beneficial effects of new nucleotide/nucleoside analogs as maintenance once HIBIG therapy was stopped.[3] It has been demonstrated that entecavir monotherapy has been very effective in HBsAg and HBV DNA clearance rate approaching 90-100% with a sustained effect between 8 to 9 years following liver transplantation for chronic HBV infections.[4]

Manini et al.[5] have reported that maintenance therapy with Entecavir and Tenofovir after HIBIG and nucleotide/ nucleoside analog combination therapy for 6 months was very effective in preventing HBV relapse after liver transplantation performed for chronic HBV-related liver disease.

The Spanish Association for the Study of the Liver has stated that HIBIG treatment can be stopped 4 months after liver transplantation in low-risk individuals. If the recipient had a positive HBV DNA before the liver transplant, they recommend continuing the HIBIG treatment for 1 year. In addition, they recommend HIBIG therapy indefinitely in high-risk individuals who have HCC or coinfection with HIV or HDV.[6]

The Turkish Acute Liver Failure and Liver Transplantation Special Interest Group emphasized the necessity for discontinuation of HIBIG therapy to prevent adverse effects and to reduce the costs of the treatment.[1] In low-risk patients, the preferred treatment protocol includes a brief period of low-dose HIBIG and nucleotide/nucleoside analogs followed by monotherapy with potent antiviral therapies. On the other hand, in high-risk patients, discontinuation of HIBIG requires close surveillance of the patients. A study by Sheng et al. has shown the efficacy and safety of nucleotide/nucleoside analog monotherapy in comparison to combination with HIBIG therapy.[7] Combination therapy seems to be a reasonable approach for the prevention of HBV relapse following liver transplantation for HBV. Indefinite use of HIBIG treatment in combined with potent antivirals is more effective in preventing HBV recurrence when compared to a shorter duration of HIBIG therapy. On the other hand, while tapering the HIBIG titers, slow reduction is more effective than rapid reduction of the HIBIG titers in prevention of the HBV relapse.[8,9]

A combination of HIBIG with older antivirals is more effective than monotherapies. Therefore, the presence of HIBIG in combination with antiviral medications has lower HBV recurrence rates.[10] On the other hand, studies evaluating the combination versus monotherapy of HIBIG with newer and more potent nucleotide/nucleoside analogs are needed. On the other hand, the combination of HIBIG with nucleotide and nucleoside analogs is more effective in high-risk groups. The efficacy of combining HIBIG with antiviral therapies has no superior effect on HBV recurrence in low-risk patients.[11]

The European Association for the Study of the Liver (EASL)[12] recommends a combination of HIBIG and potent antiviral agents for the prevention of post-transplant HBV recurrence ((Evidence level II- 1, grade of recommendation 1). On the other hand, they recommend discontinuation of HIBIG in low-risk patients followed by monotherapy with a potent nucleotide/nucleoside analog (Evidence level II-1, grade of recommendation 2).[12]

American Association for the Study of Liver Diseases (AASLD)[13] recommends that all patients with HBV undergoing liver transplantation should receive nucleotide/nucleoside analogs with or without HIBIG regardless of the HBeAg and HBV-DNA concentration of the

Table 2. The summary of the recommendations of the Acute Liver Failure and Liver Transplantation Special Interest Group.

The recommendations of the Acute Liver Failure and Liver Transplantation Special Interest Group
Anhepatic Phase
5000 IU HIBIG in low-risk patients
10000 IU HIBIG in high-risk patients
Post-transplant early period (first two weeks following the procedure)
Daily 2000IU HIBIG for 7 days followed by surveillance of HBsAg and/or HBV DNA
If HBsAg and/or HBV DNA negative, daily HIBIG administration is discontinued and a monthly maintenance dose of 2000 IU is initiated
If HBsAg and/or HBV DNA positive, another 7-day course of daily 2000IU HIBIG is continued which is followed by maintenance therapy regardless of the HBsAg and HBV DNA status
If there is a coinfection with HDV, another 14-day (a total of 28 days) course of 2000IU HIBIG can be given before the initiation of the maintenance therapy
Maintenance Therapy
A monthly dose of 2000 IU HIBIG is given for 1 year in low-risk groups
A monthly dose of 2000IU HIBIG is given for a long period (inconclusive statement) in high-risk patients for
The target anti-HBs antibody titers should be >50 IU/l and the monthly dose could be waived if the anti-HBs antibody titers are > 200 IU/l

HBV: Hepatitis B Virus; HBs Ag: Hepatitis B surface antigen; HBV DNA: HBV deoxyribonucleic acid; HIBIG: Hepatitis B Immunoglobulin; HDV: Delta hepatitis virus.

patients. HIBIG monotherapy is not recommended. Newer and more potent antiviral agents (such as Entecavir, Tenofovir disoproxil, and Tenofovir alafenamide) have a low rate of resistance and therefore they are recommended. In low-risk patients, HIBIG may be discontinued in 5 to 7 days following the transplant procedure or may not be initiated. A combination of HIBIG and antiviral agents is more effective in high-risk patients. Therefore, individualized therapy is recommended according to different patient groups.[13]

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Approach to Patients Whose Hepatitis B Surface Antigen Does Not Become Negative and Have Early Hepatitis B Virus Recurrence After Liver Transplantation

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Abstract

There are very few publications on the effects of hepatitis B recurrence on transplanted liver and the management of these patients. The aim of this paper is to summarize the approach to patients whose Hepatitis B surface antigen (HBsAg) does not become negative and experience early hepatitis B virus (HBV) recurrence after liver transplantation (LT). Definition of hepatitis B recurrence is reappearance or persistence of circulating HBsAg with or without detectable HBV DNA. Although there are studies reporting that HBsAg positivity alone under antiviral treatment may not have a negative impact on patient and graft survival during antiviral treatment, some studies suggest the opposite. HBV recurrence after liver transplantation is an important risk factor for hepatocellular carcinoma (HCC) recurrence. Recurrent HBV patients should be evaluated in detail in terms of treatment compliance, and treatment should be changed if necessary. HBIG treatment should be discontinued and lifelong antiviral treatment should be given.

Key words: Liver Transplantation, hepatitis B, hepatitis B recurrence

Introduction

The course of hepatitis B after transplantation and its effects on patient and graft survival are still intensely debated in the transplant community. The aim of this article is to summarize the approach to patients whose Hepatitis B surface antigen (HBsAg) does not become negative and experience early hepatitis B virus (HBV) recurrence after liver transplantation (LT).

Definition of Hepatitis B recurrence

It is commonly based on the reappearance or persistence of circulating HBsAg with or without detectable HBV DNA.[1] It is not clear how long to wait for HBsAg to become negative after transplantation.

Outcomes of Hepatitis B recurrence

It has been reported that clinically significant HBV relapse (increase in aminotransferase levels and acute or chronic hepatitis) is observed only in patients with persistent HBV DNA positivity. Additionally, in cases of HBV DNA negativity in serum, persistence or reappearance of HBsAg positivity is not associated with graft hepatitis.[2] Fung et al. reported that elastography results were not significantly different between patients those with and without HBsAg seroclearance, and with HBsAg re-appearance. Moreover, this result was associated with an overall 85% 9-year survival, without any graft loss or death due to HBV recurrence.[3] Contrary to these studies, there are also studies reporting that post-transplantation HBV recurrence leads to important consequences. For example, Lerut et al reported that 3 of 16 recurrent HBV patients had developed fibrosing cholestatic hepatitis and all patients died within the first 1 year postoperatively.[4]

HBV Recurrence in Special Patient Groups

Hepatocellular Carcinoma

HBV recurrence after liver transplantation is an important risk factor for HCC recurrence. One study reported that the HCC recurrence rate in patients with HBV recurrence was significantly higher compared to patients without HBV recurrence (40% and 5.7%, respectively, $p<0.001$).[5]

Hepatitis D

Patients with hepatitis D are considered to be at low risk of HBV recurrence after liver transplantation.[1] Data on HDV recurrence after liver transplantation and its long-term consequences are very limited.[6] There is currently no treatment available for Hepatitis D recurrence after liver transplantation. A review published in 2022 reported that patients who underwent liver transplantation in Europe due to HBV/HDV cirrhosis had a good prognosis and long-term results despite recurrent infection.[7]

Survival in Patients with HBV Recurrence

In one study, the 5-year overall survival rate and recurrence-free survival rate after liver transplantation in recipients with HBV reactivation were significantly lower than those without (32.0% vs 62.3%; $p<0.01$, and 16.4% vs 63.1%; $p<0.01$, respectively).[8]

Treatment of HBV Recurrence

The British Transplantation Society Guidelines, published in 2018, recommend careful questioning of antiviral drug compliance and lifelong antiviral treatment in all recurrent HBV patients.[9] EASL and The British Transplantation Society Guidelines recommend that treatment with entecavir and tenofovir should be started immediately.[10] When choosing a medication, it is recommended to take into consideration the history of antiviral use in the past and to prefer tenofovir in patients using lamivudine. In patients who use their medication properly, switching to another antiviral or combination therapy and additional resistance testing are recommended.[11] It is recommended that hepatitis B immunglobuline (HBIG) treatment be discontinued in recurrent HBV patients and management be carried out in cooperation with a hepatologist.[12]

In conclusion, HBV recurrence is very important, especially in HCC patients. Recurrent HBV patients should be evaluated in detail in terms of treatment compliance, and treatment should be changed if necessary. HBIG treatment should be discontinued and lifelong antiviral treatment should be given.

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Effectiveness, Patient Contentment, and Safety Profile of Subcutaneous Hepatitis B Immunoglobulin Therapy Following Liver Transplantation

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Abstract

Recurrent hepatitis B virus (HBV) infection after liver transplantation carries substantial complications, such as graft malfunction and rejection. HBV recurrence can be prevented by combining antiviral treatment with Hepatitis B immunoglobulin (HBIG) therapy. Subcutaneous HBIG (SC HBIG) has become a successful substitute for intravenous administration, providing ease and high levels of patient contentment. This study focuses on the effectiveness, safety, and level of satisfaction experienced by patients who underwent (SC HBIG) treatment after liver transplantation.

Keywords: HBV recurrence, liver transplantation, hepatitis B, immunoglobulin therapy

Introduction

The occurrence of hepatitis B virus (HBV) infection again after liver transplantation is a major risk to the health of patients and the survival of the transplanted organ. Although there have been improvements in transplantation medicine, the recurrence of HBV continues to be a difficult problem, sometimes resulting in negative consequences such as malfunction of the transplanted organ, rejection, and death.[1] Therefore, it is crucial to implement efficient preventive measures in order to avoid HBV reinfection after transplantation.[2]

Recent research has yielded persuasive findings concerning the effectiveness of subcutaneous HBIG (SC HBIG) in mitigating the recurrence of HBV following liver transplantation.[3-5] The efficacy of SC HBIG in combination with nucleoside analogues (NA) in preserving protective anti-HBs levels and decreasing the likelihood of HBV reinfection in comparison to HBIG therapy cessation has been established by these studies.[5-7] By combining SC HBIG and NA therapy, HBV recurrence can be effectively prevented prophylactically, leading to improved patient outcomes and graft survival.[7-10]

An essential advantage of SC HBIG is its ease of administration, which contributes to improved patient satisfaction.[11] Unlike intravenous HBIG (IV HBIG), which often requires hospital-based administration, SC HBIG can be self-administered by patients in an outpatient setting.[12] This convenience factor significantly enhances patient compliance and adherence to the prophylactic regimen. Patients report high levels of satisfaction with SC HBIG, citing its user-friendly nature and the ability to incorporate it seamlessly into their post-transplant routine.[13] Moreover, the option for self-administration empowers patients, giving them a sense of control over their treatment regimen.[14]

Beyond its clinical efficacy, SC HBIG may offer cost advantages over IV HBIG, making it an economically viable option for HBV prophylaxis post-transplantation. The transition from IV to SC HBIG has been associated with cost savings, primarily due to reduced dosage requirements and lower administration costs.[15] Additionally, the ability for patients to self-administer SC HBIG reduces the need for healthcare facility resources, further contributing to cost savings over time. As healthcare systems continue to prioritize cost-effective interventions, SC HBIG emerges as a financially prudent choice for HBV prophylaxis in the post-transplant setting.[16]

SC HBIG has an overall favorable safety profile, as the majority of adverse events are modest and controllable. Injection site reactions, including erythema and pain, are frequent adverse effects that are generally temporary in nature and resolve on their own.[17] Although hypersensitivity reactions and other rare adverse events have been documented, the overall incidence is minimal. Therefore, for the overwhelming majority of patients, the benefits of SC HBIG outweigh the associated risks. Adverse event management and vigilant observation guarantee the health and safety of patients undergoing SC HBIG therapy.[18]

Conclusion

To summarize, the subcutaneous injection of HBIG is an effective approach to prevent the return of HBV after liver transplantation. The shown effectiveness, together with benefits such as simplicity of use, cost efficiency, and a positive safety record, make SC HBIG the recommended option for doctors who are responsible for monitoring post-transplant HBV prophylaxis. By integrating SC HBIG into transplant procedures, healthcare practitioners can maximize patient outcomes and improve the long-term effectiveness of liver transplantation.

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HBV Prophylaxis After Liver Transplantation in HCC

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Abstract

Hepatitis B Virus (HBV) infection remains a major cause of chronic liver disease. Hepatitis B virus infection has a wide spectrum of clinical manifestations including: acute HBV infection, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). After the advent of HBIG monotherapy, the risk of HBV recurrence after LT was reduced and survival rates improved. After LT, Entekavir and tenofovir disoproxil fumarate (TDF) have been shown to be effective in preventing HBV relapse with HBIG combined with potent NA (nucleotide analogs). Recurrence after LT is defined as HBsAg positivity and/or detectable HBV DNA levels. HBIG and potent antivirals (ETV, TDF and TAF) are recommended to prevent HBV recurrence after liver transplantation. Serum HBV DNA, HBeAg positivity, presence of HCC, HDV and HIV co-infections before liver transplantation increase the risk of HBV recurrence after transplantation. To prevent HBV recurrence in patients with HCC, HDV and HIV co-infections, the combination of HBIG and antiviral therapy should be given for a long time, perhaps lifelong.

Introduction

Hepatitis B Virus (HBV) infection remains a major cause of chronic liver disease. Despite the successful HBV vaccination program in Turkey and efforts to reduce HBV transmission and prevention in the adult population, the infection remains a major public health problem. According to an epidemiologic study, hepatitis B surface antigen (HBsAg) positivity in the adult population in Turkey is around 4% and hepatitis B core antibody (anti-HBc) positivity is 31%.[1]

Clinical Course

Hepatitis B virus infection has a wide spectrum of clinical manifestations including: acute HBV infection, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). HBV infection is present in 50% of patients with HCC and most of them are also cirrhotic. HBV is also the cause of 40-50% of end-stage liver diseases leading to liver transplantation, with or without HCC.[2]

HBV Prophylaxis

Before the introduction of hepatitis B immunoglobulin (HBIG), patients with HBV-associated cirrhosis were not suitable candidates for LT due to high post-transplant HBV recurrence rates, resulting in low patient and graft survival rates.[3] After the advent of HBIG monotherapy, the risk of HBV recurrence after LT was reduced and survival rates improved. After LT, Entekavir and tenofovir disoproxil fumarate (TDF) have been shown to be effective in preventing HBV relapse with HBIG combined with potent NA (nucleotide analogs).[4]

Mechanism of Action of HBIG

The mechanism of action of HBIG is not known clearly, probably Hepatitis B immunoglobulin neutralizes HBV. HBIG has been shown to neutralize circulating virions, facilitate lysis of infected hepatocytes through antibody-dependent cellular cytotoxicity and block HBV receptors on hepatocytes. The half-life of HBIG is approximately 22 days.[5]

The disadvantages of HBIG are the need for lifelong treatment and the possibility of mutation in the "a" determinant region of the HBV surface gene,futhermore causing resistance disadvantage to treatment its high cost and parenteral administration are also.[6]

Recurrence After LT

Recurrence after LT is defined as HBsAg positivity and/or detectable HBV DNA levels. It has been reported that the presence of HCC before liver transplantation is associated with HBV recurrence after transplantation. In a study conducted in our country, it was reported that after 46 months of follow-up of 296 patients who underwent liver transplantation due to HBV, 8 of the patients developed HBV recurrence and 7 of these patients had HCC before transplantation. The investigators reported that the presence of HCC before liver transplantation increased post-transplant HBV recurrence risk by 12 folds.[7]

Of the 1005 HBV-related LT patients in our clinic, 163 patients underwent LT due to HBV+HCC and 31 patients underwent LT due to HBV+HDV+HCC. While 16 of these patients developed HCC recurrence with HBV, 13 developed HCC recurrence without HBV. Here, in the HDV-positive group, HCC recurrence was observed in all 7 HBV-positive patients who were excluded from the Milan criteria. Here we see how important HDV is in HCC recurrence. Considering that HBV

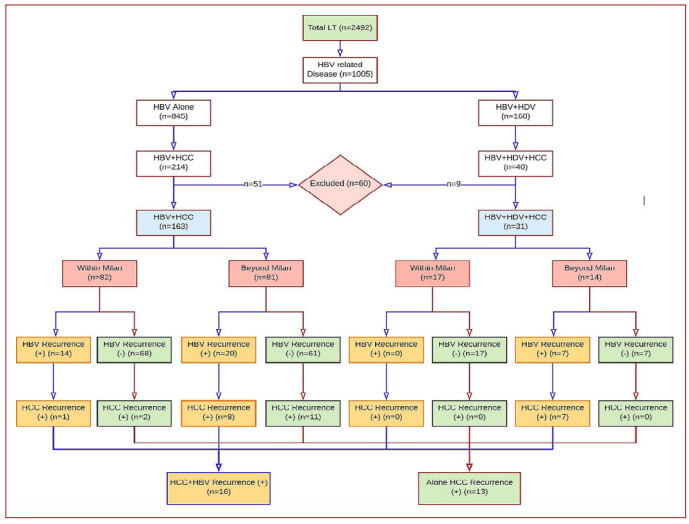

Figure 1. The processes of LT patients with HBV alone and HBV-HDV coinfection until HCC recurrence.

is needed for HDV to become positive, it will be understood how important HBV prophylaxis is in HCC recurrence (Fig. 1).[8]

In order to prevent HBV reccurence following LT, in 5000 IU HBIG should be administered intravenously to low-risk patients and 10 000 IU to high-risk patients. In anhepatic phase during the first 7 days after LT, HBIG administration continue continued at a maximum daily dose of 2000 IU until HBsAg seroconversion. Is achieved if seroconversion is not achieved in postoperative 7 days, 2000 IU per day HBIG is continued for an additional 7 days (Table1).[9]

Our prophylaxis protocol for the prevention of postoperative HBV recurrence after LT is as follows:

Cirrhotic patients with HBsAg (+) and HBVDNA (-) received 5000 IU HBIG and 2000 IU/day HBIG immediately after graft implantation. It was administered for 7 days postoperatively. The goal is to maintain anti-HBs titers above 50 IU/dL.

HBsAg (+) and HBVDNA (+) cirrhotic patients received 10,000 IU HBIG immediately after graft implantation and 2000 IU/day IV HBIG for 7 days postoperatively. The goal to maintain anti-HBs titers above 100 IU/dL.

Cirrhotic patients with HbsAg (+) and HBV-DNA (+) with HDV-free HCC receive 10,000 IU HBIG immediately after liver graft implantation and 10,000 IU/day IV HBIG for postoperative 7 days. The goal of target therapy is to maintain anti-HBs titers above 500 IU/dl.

Some centers suggest that anti-HBs titer should be > 500 IU/L first 3 months after transplantation, > 250 IU/L between 6 to 12 months, and > 100 IU/L thereafter.[10]

Table 1. High and low risk groups for HBV recurrence

High risk groups for HBV recurrence	Low risk groups for HBV recurrence
HBV DNA positivity before transplantation	HBV DNA negativity before transplantation*
HBeAg positivity before transplantation	HBeAg negativity before transplantation*
Presence of HCC before transplantation	No HSK before transplantation
Low adherence to antiviral therapy	High compliance with antiviral treatment
Antiviral drug resistance	No antiviral drug resistance
Concomitant HDV or HIV infection	No accompanying HDV or HIV infection

Maintenance HBIG should be administered at a monthly dose of 2000 IU and anti-HBs titers should be kept above 50 IU/L. If the anti-HBs titer is above 200 IU/dl, the HBIG dose should be skipped. HBIG is administered in 3 ways; IV, IM and SK.Different modes of administration has no difference in terms of efficiency.[11]

In the consensus report prepared by the Spanish Association for Liver Research, it was recommended that HBIG administration could be terminated at four weeks in patients who do not have risk factors for HBV recurrence, HBIG administration is recommended for up to 1 year in patients with positive HBV DNA levels before transplantation, and HBIG administration should be used continuously in the presence of HCC, HDV and HIV.[12]

Lifelong HBIG administration is recommended in high-risk patients or patients who do not comply to postoperative follow up. In low-risk patients, it is recommended to continue potent NA monotherapy following short-term HBIG administration after transplantation. Some centers recommend administration of from Turkey, HBV vaccines for anti-HBs formation after discontinuation of HBIG.[13]

In a retrospective study 128 patients with delta hepatitis received HBIG and antiviral therapy after transplantation, and no HDV recurrence was observed in any of the patients in a mean follow-up of 30 months.[14]

In another study, 104 patients with delta hepatitis received prophylaxis with HBIG and antiviral combination therapy in the post-transplant period, and HDV recurrence was observed in 13% of the patients at a mean follow-up of 82 months.[15]

Lifelong HBIG administration with antiviral therapy is recommended to prevent HBV recurrence in patients who underwent liver transplantation for delta hepatitis.

Conclusion

HBIG and potent antivirals (ETV, TDF and TAF) are recommended to prevent HBV recurrence after liver transplantation. HBIG treatment can be administered by IV, SC, IM route. The method of administration should be decided on a patient basis. Serum HBV DNA, HBeAg positivity, presence of HCC, HDV and HIV co-infections before liver transplantation increase the risk of HBV recurrence after transplantation. To prevent HBV recurrence in patients with HCC, HDV and HIV co-infections, the combination of HBIG and antiviral therapy should be given for a long time, perhaps lifelong. To prevent HBV recurrence in low-risk patients, short-term HBIG administration and continuous potent antiviral therapy is recommended. In the anhepatic phase, 10 000 IU of HBIG is recommended IV for high-risk patients and 5 000 IU for low-risk patients. In maintenance therapy, HBIG treatment should be individualized according to anti-HBs titer and anti-HBs titer should be kept above 50 IU/L.

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